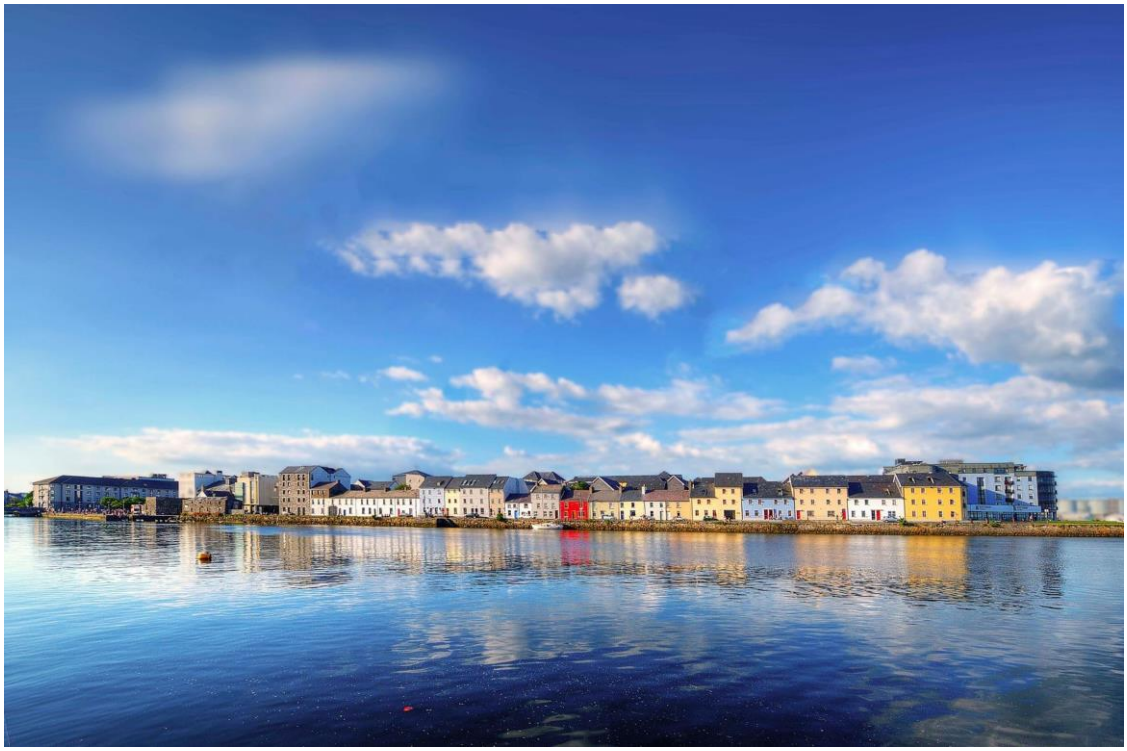
HAEMATOLOGY ASSOCIATION OF IRELAND ANNUAL MEETING 2023

Galway Bay Hotel, Galway
Friday 13 and Saturday 14 October 2023



ANNUAL MEDICAL &
SCIENTIFIC MEETING: FRIDAY 13 & SATURDAY 14 OCTOBER 2023

ANNUAL NURSES &
AHPs GROUP MEETING: FRIDAY 13 & SATURDAY 14 OCTOBER 2023

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HAEMATOLOGY ASSOCIATION OF IRELAND

OCTOBER 2023

Dear Colleagues

Welcome to Galway!

It is hard to believe that it has been 4 years since we were last here. This year, we have packed programmes at all the sessions.

As always, I would like to extend a very warm welcome to everyone for making the effort to attend in-person, in particular, to all of you who have submitted abstracts to this year's conference. This year we received a total of 143 abstract submissions, which is our highest number ever so thank you for helping the HAI grow in strength year on year.

A very special thanks to all our guest speakers who have travelled from near and far to be here with us. We are most grateful to each and every speaker for taking the time out of their very busy schedules to share their knowledge with us.

Once again, it gives me great pleasure to announce that Novartis have agreed to continue their sponsorship of the Novartis Career Development & Nursing Professional Development Awards in the amount of €10,000 and €3000 respectively. Details of how to apply for these awards will be announced at the conference. This award will provide funding for further education, research or the acquisition of a technique or skill which would be of benefit to medical education. Our sincere thanks go to Novartis for sponsoring this Educational Grant.

Lastly, as my term of President of the HAI comes to an end, I would like to extend a warm welcome to our President-Elect, Prof. Paul Browne. I would like to wish him the very best of luck in this role. I hope he enjoys it as much as I have.

I would like to thank the HAI Committee for all their support and hard work throughout my term as President. In particular, I would like to acknowledge the work of Dr Su Maung, who is stepping down as our Secretary/Treasurer and also Dr Kathryn Clarke who, as usual, have put together a superb programme for this year's meeting. I would also like to extend my sincere thanks to everyone who has assisted in the review of abstracts as without this support, we would not be able to run the meetings as successfully as we do.

Finally, on behalf of the HAI Committee I hope you enjoy the meeting!

Feargal

Dr Feargal McNicholl, President

ANNUAL MEETING PROGRAMME Friday 13th October 2023, Galway Bay Hotel (CPD Accredited – 6 CPD Credits 13.10.23)	
08.00-08.45	**Tea/Coffee/Scones/Meet the Sponsors** ***(All sponsors who support this meeting through the sponsorship of exhibition space alone have no input into the Agenda, speaker selection or content of this meeting)***
08.45-09.00	**Opening of the Annual HAI Meeting – Dr Feargal McNicholl, President**
SESSION 1 – Oral Presentations 6 x 10 minute Presentations **Chairpersons: Dr Feargal McNicholl and Dr Su Maung**	
09.00-09.10	**IDENTIFICATION OF POTENTIAL THERAPEUTIC TARGETS TO REVERT NATURAL KILLER CELL EXHAUSTION IN MULTIPLE MYELOMA THROUGH SINGLE-CELL RNA-SEQ ANALYSIS** **Jacopo Umberto Verga[1,2]**, M O'Dwyer[3], E Szegezdi[1,2] [1]Centre for Research Training in Genomics Data Science, School of Biological, University of Galway, Galway, [2]Apoptosis Research Centre, School of Biological and Chemical Sciences, University of Galway, Galway, [3]School of Medicine, Haematology Department, University of Galway, Galway
09.10-09.20	**SODIUM-GLUCOSE CO-TRANSPORTER-2 (SGLT2) INHIBITOR INDUCED APPARENT ERYTHROCYTOSIS.** **Stuart Macleod[1]**, SG Grennan[1], KP Perera[1], SGaffey[1], M Kelly[1], K Drumm[1], J Archutick[1,2], A Hussain[1], I Ul Haq[1], G Crotty[1] [1]Haematology, MRHT, Tullamore, [2]Medicine, UL, Limerick
09.20-09.30	**ENHANCING THE CYTOTOXICITY OF NATURAL KILLER CELLS ON NON-HODGKIN'S LYMPHOMA USING SMAC MIMETIC BIRINAPANT** **Soumyadipta Kundu[1,2]**, E Szegezdi[1], M O'Dwyer[1,2] [1]Apoptosis Research Centre, University of Galway, Galway, [2], ONK Therapeutics Ltd., Galway, Ireland
09.30-19.40	**A SMALL MOLECULE DRUG THAT SELECTIVELY IMPAIRS INFLAMMATION-INDUCED ANTIFIBRINOLYTIC ACTIVITY TO RESTORE PLASMIN GENERATION** **Paula Austra Klavina[1, 2]**, AM Rehill[1], SJ Humphreys[3], F Nally[2], CS Whyte[3], NJ Mutch[3], AM Curtis[2], RJS Preston[1] [1]Irish Centre for Vascular Biology, School of Pharmacy and Biomolecular Sciences, RCSI, Dublin, [2]Curtis Clock Laboratory, School of Pharmacy and Biomolecular Sciences, RCSI, Dublin, [3]Aberdeen Cardiovascular and Diabetes Centre, Institute of Medical Sciences, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen
09.40-09.50	**UNRAVELLING THE MOLECULAR EFFECTS OF A NOVEL LEUKAEMIA-RELATED GENE FUSION** **Emma Grady[1]**, T Dias[1,2], P McCarthy[1,2,3], S Biswas[1,2], A Trinquand[3], D Betts[3], A Malone[3], J Bond[1,2,3] [1]School of Medicine, University College Dublin, Belfield, Dublin 4, [2]UCD Systems Biology Ireland, University College Dublin, Dublin, [3]Children's Health Ireland, Crumlin, Dublin
09.50-10.00	**THE PROGNOSTIC VALUE OF DETERMINING MYC TRANSLOCATION PARTNER GENES IN DLBCL. RE-EVALUATING THE SIGNIFICANCE OF NON-IMMUNOGLOBULIN PARTNER GENES.** **Seosamh McCauley[1]**, O Sheehy[1], M Catherwood[1] [1]Department of Haematology, Belfast City Hospital, Belfast , UK
10.00-10.35	**STATE OF THE ART LECTURE: Introduced by: Dr Kathryn Clarke** ***Dr Nick Gleadall, University of Cambridge*** ***"Genomics and Machine Learning in Transfusion Medicine"***
10.35-11.05	**TEA/COFFEE/POSTERS AND MEET THE SPONSORS** ***(All sponsors have supported this meeting through the sponsorship of exhibition space alone and have had no input into the Agenda, speaker selection or content of this meeting)***

ANNUAL MEETING PROGRAMME ***Friday 13th October 2023, Galway Bay Hotel***	
SESSION 2 – State of the Art Lectures followed by AGM **Chairpersons: Dr Conal McConville and Dr Amjad Hyatt**	
11.05-11.40	**STATE OF THE ART LECTURE: Introduced by: Dr Barry Kevane** ***Prof. James O'Donnell, Consultant Haematologist, St James's Hospital, Dublin*** **Roles for VWF beyond blood clotting**
11.40-12.15	**STATE OF THE ART LECTURE: Introduced by: Dr Amjad Hyatt** ***Prof. Tim Illidge, The University of Manchester*** **Early and Intermediate Stage Hodgkin Lymphoma**
12.15-12.50	**STATE OF THE ART LECTURE – Introduced by: Prof. Paul Browne** ***Prof. Gordon Cook, Professor of Haematology*** ***Clinical Director (Haematology), Clinical Trials Research Unit, Leeds Cancer Centre, St James's University Hospital, Leeds*** **Treatment Fitness: frailty adapted treatment approaches**
12.50-13.15	**AGM – All Welcome!**
13.15-14.15	**Lunch**
SESSION 3: 6 x 10 Minute Presentations and State of the Art Lecture **Chairpersons: Dr Claire Andrews and Dr Larry Bacon**	
14.15-14.25	**Targeted Inhibition of Phosphodiesterase (PDE) 4 in Endothelial Cells as a Novel Therapy for Von Willebrand disease** **Dearbhla Doherty[1, 2]**, E Karampini [1], C Byrne[1], I Schoen [1], R Preston[1], JM O'Sullivan[1], M Lavin[1, 2], JS O'Donnell[1, 2] [1]Irish Centre for Vascular Biology, School of PBS, Royal College of Surgeons in Ireland (RCSI), Dublin, [2]National Coagulation Centre, St James's Hospital, Dublin, Ireland
14.25-14.35	**EVOLUTION OF CELLULAR THERAPIES FOR MANTLE CELL LYMPHOMA: A LYMPHOMA NETWORK SERIES OF PATIENTS TREATED AT THE NATIONAL ALLOGENEIC STEM CELL AND CAR-T CENTRE (NASCCT) AT ST JAMES' HOSPITAL** **James Nolan[1]**, Orla Gildea[2], James Dillon[3], Katie Liston[4], Janet Tan[4], Edward Jones[5], Cormac Jennings[6], Stuart Macleod[7], Anne Fortune[2], Helen Enright[5], Johnny McHugh[5], Derville O'Shea[4], Su Maung[2], Kanthi Perera[7], Brian Bird[8], Ezzat Elhassadi[9], Brian Hennessy[9], Senthil Kumar[9], John Quinn[6], Hilary O'Leary[5], Ruth Clifford[5], Ronan Desmond[3], Mary Cahill[4], Eoghan Molloy[4], Greg Lee[1], Paul Browne[1], Larry Bacon[1], Richie Flavin[10], Fiona Quinn[11], Elisabeth Vandenberghe[1] ***(Please refer to abstract for full author institution listing)***
14.35-14.45	**Use of DA-R-EPOCH for high grade B-cell lymphoma from 2014 to 2023 at Mater Misericordiae University Hospital** **Conor Hughes[1]**, M Aly[1], B Dillon[1], I Loftus[1], O Gildea[1], C Fox[1], E O' Rourke[1], S Maung[1, 2], M Fay[1, 2], A Fortune[1, 2] [1]Haematology Department, Mater Misericordiae University Hospital, Dublin, Ireland [2]School of Medicine, University College Dublin, Dublin
14.45-14.55	**Discovery of distinct signal transduction interactions leading to thrombo-inflammatory versus cytoprotective protease-activated receptor 1 signalling** **David Noone[1,2]**, A Tashakor[1,2], E Soule[1,2], O Willis-Fox[1,2], H Fleming[1,2], AM Rehill[1,2], G Leon[1,2], RJS Preston[1,2,3] [1]Irish Centre for Vascular Biology, RCSI University of Medicine and Health Sciences, Dublin, [2]School of Pharmacy and Biomolecular Sciences, RCSI University of Medicine and Health Sciences, Dublin, [3]National Children's Research Centre, Our Lady's Children's Hospital Crumlin, Dublin

ANNUAL MEETING PROGRAMME ***Friday 13th October 2023, Galway Bay Hotel***	
14.55-15.05	**APPLICATION OF THE ONLINE ACUTE MYELOID LEUKAEMIA CLASSIFICATION AND RISK STRATIFICATION CALCULATOR IN A REAL-WORLD COHORT OF AML PATIENTS FROM NORTHERN IRELAND** **Kathryn Clarke[1]**, M Maguire[2], N Cunningham[1], D Finnegan[1], C Arnold[1], MF McMullin[3], M Catherwood[1] [1]Haematology Department, Belfast Health and Social Care Trust, Belfast, Northern Ireland [2]Northern Ireland Centre for Stratified Medicine, School of Biomedical Sciences, University of Ulster, Derry, Northern Ireland, [3]Centre for Medical Education, Queen's University Belfast, Belfast, Northern Ireland
15.05-15.15	**A CYTOGENETIC AND MINIMAL RESIDUAL DISEASE RISK ADAPTED STRATEGY IN THE MANAGEMENT OF ADULT ACUTE LYMPHOBLASTIC LEUKAEMIA: A SINGLE CENTRE 10 YEAR EXPERIENCE.** **Conor Browne[1]**, S Toolan[1], I Hughes[1], A Polion[1], M Brennan[1], G Lee[1], D Waldron[1], M Regan[1], L Brennan[1], C Waldron[1], CM Flynn[1], E Conneally[1], PJ Hayden[1], R Henderson[1], E Vandenberghe[1], CL Bacon[1,] [1]Department of Haematology, St James' Hospital , Dublin
15.15-15.55	**STATE OF THE ART LECTURE – Introduced by: Dr Feargal McNicholl** ***Dr Kostas Stamatopoulos, Director of the Institute of Applied Biosciences at CERTH, the Centre for Research and Technology Hellas, Thessaloniki, Greece*** ***Realizing precision treatment of chronic lymphocytic leukemia***
15.55-16.20	**TEA/COFFEE/POSTERS AND MEET THE SPONSORS** ***(All sponsors who support this meeting through the sponsorship of exhibition space alone have no input into the Agenda, speaker selection or content of this meeting)***
PRESIDENT'S SYMPOSIUM – followed by the Liam O'Connell Lecture **Chairpersons: Dr Feargal McNicholl and Dr Su Maung**	
16.20-16.35	**ANALYSIS OF THE PLATELET PROTEOME REVEALS INSIGHTS INTO THE PRO-INFLAMMATORY AND PRO-THROMBOTIC STATE ASSOCIATED WITH THE PHILADELPHIA CHROMOSOME-NEGATIVE MYELOPROLIFERATIVE NEOPLASMS** **Sarah Kelliher[1,2,3]**, A Krishnan[4, 5], A Falanga[6, 7], A Fortune[1, 2], S Maung[1, 2], M Fay[1, 2], C Andrews[2, 8], L Smyth[2, 8], K Fadalla[2, 8], L Weiss[3, 9], K Bennett[10], S Macleod[8], R Power[1], E Conneally[11,12], MF McMullin[13], F Ní Áinle[1,2,3], P Maguire[3,9], B Kevane[1,2,3] ***(Please refer to abstract for full author institution listing)***
16.35-16.50	**AEBP2 IS A NOVEL GENETIC DEPENDENCY IN EZH2 MUTANT B-CELL NON-HODGKIN LYMPHOMA** **James Nolan[1,2,3]**, D Angelov[1,2], D Nimmo[1], M Mucha[1], G Brien[1], CW Chen[4], E Vandenberghe[2,3], E Conway[1], AP Bracken[1,2] [1]Cancer Chromatin Biology Laboratory, Smurfit Institute of Genetics, Trinity College Dublin, Dublin 2, [2]Trinity St James' Cancer Institute, St James' Hospital, Dublin 8, Ireland [3]Department of Haematology, St James' Hospital, Dublin 8, Ireland [4]Department of Systems Biology, City of Hope Comprehensive Cancer Centre, Duarte, California
16.50-17.05	**Child and Young Adolescent *TLX3* rearranged T Acute Lymphoblastic Leukaemia (*TLX3r* T-ALL): A National cohort analysis** **Amélie Trinquand[1]**, DR Betts[2], S Rooney[3], L Storey[1], S Augustine[1], S McLoughlin[1], S Jacob[1], P McCarthy[1], N Barrett[1], V Broderick[1], P Evans[1], J Bond[1], A Malone[1], A O'Marcaigh[1], OP Smith[1] [1]National Children's Cancer Service, Children's Health Ireland at Crumlin, Dublin, [2]Department of Clinical Genetics , Children's Health Ireland at Crumlin, Dublin [3]Haematology Laboratory, Children's Health Ireland at Crumlin, Dublin

ANNUAL MEETING PROGRAMME ***Friday 13th October 2023, Galway Bay Hotel***	
17.05-17.20	**Inhibition of HUWE1 Results in Sensitivity to Bortezomib and an Impaired Replicative Stress Response in Multiple Myeloma** **Jonathan J Morgan**[1], BG Kennedy[1], R Williams[1], KI Mills[1], LJ Crawford [1] [1]The Patrick G Johnston Centre for Cancer Research , Queen's University Belfast, Belfast , Northern Ireland
17.20-18.20	**LIAM O'CONNELL LECTURE - Introduced by: Dr Catherine Flynn** ***Dr Richard Dillon, Kings College London*** **"What Have Molecular Biologists Ever Done for Us?"**
18.30-19.45	**OFFICIAL POSTER VIEWING AND ADJUDICATION**

Time: 18.30-19.45

Poster Board Presentations

(Poster Board Presentation Walkabout and Adjudication)

CPD Accredited – 6 CPD Credits

(13 October 2023)

ANNUAL MEETING PROGRAMME ***SATURDAY 14TH OCTOBER 2023*** ***CPD Accredited – 4 CPD Credits (14.10.23)***	
09.30-09.40	**Opening of Day 2 – Dr Feargal McNicholl, President**
SESSION 5: Chairpersons: Dr Aaron Niblock and Dr Sorcha Ni Loingsigh **Clinical Vignettes & Oral Presentations Session**	
09.40-10.10	**Clinical Vignettes Presentations – 6 x 5 Minute Presentations**
09.40-09.45	**ISOLATED UTERINE CERVIX PLASMACYTOMA TREATMENT CONUNDRUM** K Samuel[1], W.R Huddleston[2], S Rajendran[2], **Aaron Niblock[1,3]** [1]Haematology department, Antrim Area Hospital, Northern Ireland [2]Pathology department, Antrim Area Hospital, Northern Ireland [3]School of Medicine, Ulster University, Northern Ireland
09.45-09.50	**A CASE OF COPPER DEFICIENCY ASSOCIATED CYTOPENIAS AND MYELOPATHY** **Jack Fitzgerald[1]**, J Tan[1], SY Chai[1], S Ni Loingsigh[1,2] [1]Haematology department, Galway University Hospital, Galway [2]Haematology, Mayo University Hospital, Mayo
09.50-09.55	**BING–NEEL SYNDROME WITH CHRONIC LYMPHOCYTIC LEUKAEMIA: A CASE OF COMPOSITE LYMPHOMA** **Karolina Chmielowiec[1]**, A Abladey[2], K Clarke[1], M Catherwood[2], M Moore[3], D Donaldson [1] [1]Department of Clinical Haematology, Belfast City Hospital, Belfast, Northern Ireland [2]Regional Molecular Diagnostics Service, Belfast City Hospital, Belfast, Northern Ireland [3]Histopathology Department, Royal Victoria Hospital, Belfast, Northern Ireland
09.55-10.00	**Rosai-Dorfman-Destombes Disease: A Rare Diagnosis in a Child with Massive Cervical Adenopathy.** **John Harford[1]**, L Feeley[2], D Mullane[3], J Pears[4], R Leahy[5], C Ryan[1] [1]Department of Paediatric Haematology, Mercy University Hospital, Cork, [2]Department of Histopathology, Cork University Hospital, [3]Department of Paediatric Medicine, Cork University Hospital, Cork, [4]Department of Paediatric Oncology, Children's Health Ireland, Crumlin, Dublin, [5]Department of Paediatric Immunology, Children's Health Ireland, Crumlin, Dublin
10.00-10.05	**Paediatric Non-Hodgkin's Lymphoma presenting in the oral cavity: a brief review of the literature and case series.** **Alanna Allen**, K FitzGerald, Y MacAuley, A Cant, D Murray, A Beattie, A Malone, O Smith, L Storey, A O'Marcaigh, N Barrett, P McCarthy, P Evans, V Broderick [1]Department of Haematology, CHI, Dublin, [2]Department of Dentistry , CHI, Dublin
10.05-10.10	**A rare case of polycythaemia vera driven by the JAK2 R564L mutation** **ALi Al-Baghdadi[1]**, A Nee[1] [1]Haemtology, University hospital Limerick , Limerick
10.10-10.50	**5 x 10 Minute Oral Presentations**
10.10-10.20	**VIRUS-INDUCED ENDOTHELIAL CELL 'MEMORY' ENHANCES PRO-INFLAMMATORY AND PRO-THROMBOTIC ACTIVITY TO SUBSEQUENT STIMULATION** **Zhongmin Wang[1,3]**, AM Rehill[1,2], G Leon[1,2], P Deng[1,3], RJS Preston[1,2] [1]Irish Centre for Vascular Biology, Royal College of Surgeons in Ireland, Dublin, [2]National Children's Research Centre, Our Lady's Children's Hospital Crumlin, Dublin, [3]Center for Drug Metabolism and Pharmacokinetics, Soochow University, Suzhou, China
10.20-10.30	**THE RELATIONSHIP BETWEEN LOW VON WILLEBRAND FACTOR, TYPE 1 VON WILLEBRAND DISEASE AND AGEING - NOVEL INSIGHTS FROM THE LOVIC AND WIN COHORT STUDIES** F Atiq[1, 2], R Blok[2], CB van Kwawegen[2], **Dearbhla Doherty[1]**, M Lavin[1, 3], JG van der Bom[4], NM O'Connell[3], J de Meris[5], K Ryan[3], SEM Schols[6], M Byrne[3], FCJI Heubel-Moenen[7], KPM van Galen[8], RJS Preston[1], CJ Fijnvandraat[9], RI Baker[10,11], K Meijer[12], P James[13], J Di Paola[14], HCJ Eikenboom[15] ***(Please refer to abstract for full author institution listing)***

ANNUAL MEETING PROGRAMME SATURDAY 14TH OCTOBER 2023	
10.30-10.40	**EXPLORING THE METABOLIC PROFILING OF MULTIPLE MYELOMA: IMPLICATIONS FOR TARGETED THERAPIES** **Ludovica Di Martino[1]**, SG GILMORE[1], YW WANG[1], SG GLAVEY[2], TNC NI CHONGHAILE[1] [1]1. Department of Physiology and Medical Physics, Royal College of Surgeons in Ireland, Dublin, [2]2. Department of Haematology, Beaumont Hospital, Dublin
10.40-10.50	**EXTRACELLULAR VESICLE-MEDIATED MOLECULAR MECHANISMS IN THE PROGRESSION OF MULTIPLE MYELOMA.** **Chloe Wylie[1]**, D Malinova[2], L Crawford[1] [1]Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, Belfast, Northern Ireland, [2]Wellcome Wolfson Institute for Experimental Medicine, Queen's University Belfast, Belfast, Northern Ireland
10.50-11.00	**CLINICAL FEATURES AND OUTCOMES OF ADULTS DIAGNOSED WITH HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) OVER A FIVE YEAR PERIOD FROM 2018 – 2023 IN A TERTIARY REFERRAL HOSPITAL : A SINGLE CENTRE STUDY** **Cormac Jennings[1]**, K Fadalla[1,2], K Murphy[1,2], C Andrews[1,2], M Coyne[1,2], DG Connaghan[1,2], J Fitzgerald[1,2], M Power[1,2], N Swan[2,3], E Feeney[2,5], E Molloy[2,6], R Hughes[2,7], O Solymus[2,8], C Collins[2,4], J Wade[1], L Smyth[1,2] [1]Department of Haematology, St Vincents University Hospital, Dublin, [2]School of Medicine, University College Dublin, Dublin, [3]Histopathology Department, St Vincents University Hospital, Dublin, [4]Department of Radiology, St Vincents University Hospital, Dublin, [5]Infectious Disease Department, St Vincents University Hospital, Dublin, [6]Department of Rheumatology, St Vincents University Hospital, Dublin, [7]Department of Dermatology, St Vincents University Hospital, Dublin, [8]Department of Anaesthetics, St Vincents University Hospital, Dublin
11.00-11.20	**TEA/COFFEE AND MEET THE SPONSORS** ***(All sponsors who support this meeting through the sponsorship of exhibition space alone have no input into the Agenda, speaker selection or content of this meeting)***
SESSION 6: Chairpersons: Dr Feargal McNicholl and Prof. Paul Browne Guest Speaker Lectures	
11.20-12.00	**Guest Speaker Lecture – Introduced by: Dr Feargal McNicholl** ***Creating and maintaining excellence in Haematology: lessons from elite sport*** **Prof. Eamon O'Shea, Professor in the School of Business & Economics and was Inaugural Director of the Irish Centre for Social Gerontology (ICSG) at the University of Galway**
12.00-12.20	**Guest Speaker Lecture – Introduced by: Dr Conal McConville** **Prof. Andrea Piccin, NIBTS, Belfast** **UK PATHOGEN INACTIVATION AND REDUCTION TECHNOLOGY. SHOULD WE STAY OR SHOULD WE GO … (FOR IT)?**
12.20-12.55	**STATE OF THE ART LECTURE: Introduced by: Dr Larry Bacon** ***Dr Carmel Waldron, Consultant Haematologist, St James's Hospital*** **THE EPIDEMIOLOGY OF CLL IN IRELAND AND THE VALUE OF ESTABLISHING A PROGNOSTIC BIOMARKER PANEL AT DIAGNOSIS**
12.55-13.05	**Close of Conference and Awarding of Educational Awards**
13.05	**Lunch**

Saturday 14th October 2023 Joint EHA/HAI Education Symposium (Recognised SpR Session)	
14:00-14:05	Opening by Dr Su Maung (HAI)
14:05-14:15	Dr James Nolan (HAI) HAEMATOLOGY TRAINING IN IRELAND- OVERVIEW AND PERSONAL EXPERIENCE
14:15-14:25	Dr Mandy Lauw (President of YoungEHA) WHAT IS YoungEHA?
14:25-14:35	Dr Nuno Borges (Young EHA committee member) YoungEHA MEMBERSHIP- EXPERIENCE AND FUTURE DIRECTIONS
14:35-14:45	SHORT Q&A SESSION
14:45-15:05	IRISH EXPERIENCE Dr Daniel Angelov Dr Sarah Kelliher Dr Greame Greenfield
15:05-15:35	PANEL DISCUSSION: SUPPORTING YOUNG TRAINEES IN RESEARCH AND CAREER PROGRESSION Panellists: Dr Mandy Lauw, Dr Nuno Borges, Dr Barry Kevane, Dr Nina Orfali
15:35	Close of session by chair

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(14 October 2023)

HAEMATOLOGY ASSOCIATION OF IRELAND

HAI NURSES & AHPs ANNUAL MEETING PROGRAMME
FRIDAY 13 OCTOBER, 2023

08.00 – 09.30	**REGISTRATION AND MEET THE SPONSORS/DISPLAY POSTERS**	
CHAIRS: Fidelma Hackett and Lorna Storey		
TIME	**TOPIC**	**SPEAKER**
09.30-09.40	**Welcome and Introduction**	***Fidelma Hackett,*** *Chairperson, HAI Nursing/AHP Group*
09.40-10.40	**Lymphoma in Adolescents and Young Adults** **Patient Perspective**	***Dr Eoghan Molloy, Consultant Haematologist and AYA Cancer Lead, Cork University Hospital*** ***And*** ***Shauna Reilly***
10.40-11.10	***Tea/Coffee/Meet the Sponsors/Posters***	
11.10-12.10	***Scientific Emerging Therapies for Myeloma***	***Elaine Vickers, Science Communicated Ltd***
12.10-12.40	***Evolving Therapies for Myeloma and Nursing Considerations***	***Teresa Meenaghan, ANP & Deirbhle Cox CNS Haem, NUIG, Galway***
12.40-14.00	***Lunch***	
CHAIRS: Louise Gribben and Ann-Marie Murphy-Cruse **Oral Presentations – 4 x 15 Minute presentations**		
14.00-14.15	**AUDIT ON THE SCREENING AND MANAGEMENT OF LATE AND LONG-TERM CONSEQUENCES OF MYELOMA AND ITS TREATMENT**	***Kerrie Sweeney, Haematology Department, Antrim Area Hospital, N. Ireland***
14.15-14.30	**WHAT IS THE IMPACT OF A MINDFULNESS-BASED INTERVENTION ON DEPRESSION AND BIOPSYCHOSOCIAL VARIABLES AMONG HAEMATOPOIETIC STEM CELL TRANSPLANT PATIENTS DURING HOSPITALISATION**	***Marie Roche, Denis Burkitt Ward, RCSI, Dublin***
14.30-14.45	**LYMPHOMA FOLLOW-UP IN THE MID-WEST: A 10 YEAR RETROSPECTIVE REVIEW TO GUIDE PRACTICE**	***Fidelma Hackett, ANP, Limerick University Hospital***
14.45-15.00	**EMPOWERING CARE: ADVANCED NURSE PRACTITIONER LED ORAL ANTI-CANCER MEDICATION (OAMS) CLINICS LEADING THE WAY IN EXPANSION OF CANCER CARE**	***Ger Walpole, ANP, Sligo University Hospital***
15.00-15.20	**Short Tea/Coffee/Meet the Sponsors**	
CHAIRS: Niamh O'Sullivan and Caroline McCaughey		
15.20-16.05	**Meet the Expert – Case Studies on:** **Patient Identification Error** **Transfusion Associated Circulatory Overload** **Transfusion Reaction**	 ***Joanne Stewart, Ward Sister, Belfast Trust*** **Louise Gribben, Haematology Advanced Nurse Practitioner, Southern Trust** ***Prof. Andrea Piccin, Consultant Haematologist, NIBTS, Belfast***
16.05-16.35	**'Stepping into Research: Where to Start'**	***Prof. Emer Guinan, Associate Professor in Cancer Rehabilitation and Survivorship, Trinity College Dublin***

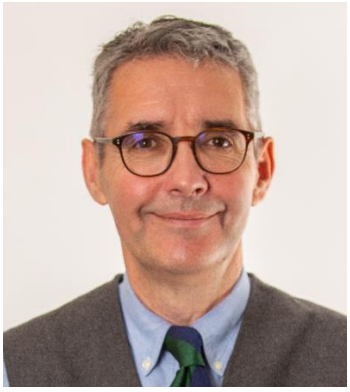
HAI NURSES & AHPs ANNUAL MEETING PROGRAMME *FRIDAY 13 OCTOBER, 2023*		
TIME	**TOPIC**	**SPEAKER**
17.20-18.20	**LIAM O'CONNELL LECTURE - Introduced by: Dr Catherine Flynn** ***Dr Richard Dillon, Kings College London*** **"What Have Molecular Biologists Ever Done for Us?"**	**In Main Conference Room**
18.30 – 20.00	**Poster viewing followed by Conference Dinner**	

HAEMATOLOGY ASSOCIATION OF IRELAND

HAI NURSES & AHPs ANNUAL MEETING PROGRAMME
SATURDAY 14th October 2023

CHAIRS: Ruth Thompson and Aoife McCormack

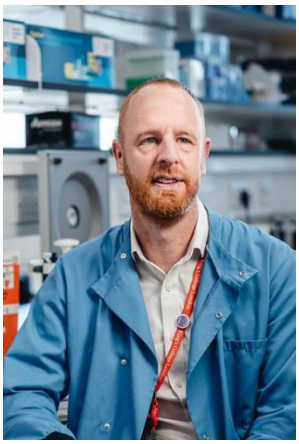
TIME	TOPIC	SPEAKER
10.00-11.00	***Recognising and Responding to Compassion Fatigue***	***Jayne Ellis, Managing Director, EF Training***
11.00-11.30	***Acute Haematology Oncology Nurse Service***	***MarieClare McEvoy, Beaumont Hospital, Dublin***
11.30-11.40	**Educational Funding Update**	***Marie Roche***
11.40-11.50	**Educational Funding Update**	***Lily Brewin***
11.50-12.00	**Educational Funding Update**	***Carmel Ann Galligan***
12.00-12.10	**Educational Funding Update**	***Deirdre Cleary***
12.10-12.25	**Highlights from the main conference**	
12.25-12.45	***Close of Conference and Awarding of Prizes***	
12.45-14.00	**Lunch**	



Professor Gordon Cook, MB ChB, PhD, FRCP (Glas), FRCPath

I am a graduate of the University of Glasgow School of Medicine & received my higher professional training in haematology in the West of Scotland. After completion of my PhD, I was appointed as a Consultant Haematologist in the West of Scotland before moving to take up the post of Director of Stem Cell Transplantation at Leeds Teaching Hospitals in 2002. In 2013 I was appointed as Professor of Haematology, University of Leeds where I lead the myeloma clinical and translational research programme with a primary interest in tumour immunology and immunotherapy.

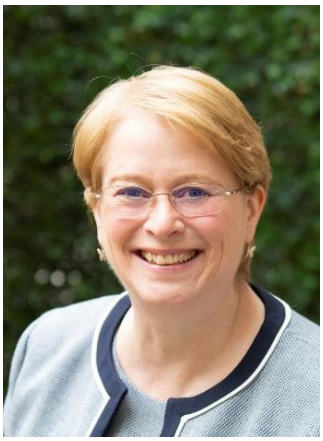
I was the founder & first Chair of the UK Myeloma Research Alliance. I am the past-chair of the UK Myeloma Society and established the College of Myeloma (UK) which elected its first fellows in 2019. I have represented the interests of both myeloma clinicians and patients in National Institute of Clinical care & Excellence reviews and technology appraisals. I am the NHS England Advanced Cellular Therapies Lead for myeloma and am a current committee member of the NHS England Chemotherapy CRG. I have been appointed as the NCRI Haemato-oncologist Clinical Studies Group in 2022. I have developed and delivered an extensive national clinical research portfolio. Currently, I am Chief Investigator for NCRI Myeloma X (completed), UKMRA Myeloma XII (in follow-up), UKMRA Myeloma XIV (in recruitment), UKMRA Myeloma XVIII iFIT (at funding) MUK*eight* (completed) and MUK*eleven* (completed). My collaboration with industry includes my position as the UK Chief investigator for 6 industry international phase III and IIIb studies. I hold the posts of Clinical Director of National Institute of Health Research (Leeds) Medtech & *In Vitro* Diagnostics Cooperative and Clinical Director (Haematology), Clinical Trials Research Unit, University of Leeds.



Dr Richard Dillon

Clinical Senior Lecturer in Cancer Genetics, King's College London and Consultant Haematologist, Guy's and St Thomas' NHS Foundation Trust

Dr Richard Dillon is a Consultant Haematologist at Guy's Hospital and a Clinical Senior Lecturer in Cancer Genetics in the Department of Medical & Molecular Genetics at King's College London. Dr Dillon's work is focussed on acute myeloid leukaemia, in particular the development of molecular diagnostics and molecularly targeted therapies. Dr Dillon contributes extensively to clinical trials in AML: he leads on molecular MRD for the UK NCRI AML trials and is currently the chief investigator of the VICTOR and BlinAML studies, which are investigating an MRD guided approach to therapy.

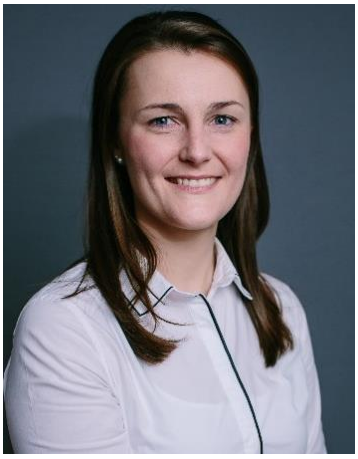


Jayne Ellis Founder and CEO

Jayne has worked in healthcare for over 30 years as a nurse and an educator. She is a published autho r and regularly speaks at conferences and events on the subject of Compassion Fatigue all over the UK.

EF training is the only UK training organisation that provides quality, evidence-based training that pro-actively addresses the impact of Compassion Fatigue on individuals and organisations. Having experienced compassion fatigue herself Jayne is acutely aware of the emotional impact that working in any caring role has. She is committed to raising awareness about Compassion Fatigue and is campaigning for emotional health and safety to be seen as having equal status to physical health and safety in every industry across the UK.

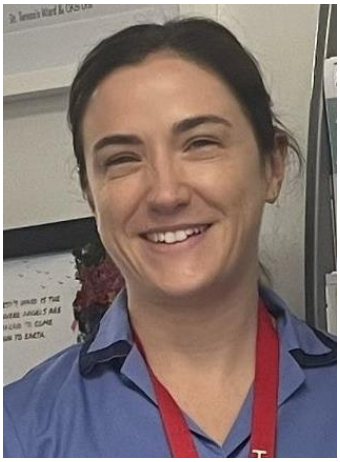
Dr Nick Gleadall is an Assistant Professor at the University of Cambridge, from which he was awarded his PhD in 2020. He holds honorary appointments with Cambridge University Hospitals, University College London Hospitals and NHS Blood and Transplant. He is the Chief Analyst of the Blood transfusion Genomics Consortium. Nick's current research is focused on genomics and AI in transfusion medicine, in particular the application of high-throughput genotyping or sequencing technologies and the exploitation of large datasets to improve the matching for blood groups between patients and donors. He is a key member of a team applying machine learning to complete blood count results with the aim to discover signatures of pathogen infection for use in population surveillance. Earlier in his career he pioneered new sequencing based tests for infectious disease detection and he developed the bioinformatical infrastructure for the first diagnostic whole exome sequencing platform for rare diseases in the NHS.



Associate Professor Emer Guinan is an Associate Professor and Principal Investigator in Cancer Rehabilitation and Survivorship at the School of Medicine Trinity College Dublin. A CORU registered physiotherapist, Dr Guinan has over 12 years of experience as a researcher in cancer rehabilitation and survivorship. Her work has delivered 70 peer reviewed publications and she has received >€3 million in external grant funding. She has fulfilled multiple research roles over her career including trial project manager (PREPARE & ReStOre trials), protocol development group for an international multi-site randomised controlled trial (INTERVAL-GAP4 trial), trial management group committee (ExPeCT, ReStOre & PreHIIT trials), co-Principal Investigator (PreHIIT trial) and Principal Investigator (PERCS).

Professor Tim Illidge BSc MB BS PhD FRCP FRCR FRCPath FMedSci
Professor of Targeted Therapy and Oncology (University of Manchester) and honorary consultant clinical oncologist (Christie NHS Foundation Trust)

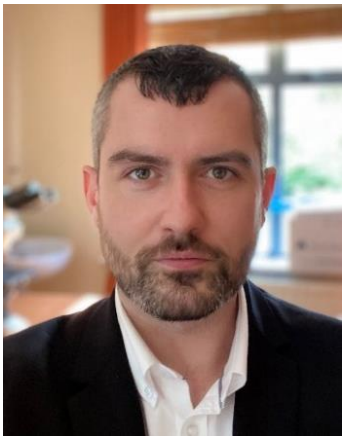
Dr Illidge completed his undergraduate degrees with a BSc in Biochemistry (London) and medicine (MB BS) at Guy's Hospital, Royal College of Physicians (1993) and trained in oncology in Southampton gaining Fellow of Royal College of Radiologists in 1997. In worked as CRUK Senior Clinical Research Fellow at University of Southampton 1998-2004 and was appointed Professor of Targeted Therapy and Oncology at University of Manchester in 2004. His clinical research is focused on lymphoma and has led to a number of practice changing clinical trials in B and T cell lymphomas as well as Hodgkin Lymphoma. His awards have included cancer researcher of the year by University of Manchester in 2012, researcher of the year for the Faculty of Medical and Life sciences in 2013, the Royal College of Radiologists gold medal in 2018, Skeggs medal in 2019, a Senior National Institute of Health Research (NIHR) investigator award in 2019 and 2023. He was elected as Fellow of the Academy of Medical Sciences in 2022.



Marie Claire McEvoy, Beaumont Hospital

I work as a Clinical Nurse Specialist within the Haematology service in Beaumont Hospital, Dublin. I have been based in Oncology/Haematology since 2011 in both inpatient and outpatient settings. My current role is oversight of the Telephone Triage service which is provided to Haematology patients who may have disease/treatment related immunosuppression or who are receiving Systemic Anti-Cancer Treatment. Since commencing this role in 2020 I have established a formalised pathway for the telephone triage of the haematology patient cohort. The UKONS telephone triage tool to grade symptoms/side effects and direct care of patients who are unwell at home has been introduced in conjunction with this. The triage tool is an excellent risk assessment tool for Haematology/Oncology patients and allows the user to give the most appropriate advice to a vulnerable patient group. The tool is used by myself, and the nursing staff in the Haematology inpatient and outpatient wards for patients who contact our service unwell at home . Advice is then given to patients on how to proceed including directing them to their GP or local ED. The service is available 24/7 365 days a year.

Teresa Meenaghan is a Registered Advanced Nurse Practitioner in Haematology at GUH for the past 12 years. She holds a qualification for medicinal prescribing as well as ionising radiation. She has a keen interest in myeloma, acute leukaemia, ITP as well as CLL. She has experience in working in many different fields in haematology including autologous and allogeneic transplant, liaison nurse and palliative care. She is involved in education and actively takes part in tutoring at undergraduate and post graduate level at NUI Galway. She has a many publications based on her areas of interest and presents at local and national levels. She enjoys walking, spending time with family and has recently taken up golf in preparation for retirement!!



Dr Eoghan Molloy, MB BCh BAO, LRCP & SI, MRCPI, FRCPath

Dr Molloy is a Consultant Haematologist Cork University Hospital. Dr Molloy received his undergraduate medical education at the Royal College of Surgeons in Dublin. He then completed Basic Specialist Training at Beaumont Hospital and following this commenced Higher Specialist Training in Haematology. After completion of HST, he moved to the US for fellowship training at the National Institutes of Health (NIH), Bethesda, Maryland. At the NIH, he received subspecialty training in Cellular Therapy, including Haematopoietic Stem Cell Transplantation, Gene Therapy and CAR-T Cell Therapy. He also worked at the Johns Hopkins Hospital, Baltimore MD, and Children's National Hospital, Washington, DC, where he received further training in Transfusion Medicine, Apheresis and Patient Blood Management.

Dr Molloy participates in clinical trials and research as a member of Cancer Trials Ireland, Blood Cancer Network Ireland and the UCC Cancer Trials Group. His research interests include novel targeted drug therapy for refractory B-Cell malignancies. Dr Molloy's main clinical practice is in malignant Haematology. He has specific expertise in the management of lymphoma, myeloma and acute lymphoblastic leukaemia. In 2022, CUH was designated as an Adolescent and Young Adult (AYA) Cancer Centre, and Dr Molloy serves as the first appointed Clinical Lead for AYA Cancer in Cork. Dr Molloy's laboratory practice includes Transfusion Medicine and Immuno-Haematology at CUH. He also provides for Laboratory Consultation in Maternity and Neonatal Transfusion for Cork University Maternity Hospital.

Professor James O'Donnell received his medical degree from Trinity College Dublin and subsequently a PhD from Imperial College London. He completed haematology training in the Hammersmith and Royal Free Hospitals in London. He is a Fellow of both the Royal College of Physicians of Ireland, and the Royal College of Pathologists (UK). Prof O'Donnell is currently Professor of Vascular Biology in the Royal College of Surgeons in Ireland; Director of the Irish Centre for Vascular Biology; and a Consultant Haematologist in the National Coagulation Centre in Dublin. Over the past 20 years, the Haemostasis Research laboratory led by Prof. O'Donnell has focussed on clinical bleeding and thrombosis disorders. He has published more than 200 publications in high impact journals (h-index = 44 with > 7,000 citations) and received > €12M in peer-reviewed grant funding awards, including awards from the Science Foundation Ireland, the Wellcome Trust and the NIH. In 2022, he was elected a Member of the Royal Irish Academy.

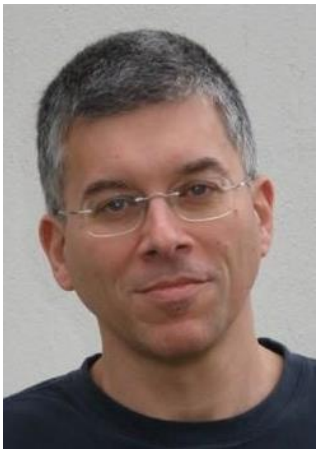
Prof. Eamon O'Shea is a Professor of Economics in the School of Business & Economics at the University of Galway. He was founder and inaugural Director of the Irish Centre for Social Gerontology (ICSG). He is currently Director of the Centre for Economic and Social Research on Dementia at University of Galway. He holds an M.A. from University College Dublin, an M.Sc. from the University of York and a Ph.D from the University of Leicester. He has published close to 200 scientific papers in refereed journals, including publications in top-ranked journals such as the Journal of Health Economics, Social Science and Medicine, Age and Ageing, British Medical Journal and the International Journal of Geriatric Psychiatry. Professor O'Shea has authored/co-authored 15 books and monographs, mainly in the field of ageing, dementia and social policy. His work has been influential in setting the agenda for the reform of services and policies for people with dementia in Ireland. He was Chair of the National Economic and Social Forum Expert Group on *Care of the Elderly* in 2005/06 and co-authored the influential *Creating Excellence in Dementia Care* report in 2012. He was awarded a five-year Health Research Board (HRB) Research Leader grant in dementia in 2015 and is currently part of a Marie Sklodowska-Curie doctoral network (HOMEDEM), exploring home care for people with dementia in Europe.

Professor Andrea Piccin is a Consultant Haematologist with experience in Transfusion Medicine, Paediatric Haematology, Adult Haematology. He has previously worked in Italy, Austria, the Republic of Ireland. He is currently working at Northern Ireland Blood Transfusion Service (NIBTS) in Belfast. In 1996 he received his Medical Degree at Padua University, in Italy. In 2002 he obtained his Higher Specialist Degree in Haematology at Verona University, in Italy. In 2009 he completed a PhD degree at Trinity College Dublin on "*New Insights in Sickle Cell Anemia Pathophysiology*". In 2018 he became Associate Professor with the Medical University of Innsbruck in Austria and completed a second PhD thesis on "*Endothelial damage in Myeloproliferative Diseases".*

Relevant activities include:

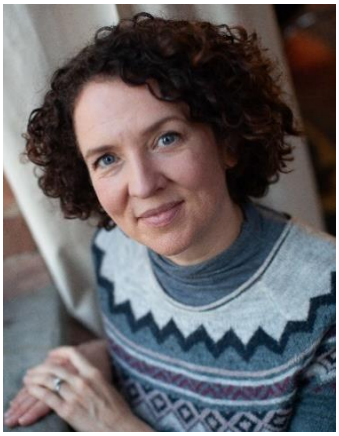
- a MD thesis on "*Tandem Transplant for Multiple Myeloma*" a second MD degree on Gene Therapy in Pediatric onco-haematology,
- an international study on "*Autologus Recovery in Aplastic Anaemia*"; studies on Sickle Cell Disease, Microparticles detection, Regenerative Medicine and Transfusion Medicine
- He is the author of > 100 peer reviewed publications.
- He has given oral presentations at > 60 international meetings.

For his scientific contribution he has been awarded with the honor of Sir/*Cavaliere* of the Italian Republic.



Dr Kostas Stamatopoulos is Director of the Institute of Applied Biosciences at CERTH, the Centre for Research and Technology Hellas, in Thessaloniki, Greece. He is also Scientific Collaborator of the Molecular Diagnostics lab of the G. Papanicolaou Hospital in Thessaloniki Greece, under a memorandum of understanding. Following his graduation as a medical doctor in 1990 and clinical haematology experience gained in the Athens University School of Medicine, Dr Stamatopoulos obtained a PhD in Immunoglobulin genes in B-cell malignancies in 1997.

He has been involved in CLL and lymphoma research since 1994 and is a founding member of the IMGT CLL-DB initiative (Http://Www.Imgt.Org/CLLDBInterface) and the IG CLL group (Http://Www.Igcll.Org), operating under the auspices of ERIC (European Research Initiative on CLL). He has published extensively about the immunobiology of CLL and other lymphomas in several peer-reviewed journals. His current research interests focus on the role of microenvironmental interactions in human lymphomas and the study of antigen receptor gene repertoires in health and disease.



Elaine Vickers has worked as a cancer educator and writer for twenty years. Since setting up her company, Science Communicated Ltd (sciencecommunicated.co.uk), Elaine has developed a wide range of study days and teaching materials that explain cancer biology and the science behind targeted cancer treatments and immunotherapies.

Each year, Elaine teaches hundreds of cancer nurses, doctors, and allied cancer professionals in hospitals and research centres throughout the UK. Her book, "A Beginner's Guide to Targeted Cancer Treatments" was highly commended by the British Medical Association Medical Book Awards in 2019. She is currently working on a second edition, due out in 2024. Elaine delivers a regular programme of study days for the Royal Marsden Hospital in London and speaks at numerous cancer conferences in the UK and Europe. Elaine has a degree in Medical Science from the University of Birmingham and a PhD in Molecular Biology from the University of Manchester. Her goal is to unravel the complexities of cancer biology and new cancer treatments and to make these topics interesting and accessible to non-scientists.

Dr Carmel Waldron was appointed as a Consultant Haematologist in St. James's hospital in 2022 following the completion of a lymphoma fellowship in Princess Margaret Cancer Care Centre in Toronto. Her special interests are focused on chronic lymphoproliferative disorders and CLL and she has recently co-authored several peer-reviewed articles on CLL. She has an interest in clinical trials and is currently the PI and CI on a number of trials.

IDENTIFICATION OF POTENTIAL THERAPEUTIC TARGETS TO REVERT NATURAL KILLER CELL EXHAUSTION IN MULTIPLE MYELOMA THROUGH SINGLE-CELL RNA-SEQ ANALYSIS

JU Verga[1,2], M O'Dwyer[3], E Szegezdi[1,2]
[1]Centre for Research Training in Genomics Data Science, School of Biological, University of Galway
[2]Apoptosis Research Centre, School of Biological and Chemical Sciences, University of Galway
[3]School of Medicine, Haematology Department, University of Galway

Introduction: Multiple myeloma (MM) is a blood cancer caused by the accumulation of plasma cells in the bone marrow. Disease progression is associated with immune suppression. Natural Killer (NK) cells, part of the innate immune system, play a pivotal role in anti-tumor surveillance. We aimed to understand whether and how the NK cells may be impacted by MM and how NK cell dysfunction in MM can be reverted.

Methods: scRNA-Seq datasets were integrated using Seurat(1) and scVI(2). SingleR(3) and a reference dataset(4) were used to identify the different cell types. To classify NK cells as active, tissue-resident (rNK), or exhausted (eNK), we developed an algorithm (ScoreMarkers(5)) that scores the cell state based on a gene expression signature(6). The classification has been validated using scGSEA(7) and gene sets from MSigDB. Then NK cells were characterized through Differential gene expression (DGE) with Seurat (method =”LR”, FDR<0.05), gene ontology (GO) enrichment analysis with ClusterProfiler(8) and GOSemSim(9). Active ligand-receptor pairs have been identified with LIANA(10,11) and active Transcription Factors (TF) in NK cells with pyScenic(12). An immune checkpoint (IC) signaling cascade network has been built with NicheNet(13) using ligands from LIANA and target genes from pyScenic as inputs. Genes in the identified IC cascades were ranked by integrating PageRank, Betweenness centrality, Percolation, and Ricci Curvature.

Results: Because the NK cell population is heterogeneous, we used single-cell level analyses. We have integrated 6 scRNA-Seq studies containing samples that encompass all stages of MM disease progression. The dataset contains 14,103 and 7,596 NK cells in MM and healthy samples respectively, which were dichotomized into rNK and eNK cells. The proportion of eNK cells increased in all the disease stages (p.value<0.01). eNK cells in MM up-regulated several IC receptors, genes associated with the development of malignancies, and altered tumor immune microenvironment. Only a minority of DEG, enriched Biological Processes and TF were shared by eNK cells in MM and healthy samples. This suggests disease-specific pathways driving NK cell exhaustion in MM. Cell-cell interactions suggest the tumor microenvironment actively supports immune exhaustion by activating several IC Receptors. With the network analysis, we established and ranked the IC signaling cascade genes. The expression patterns of the highest-ranking genes exhibited a significant correlation with exhaustion scores determined by ScoreMarkers. These top-ranking genes encompass a diverse range of functional categories, including nuclear receptors, TFs, and phosphatases and many of them play pivotal roles in regulating NK activity, while others have yet to be implicated in this context. We are currently in the process of planning *in vitro* experiments to validate the identified genes and potentially uncover new functional roles, providing substantial evidence for our findings.

Conclusions: Our investigation has identified distinctive myeloma-specific pathways driving the exhaustion of NK cells, already at the earliest phases of the disease, indicating a pivotal role in disease progression. By accurately delineating the signaling cascades orchestrating immune exhaustion, we have pinpointed potential therapeutic targets. These targets are anticipated for experimental evaluation, to design NK cells resistant to the debilitating influences of the tumor microenvironment.

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Sodium-Glucose Co-Transporter-2 (SGLT2) Inhibitor Induced Apparent Erythrocytosis.

SM Macleod[1], SG GRENNAN[1], KP PERERA[1], SG GAFFEY[1], MK KELLY[1], KD DRUMM[1], JA ARCHUTICK[1,2], AH HUSSAIN[1], IH UL HAQ[1], GMC CROTTY[1]
[1]Haematology, MRHT, Tullamore, Ireland
[2]Medicine, UL, Limerick, Ireland

Introduction/Background

Referrals for investigation and management advice in patients with Erythrocytosis are common in the Haematology Outpatient clinic. These referrals are often directly concerned with the possibility of a diagnosis of Polycythaemia Vera (PV). Guidelines have been published regarding the diagnostic approach to PV and the comprehensive investigation of a patient with Erythrocytosis. These guidelines include the 2018 British Society of Haematology guideline[1]. This specific guideline includes a proposed investigation algorithm. The first step in this, following the confirmation of a persistent Erythrocytosis, includes performing a history, exam and initial investigations including serum Erythropoietin (EPO). The guideline outlines the importance of considering secondary causes of erythrocytosis, including drug induced for example with exogenous EPO, diuretics, or androgen preparations. There have been several reports in the literature of SGLT2 inhibitors also being linked to erythrocytosis[2]. The mechanism of action underlying the erythrocytosis includes increased EPO production via hypoxia-induced activation of HIF2a, modulation of iron metabolism through hepcidin, and haemoconcentration[3]. We wanted to investigate the prevalence of this in our practise.

Materials and methods

In this study we gathered retrospective data for a 12-month period, from June 2022, in our Regional Hospital. We identified all patients who had serum EPO tested, then included any patients who had this done to investigate an erythrocytosis. We checked if JAK2 mutational analysis was performed, and searched for the medication lists of these patients to correlate if any had been on a SGLT2 inhibitor at the time of referral and investigation.

Results

We identified 65 patients investigated for an erythrocytosis with an EPO level. A drug list was available in 52, of these, 5 patients (9.6%) were taking an SGLT2 inhibitor, with 3 also taking diuretics. All patients taking SGLT2 inhibitors with erythrocytosis had a negative JAK2. There were 9 patients (17.3%) on diuretics. All 65 patients had a JAK2 mutational analysis with some also tested for CALR and MPL mutations as part of a 'Myeloproliferative Neoplasm (MPN) panel'. Out of these p5 patients, 4 (6.2%) had positive JAK2 mutations and a confirmed diagnosis of PV. One patient with erythrocytosis, who had a 'MPN panel' sent, had a MPL codon 515 mutation detected.

Conclusions

It is standard clinical practice to perform a comprehensive history and examination on any patient referred to your care. This can sometimes be made difficult, especially when confirming a comprehensive medication history for patients with polypharmacy. However, we identified that almost 1 in 10 patients referred with erythrocytosis (of those whose medication list was available), were on a SGLT2 inhibitors and 17% on some form of diuretic. SGLT2 inhibitors are a medication not currently referred to in the guidelines. This class of medication is becoming more widely used and as should be recognised as a potential cause of apparent erythrocytosis.

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ENHANCING THE CYTOTOXICITY OF NATURAL KILLER CELLS ON NON-HODGKIN'S LYMPHOMA USING SMAC MIMETIC BIRINAPANT

S Kundu[1,2], E Szegezdi[1], M O'Dwyer[1,2]
[1]Apoptosis Research Centre, University of Galway, Galway, Ireland
[2], ONK Therapeutics Ltd., Galway, Ireland

Introduction: Diffuse Large B-cell Lymphoma (DLBCL) is one of the most aggressive forms of non-Hodgkin's lymphoma (NHL) caused by the uncontrolled proliferation of B cells. Although autologous CAR-T cell therapies have been approved for DLBCL[1], NK cells offer a potential allogeneic therapeutic option. Cancer cells acquire different mechanisms to evade recognition by the immune system. Recent studies have shown that inhibition of inhibitor of apoptosis proteins (IAPs) with Second Mitochondria-derived Activator of Caspase (SMAC) mimetic drugs can overcome this mechanism of immune evasion [2–4]in different settings of haematological malignancies, e.g., acute/chronic myeloid leukaemia (AML/CML) [5], acute myeloblastic leukaemia, B-ALL [6], etc. However, our understanding in the NHL landscape with SMAC mimetics is very limited. Hence this project investigated whether the SMAC mimetic drug, birinapant, that inhibits cellular IAP1/2 can sensitize NHL cells towards NK-mediated killing and identify the underlying molecular mechanism(s).

Objectives: Our first objective was to optimise the concentration of birinapant that can inhibit Cellular Inhibitor of Apoptosis Proteins (cIAPs) on NHL cell lines without affecting their viability. Next, we tested the effect of that concentration of birinapant on NK cell viability. Finally we tested the cytotoxicity of the NK cells with NHL cells in presence of birinapant, and further studied the molecular mechanism(s) of birinapant mediated NK sensitisation of NHL.

Methods: NHL cell lines- RIVA, RAJI, OCI-LY1, OCI-LY7, OCI-LY10 were treated with birinapant to inhibit cIAP1/2. cIAP inhibition and cell viability after treatment was determined with Western blotting monitoring cIAP1-degradation and fluorescent viability staining (Zombie-NIR) using flow cytometry. NK cells were isolated from peripheral blood of healthy donors and expanded on a lymphoblastoid cell layer using NK MACS medium and 500 IU/ml IL-2. NK-mediated cytotoxicity was assessed in NHL cell-NK cell co-cultures and flow cytometry was used to measure the NK-mediated target cell lysis.

Results: Pre-treatment of NHL cells with a low, non-toxic dose of birinapant for 4 h led to full degradation of cIAP1 in NHL cell lines, and a longer, 24 h treatment led to a strong sensitisation of NHL cells towards NK-mediated cytotoxicity. The same dose of birinapant had no significant effect on cIAP expression or viability in NK cells.

Conclusions: Short duration of SMAC-mimetic birinapant treatment led to rapid cIAP degradation in NHL cells, but longer exposure was required to enhance NK-mediated cytotoxicity, indicating that downstream target(s) of cIAPs, rather than cIAPs themselves drive NK-resistance in NHL. The mediator(s) behind the enhanced NK-cytotoxicity is currently being investigated.

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A SMALL MOLECULE DRUG THAT SELECTIVELY IMPAIRS INFLAMMATION-INDUCED ANTIFIBRINOLYTIC ACTIVITY TO RESTORE PLASMIN GENERATION

PA Klavina[1, 2], AM Rehill[1], SJ Humphreys[3], F Nally[2], CS Whyte[3], NJ Mutch[3], AM Curtis[2], RJS Preston[1]
[1]Irish Centre for Vascular Biology, School of Pharmacy and Biomolecular Sciences, RCSI, Dublin,
[2]Curtis Clock Laboratory, School of Pharmacy and Biomolecular Sciences, RCSI, Dublin,
[3]Aberdeen Cardiovascular and Diabetes Centre, Institute of Medical Sciences, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, United Kingdom

Introduction/Background: Coagulopathy is a common and life-threatening complication of sepsis, characterised by the up-regulation of pro-coagulant and anti-fibrinolytic proteins in immune and endothelial cells, leading to aberrant clot formation and dissolution. Therapeutic inhibition of immunothrombosis is challenging due to the complex network of interactions between pro-inflammatory, procoagulant, and fibrinolytic pathways. In this study, we sought to evaluate the properties of a small molecule (SR9009) that was identified via screening to possess anti-immunothrombotic activity.

Materials/Methods: Bone marrow-derived macrophages (BMDMs) were obtained from mouse legs by flushing bone marrow and differentiating bone marrow cells for 7 days in the presence of cell-conditioned media containing macrophage colony-stimulating factor. BMDMs and both immortalised and primary endothelial cells (EA.hy926 and human umbilical vein endothelial cells, respectively) were stimulated with SR9009 alone, or pre-treated with SR9009 followed by pro-inflammatory activation with lipopolysaccharide (LPS). Fibrinolysis assays, including plasma clot lysis and cell-based plasmin generation assays, were performed. In addition, tissue factor-mediated thrombin generation was assessed in the presence of SR9009. RT-qPCR was used to analyse gene expression in SR9009-treated cells.

Results: At baseline, the presence of SR9009-treated endothelial cells reduced peak thrombin generated in plasma thrombin generation assays. From a fibrinolysis perspective, SR9009 did not affect plasmin generation or clot lysis in plasma in the presence or absence of endothelial cells or mouse macrophages. However, in inflammatory conditions, SR9009 potently inhibited LPS-induced expression of anti-fibrinolytic proteins plasminogen activator inhibitors 1 and 2 (PAI-1 and PAI-2) in macrophages on a gene level. Consequently, LPS-induced suppression of macrophage fibrinolytic activity, a classical phenomenon of infection-related coagulopathy, was effectively restored by SR9009 in a plasmin generation assay. Notably, the pro-fibrinolytic activity of SR9009 did not impact normal immunoregulatory activity, as LPS-induced inflammatory cytokine IL-6 and TNFa expression were not impacted by SR9009 exposure.

Conclusions: These data suggest SR9009 selectively restores fibrinolysis via inhibition of inflammation-induced anti-fibrinolytic protein generation from activated immune cells. These therapeutic properties may have potential application in restoring normal plasmin generation in individuals with dysregulated fibrinolytic activity caused by acute infection.

UNRAVELLING THE MOLECULAR EFFECTS OF A NOVEL LEUKAEMIA-RELATED GENE FUSION

E Grady[1], T Dias[1,2], P McCarthy[1,2,3], S Biswas[1,2], A Trinquand[3], D Betts[3], A Malone[3], J Bond[1,2,3]
[1]School of Medicine, University College Dublin, Belfield, Dublin 4,
[2]UCD Systems Biology Ireland, University College Dublin, Dublin,
[3]Children's Health Ireland, Crumlin, Dublin,

B-cell acute lymphoblastic leukaemia (B-ALL) is the most common childhood malignancy. It is characterised by the uncontrolled proliferation of immature B-lymphoid cells in the bone marrow and blood. While patient outcomes are generally good, with > 90% survival, current treatment regimens require identification of known genetic abnormalities to contribute to appropriate risk stratification . Transcription factor 3 (TCF3) fusions have been shown to be hallmarks of B-ALL development with their partner gene highly influencing prognosis. The most well characterised are currently TCF3::PBX1 and TCF3::HLF1, associated with both standard and poor risk disease respectively. Therefore, identifying new partners of TCF3 fusions and understanding their effects is essential to improve B-ALL risk stratification in the future.

An 11-year old female presented to the National Children's Cancer Service at Children's Health Ireland at Crumlin with a high white cell count (30.1 x 109/L) with circulating blasts seen on her blood film. Flow cytometry confirmed the diagnosis of Pre-B ALL.

Following standard protocol, bone marrow samples were acquired for both diagnostics and to identify prognostic genetic alterations. Fluorescence in situ hybridization was performed using, amongst others, a TCF3 probe, but no known re-arrangements were identified.

In the absence of any other risk factor, except for her age (>10 years), the patient commenced treatment as per UKALL 2019 Interim Guidelines Regimen B Induction.

Single nucleotide polymorphism arrays were later performed on the bone marrow sample, where a breakpoint in both the TCF3 and PIK3R1 gene was identified, suggesting the identification of a novel fusion.

Here we describe the novel TCF3::PIK3R1 fusion identified in the paediatric B-ALL patient and its downstream effects. Molecular and cytogenetic studies revealed the presence of the transcript in the cells, allowing us to design an expression vector containing the fusion sequence.

We used this vector to lentivirally transduce a cell line (HEK293) to express the TCF3::PIK3R1 fusion, allowing us to analyse its effects on signalling pathways and function. Using Western blots, a decrease in the AKT signalling pathway was noted, in line with altered PIK3R1 activity. We also saw increases in anti-apoptotic molecules, such as BCL2. Cell cycle analysis showed very little change between control cells and fusion containing cells.

Our findings, together with the clinical outcome of the patient to date, suggest that TCF3::PIK3R1 does not lead to an aggressive form of B-ALL.

THE PROGNOSTIC VALUE OF DETERMINING MYC TRANSLOCATION PARTNER GENES IN DLBCL. RE-EVALUATING THE SIGNIFICANCE OF NON-IMMUNOGLOBULIN PARTNER GENES.

S McCauley[1], O Sheehy[1], M Catherwood[1]
[1]Department of Haematology, Belfast City Hospital, Belfast , UK

Introduction

Diffuse large B-cell lymphomas (DLBCL) with MYC translocations are associated with inferior survival. MYC translocation with an immunoglobulin partner gene promotes MYC protein upregulation and oncogenesis. Studies suggest the negative impact of a MYC translocation is determined by an immunoglobulin partner gene (MYC-Ig), as opposed to a non-immunoglobulin partner gene (MYC-non-Ig)[1].

The aim of this project was to assess the prognostic value of determining the partner gene (Ig or Non-Ig) in DLBCL with MYC translocations in our centre.

Methods

A retrospective review of all patients with DLBCL were identified from 2012 to 2018 inclusively. Clinical data was collected from patient charts. MYC-translocations by FISH were performed by HMDS Leeds (Haematological Malignancy Diagnostic Service) using IGH/MYC fusion probes.

Data including IPI-scores, treatments, and results of BCL2/BCL6 rearrangements were collected. Outcomes including time to relapse, overall survival, and cause of death (if occurred) were recorded.

Results

249 patients with DLBCL were identified. 193 (78%) had biopsies with FISH assays. Cause of death was not determined in five cases. Final cohort 188 patients.

MYC translocation identified in 30 patients (16% [30/188]). 19 (63% [19/30]) had a MYC immunoglobulin partner (MYC-Ig); Five were MYC-non-Ig (17% [5/30]); and six had MYC translocations but unidentified partner genes (MYC-U). 158 patients were MYC negative.

In total, 28 cases (15% [188 patients]) relapsed within 24 months. Presence of a MYC translocation had a 27% (8/30) risk of relapse within 24 months. MYC negative cases had an 13% relapse rate (20/158) (Relative Risk [RR] 2.1). MYC-Non-Ig had a higher relapse rate (60% [3/5]) compared with MYC-Ig (21% [4/19]) (RR 2.86). 17% MYC-U relapsed within 24 months (1/6), comparable with MYC-Ig. Five cases (2.7% [5/188 patients)] relapsed beyond 24 months, all were MYC negative.

MYC translocation had 100% mortality post-relapse within 1-9 months (8 cases). MYC negative cases had a marginal survival advantage post-relapse with 75% mortality (2-17 months [15/20]).

MYC translocation had a significant mortality risk of 57% [17/30] within 24 months, all due to DLBCL per death certificate. MYC negative cases had a lower mortality risk (31% [49/158]) (RR 1.8), fewer of which were due to DLBCL (79%). MYC-Non-Ig had a higher mortality (80%) within 24 months, compared to 53% of MYC-Ig (RR 1.5). MYC-U had 50% mortality, comparable with MYC-Ig.

All MYC-Non-Ig cases were treated with R-CHOP. 89% MYC-Ig cases were treated with R-CHOP. Three were escalated to CODOX-M-IVAC per FISH results, none of which relapsed.

Conclusion

Presence of a MYC translocation correlates with a higher rate of relapse and inferior OS compared to MYC negative cases. The majority were MYC-Ig (19/30). We speculate remaining MYC-U cases had immunoglobulin partners given their comparable relapse and mortality rates. Though total numbers of MYC-non-Ig cases were small (5/30), MYC-non-Ig was associated with inferior outcomes, as opposed to MYC-Ig, contrary to current evidence[1]. The adverse impact of a non-immunoglobulin partner may reflect the majority being double hit (DH) lymphomas (80%) with concurrent BCL2-rearrangements, compared to 26% MYC-Ig being DH cases, together with higher IPI-scores and older ages. Presence of MYC-non-Ig, particularly with DH, may impact survival and need to revise prognostic discussions and treatment escalation.

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Targeted Inhibition of Phosphodiesterase (PDE) 4 in Endothelial Cells as a Novel Therapy for Von Willebrand disease

D Doherty[1, 2], E Karampini [1], C Byrne[1], I Schoen [1], R Preston[1], JM O'Sullivan[1], M Lavin[1, 2], JS O'Donnell[1, 2]
[1]Irish Centre for Vascular Biology, School of PBS, Royal College of Surgeons in Ireland (RCSI), Dublin
[2]National Coagulation Centre, St James's Hospital, Dublin, Ireland

Background: Desmopressin (DDAVP) is widely used in the treatment of von Willebrand Disease (VWD). DDAVP activates V2 receptors on endothelial cells (EC), stimulating cAMP generation and VWF release. However, DDAVP has significant limitations, including lack of oral formulation and sub-optimal responses in some patients.

Aims: Identify EMA-approved drugs that can trigger cAMP-dependent VWF secretion from EC to repurpose as novel haemostatic therapeutic agents.

Methods: Candidate drug classes were identified by mechanistic screening of EMA-approved databases and rationalized for translational relevance. For each class, prototypical drugs were tested for capacity to induce acute VWF release from macrovascular (HUVEC) and microvascular (HMVEC-L) EC (VWF antigen[Ag], propeptide[pp] and collagen binding[CB], relative to negative control[NC]). VWF string formation on EC under flow conditions was determined using fluorescent anti-VWF antibodies and confocal microscopy. Platelet aggregation was assessed by light transmission aggregometry (LTA).

Results and Discussion: Preliminary in vitro screening determined a lead candidate drug class: PDE-4 inhibitors. Previous studies have shown that cAMP-hydrolyzing PDE isoforms 2, 3 and 4 are expressed in EC and that non-selective PDE inhibition (PDE-I) with IBMX can elevate cAMP sufficiently to induce VWF release. Consistently, we observed that treatment of EC with IBMX significantly enhanced VWF secretion (median fold increase VWF:Ag 1.49,$p<0.0001$). However, PDE isoforms 2 and 3 are also present in platelets, where increased cAMP inhibits platelet aggregation. We confirmed that IBMX significantly attenuated TRAP-6-induced platelet aggregation, limiting the therapeutic relevance of non-selective PDE-I as VWF-raising agents.
We next evaluated the capacity of isoform-selective PDE-I to induce VWF release. Inhibition of PDE-2 and PDE-3 had no significant effect ($p>0.999$). In contrast, selective PDE-4 inhibition with Roflumilast (ROF) caused a dose-dependent increase in VWF:Ag secretion from HUVEC (1.51-fold,$p<0.0001$) and HMVEC-L (1.75-fold,$p=0.007$). Consistently, ROF treatment resulted in a proportionate increase in VWFpp secretion (1.74-fold,$p=0.0002$). Notably, these effects were also seen at therapeutically relevant nanomolar concentrations of ROF.

Following treatment with ROF, increased VWF:Ag was accompanied by a parallel rise in VWF:CB in the supernatant (1.50-fold,$p=0.0061$), confirming the secretion of haemostatically active VWF multimers. Under flow conditions, ROF triggered VWF string formation from HUVEC with strings visualized in most fields of view (80% ROF, 0% NC,$p=0.0003$). Critically, ROF had no inhibitory effect on platelet aggregation, consistent with lack of PDE-4 isoform activity in platelets.

ROF combined with histamine (HIS) or thrombin (THR) had synergistic effects on VWF release, suggesting ROF could prime EC to physiological agonists at times of haemostatic challenge (3.4-fold HIS vs 5.17-fold HIS+ROF,$p<0.0001$; 3.7-fold THR vs 4.3-fold THR+ROF,$p=0.0060$). Finally, ROF exhibited synergistic activity with the cAMP-raising agent Isoprenaline compared to ROF alone (1.77 vs 1.40-fold,$p=0.0040$), suggesting combination therapy as a novel therapeutic approach.
Conclusion: Drug repurposing allows for rapid and cost-effective translation into clinical practice. Our novel findings identify PDE-4 as a critical regulator of VWF secretion. We demonstrate that ROF, an EMA-approved PDE-4 inhibitor, stimulates VWF release without deleterious effects on platelet aggregation. Our data highlight the therapeutic potential of PDE-4 inhibitors, either alone or in combination with DDAVP, in the treatment of VWD.

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EVOLUTION OF CELLULAR THERAPIES FOR MANTLE CELL LYMPHOMA: A LYMPHOMA NETWORK SERIES OF PATIENTS TREATED AT THE NATIONAL ALLOGENEIC STEM CELL AND CAR-T CENTRE (NASCCT) AT ST JAMES' HOSPITAL

J Nolan[1,2,3] Orla Gildea[2], James Dillon[3], Katie Liston[4], Janet Tan[4], Edward Jones[5], Cormac Jennings[6], Stuart Macleod[7], Anne Fortune[2], Su Maung[2], Ronan Desmond[3], Helen Enright[3], Johnny McHugh[3], Mary Cahill[4], Derville O'Shea[4], Eoghan Molloy[4], Ruth Clifford[5], Hilary O'Leary[5], Jeremy Sargent[6], John Quinn[6], Kanthi Perera[7], Brian Bird[8], Ezzat Elhassadi[9], Brian Hennessy[9], Greg Lee[1], Paul Browne[1], Larry Bacon[1], Richie Flavin[10], Fiona Quinn[11], Elisabeth Vandenberghe[1]

[1]Department of Haematology, St James' Hospital, Dublin 8, Department of Haematology, Mater Misericordiae University Hospital, Dublin, Department of Haematology, Tallaght University Hospital, Dublin, Department of Haematology, Cork University Hospital, Co Cork, [2]Department of Haematology, University Hospital Limerick, Dooradoyle, Co Limerick, [3]Department of Haematology, Beaumont Hospital, Dublin, [4]Department of Haematology, Midland Regional Hospital Tullamore, Co Offaly, [5]Department of Oncology, Bon Secours Hospital Cork, Co Cork, [6]Department of Haematology, University Hospital Waterford, Co Waterford, [7]Department of Histopathology, St James' Hospital, Dublin, [8]Cancer Molecular Diagnostics Laboratory, St James' Hospital, Dublin

Introduction: Mantle cell lymphoma (MCL) is a conventionally incurable, uncommon subtype of non-Hodgkin Lymphoma, defined by t(11;14)(q13;32) and a genetically determined, heterogeneous disease course. In 2006, Rituximab and Ara-C based induction, consolidated by BEAM-conditioned autologous stem cell transplantation (auto-HCT) resulting in an overall(OS) and progression-free survival(PFS) of 12.7 and 8.5 years respectively[1], became standard first line MCL treatment for transplant-eligible patients. BTK inhibitor(BTKi) therapy for relapsed MCL became available in 2016; immature data from the Triangle Study(EMCL) suggest fixed duration ibrutinib may replace auto-SCT [2].

Allo-HCT was the only curative option for transplant-eligible refractory/relapsed (R/R) patients[3]. The CD19-directed CAR T therapy Brexucabtagene autoleucel was EMA-approved in 2021 for second line treatment of MCL and may replace allo-HCT, because of improved tolerability and equivalent efficacy with currently available (limited) follow-up[4]. Since 2021, relapsed/refractory NASCCT transplant-eligible patients in second line have been offered CAR T instead of allo-HCT.The evolving approach of cell therapies use for the treatment of MCL since 2010 at the NASCCT for nationally-referred patients is presented.

Materials and methods: Patients treated with cellular therapies (auto-HCT, allo-HCT and CAR T therapy) at the NASCCT since 2010 were included. Evaluable outcomes included Transplant-Related Mortality (TRM), OS and Event-Free Survival(EFS) (defined as time from infusion of cellular therapy product to relapse, subsequent therapy, or death). Outcomes of the effect of high MIPI, TP53 mutated and aggressive histological variants (blastoid/pleomorphic) were assessed.

Results: Sixty-four patients (52M/12F) (median age,59(*range 37-68*)) years underwent auto-HCT in MRDnegative CR1. Where evaluable, 24/53(45%) patients had high risk MIPI, 3/50(15%) were SOX11-negative, 8/64(13%) blastoid/pleomorphic MCL and 8/43(19%) were TP53 mutated. The median EFS were 8.2 and 10.1 years respectively with a 6.8 year median follow-up and no TRM. TP53 mutation was associated with an inferior OS(6.5 years vs not reached)(p=0.02), but other variables were not significant for outcome.

Thirteen patients with relapsed/refractory disease included 9 patients(median age 56 years(range 39-63)) underwent allo-SCT and 4 patients (aged 60-65 years) received CAR-T therapy. Allo-SCT patients had received 2-4(median 3) prior lines of therapy, including 3(33%) auto-HCT and 7(78%) prior BTKi. Disease status at allo-HCT was CR(n=6) and PR(n=3) respectively. No TRM occurred. Median OS was 1 year, deaths were due to: MCL progression 5(56%) and 1 progressive multifocal leukoencephalopathy. Three patients remain alive at 8.1, 5.2 and 4.3 years. The 4 CAR-T treated patients had a median of 3(range 2-4) prior lines of therapy including in all cases BTKi and all were in PR prior to CAR-T. CAR-T outcome was a TRM death at 4 weeks(HHV6 encephalitis), death from MCL progression at 7 months and 2 survivors at 3 and 20 months.

Conclusions: Auto-HCT has been integrated since 2006 into front-line therapy, but may itself be replaced by BTKi treatment if mature Triangle study data confirms non-inferiority. In the relapsed/refractory setting, allo-HCT is being superseded by CAR-T therapy and our results confirm this change to be an effective, less toxic approach. Long-term data with targeted therapies and CAR-T will be needed to endorse these pathway changes.

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Use of DA-R-EPOCH for high grade B-cell lymphoma from 2014 to 2023 at Mater Misericordiae University Hospital

C Hughes[1], M Aly[1], B Dillon[1], I Loftus[1], O Gildea[1], C Fox[1], E O' Rourke[1], S Maung[1, 2], M Fay[1, 2], A Fortune[1, 2]
[1]Haematology Department, Mater Misericordiae University Hospital, Dublin, Ireland
[2]School of Medicine, University College Dublin, Dublin, Ireland

Introduction

Dose-adjusted rituximab, etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin (DA-R-EPOCH) is frequently used over R-CHOP therapy in the treatment of certain high-grade B-cell lymphomas[1]. The use of DA-R-EPOCH has been established in MYC-rearranged B cell lymphomas including Burkitt's lymphoma, double hit, and triple hit lymphomas. In a 2014 NCI trial, DA-R-EPOCH demonstrated superior progression free survival compared to R-CHOP in double and triple hit disease, with a 4-year overall survival of 72%[2]. An NCI randomised control trial demonstrated a 95% 5-year progression free survival rate and 97% overall survival rate with this regimen in Primary Mediastinal B-Cell Lymphoma[3], but it has been challenging to replicate these initial results with real-world data[4]. Our aim is to establish response rates and survival data in our cohort over a 10-year period to compare to published studies.

Methods

A retrospective analysis of all patients having received at least one cycle of DA-R-EPOCH from February 2014 to June 2023 at the Mater Misericordiae University Hospital was performed. Data was collected from electronic patient records and BD Cato Software. Data collected included patient demographics, lymphoma subtype, R-IPI at diagnosis, response at interim and end-of-treatment PET-CT scans, patients consolidated with radiotherapy, survival data and treatment tolerability.

Results

A total of 33 patients were included in this review (22M/11F), with a median age of 50. Diagnosis included PMBCL (n=15), high grade DLBCL (n=8), Burkitt's lymphoma (n=5), confirmed Double Hit Lymphoma (n=4), and one case of Burkitt's-like post-transplant lymphoproliferative disease. R-IPI scores at diagnosis were as follows: 2 patients had R-IPI low risk disease (6%), 22 patients had R-IPI intermediate risk disease (66%), and 9 patients had R-IPI high risk disease (27%).

Response rates were determined based on the end-of-treatment PET-CT and in one instance on bone marrow aspirate and trephine in marrow-limited disease. 23 patients had complete metabolic response (69.7%), 3 patients had partial response (9%), 4 patients had progressive disease (12%). 2 patients (6%) died during treatment, with one case of neutropaenic sepsis and one case of primary refractory disease. Overall survival was 82%. Progression free survival was 78.1%, with a median follow-up of 36 months (range 1-101 months). Notably, the PMBCL cohort had a 100% overall survival rate. 3 patients with PMBCL underwent radiotherapy or a combination of surgery and radiotherapy to consolidate their response with all 3 achieving a complete response on follow up.

With regards to tolerability, 20 patients tolerated dose increases in accordance with the established protocol (60%). No patients required dose reductions of cyclophosphamide due to thrombocytopenia. 3 patients (9%) required a 50% dose reduction owing to derangement in liver function tests. Peripheral neuropathy was a common adverse effect of the therapy, with 7 patients reporting at least grade 1 symptoms (21%). 4 of these cases required a 50% dose reduction in vincristine for at least grade 2 peripheral neuropathy.

Conclusion

DA-R-EPOCH continues to be an effective regimen used in the treatment of high-grade B cell lymphomas. Good survival data, reasonable tolerability, and low rates of radiotherapy in our PMBCL cohort is encouraging.

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Discovery of distinct signal transduction interactions leading to thrombo-inflammatory versus cytoprotective protease-activated receptor 1 signalling

D Noone[1,2], A Tashakor[1,2], E Soule[1,2], O Willis-Fox[1,2], H Fleming[1,2], AM Rehill[1,2], G Leon[1,2], RJS Preston[1,2,3]
[1]Irish Centre for Vascular Biology, RCSI University of Medicine and Health Sciences, Dublin
[2]School of Pharmacy and Biomolecular Sciences, RCSI University of Medicine and Health Sciences, Dublin
[3]National Children's Research Centre, Our Lady's Children's Hospital Crumlin, Dublin

Background: Aberrant protease-activated receptor 1 (PAR1)-dependent signalling is important for thrombo-inflammatory disease pathogenesis. Interestingly, PAR1 is activated by different plasma proteases at alternative sites to induce 'biased' signalling outcomes. PAR1 activation by thrombin promotes G-protein-dependent signalling terminated by beta-arrestin (β-Arr) 1 recruitment associated with thrombo-inflammation. In contrast, PAR1 activated by endothelial protein C receptor (EPCR)-bound activated protein C (APC) requires β-Arr2 recruitment to facilitate endothelial cytoprotective signalling that is associated with anti-inflammatory vascular protection.

Aims: To evaluate if PAR1 activation by thrombin or APC induces protease-specific PAR1 conformations that promote distinct β-Arr interactions.

Methods: A recombinant tripartite green fluorescent protein (GFP) cell reporter system in which GFP fluorescence occurs only upon β-Arr recruitment to activated PAR1, was modified to enable evaluation of intracellular β-Arr1/2 recruitment following PAR1 activation by thrombin or EPCR-bound APC. GFP maturation induced by activated PAR1-β-Arr1/2 interaction(s) was determined by flow cytometry. The timing and localisation of thrombin- and APC-induced PAR1-β-Arr2 complexes were observed using confocal microscopy. PAR1 mutants were assessed to probe the intracellular structural requirements for thrombin or APC-cleaved PAR1 recruitment of β-Arr1/2.

Results: Both thrombin- and APC-activated PAR1 induced β-Arr1 or β-Arr2 recruitment and subsequent GFP formation in reporter cells. The structural requirements for β-Arr recruitment to either thrombin- or APC-cleaved PAR1 were assessed in the same assay using a library of PAR1 mutants that spanned the intracellular regions of PAR1. Notably, PAR1 mutants that prevented β-Arr recruitment to APC-cleaved PAR1, but still facilitated robust recruitment of β-Arr to thrombin-cleaved PAR1, were identified. Specifically, APC-cleaved PAR1-β-Arr2 recruitment was lost upon mutagenesis of sites within intracellular loops 1, 3 and the C-terminal tail of PAR1, whereas the same PAR1 mutants remained competent for β-Arr1 recruitment after thrombin cleavage. Moreover, the dynamics of β-Arr recruitment differed depending on the activating protease, as thrombin induced more rapid PAR1-β-Arr2 complex formation than APC. Notably, the thrombin-cleaved PAR1-β-Arr2 complex was also quickly internalised for degradation, whereas the APC-induced PAR1-β-Arr2 complexes remained at the cell surface.

Conclusions: We have identified, for the first time, critical intracellular sites for β-Arr recruitment to APC-cleaved PAR1 and shown that their disruption is incompatible with β-Arr2 recruitment and, therefore, APC-induced cytoprotective PAR1 signalling. Notably, the same mutants did not have a comparably disruptive impact upon thrombin-cleaved PAR1-β-Arr recruitment, highlighting the distinct structural requirements for β-Arr recruitment to thrombin- and APC-cleaved PAR1. Furthermore, protease-specific trafficking cellular localisation of PAR1-β-Arr complexes following thrombin and APC activation was also observed. These novel insights may facilitate selective targeting of protease-specific PAR1 signalling for therapeutic benefit.

APPLICATION OF THE ONLINE ACUTE MYELOID LEUKAEMIA CLASSIFICATION AND RISK STRATIFICATION CALCULATOR IN A REAL-WORLD COHORT OF AML PATIENTS FROM NORTHERN IRELAND

K Clarke[1], M Maguire[2], N Cunningham[1], D Finnegan[1], C Arnold[1], MF McMullin[3], M Catherwood[1]
[1]Haematology Department, Belfast Health and Social Care Trust, Belfast, Northern Ireland
[2]Northern Ireland Centre for Stratified Medicine, School of Biomedical Sciences, University of Ulster, Derry, Northern Ireland
[3]Centre for Medical Education, Queen's University Belfast, Belfast, Northern Ireland

Acute myeloid leukaemia (AML) is a clonal disorder of the bone marrow responsible for 80% of adult leukaemia cases[1]. It is attributable to genetic alterations within haematopoietic stem cells, leading to clonal stem cell overproduction[2]. The 5th edition of WHO Classification places significant emphasis on the inclusion of molecular genetics for AML resulting in the introduction of new genetic subgroups.

Tazi *et al.,* have developed a unified classification and risk stratification tool for AML based on the correlation between clinical presentation, cytogenetics and a novel 32 gene signature[3]. The online "AML Clinical Support" calculator enables clinicians to classify patients rapidly to one of 16 novel molecular sub-classes describing 100% of AML patients[3].

The aim of this retrospective study was to investigate the utility of this online calculator to stratify real-world AML data into the appropriate classification and risk group. Anonymised data was available on 159 patients diagnosed with AML between 2017 and 2023. Diagnostic NGS, cytogenetics, and clinical presentation features were compiled for analysis. A total of 136 cases (86%) were fully annotated. Data was inputted into the AML Clinical support calculator available at https://www.aml-risk-model.com/calculator.

The calculator reclassified 22% of patients into the previously undefined sAML2 (secondary acute myeloid leukaemia class 2) category, 15% into the NPM1 category and 12% were differentiated as mNOS (molecularly Not Otherwise Specified). The remaining patients were equally distributed amongst the remaining categories (TP53, sAML1, t(8;21), no events, inv3, inv16, trisomies, t(15;17), DNMT3A, IDH, WT1 t(11;x), t(6;9), or biCEPBA).

Based on ELN 2017, 4/30 sAML2 classified patients (13%) were placed into the intermediate risk category, the remainder were in the adverse risk group (87%). These 4 patients were reclassified using the Tazi calculator, which placed them into the adverse risk group.

A total of 20 patients (19%) were allocated into the NPM1 subtype. No reclassification occurred when comparing ELN vs Tazi for this cohort, all categorised as favourable risk according to both models. The mNOS subtype includes patients who were unable to be clustered with other molecular classes [3]. Of those patients classified as mNOS, 5 (31%) were considered to have adverse risk according to ELN 2017. The remainder were intermediate risk. These 5 patients were deemed adverse risk by ELN 2017 but were subsequently reclassified to intermediate risk.

According to ELN 2017, 26.5% of the patient cohort was characterised as favourable, 26.5% as intermediate and 47% as adverse. The predicted prognostic risk generated by the Tazi calculator proposed favourable, intermediate, and adverse risk as 30%, 28%, 42% respectively. A total of 20 patients (15%) had their risk group reclassified using the Tazi calculator. The risk score of 16 patients (12%) improved however the score of 4 individuals (3%) was made worse.

In conclusion, the Tazi calculator is a reliable tool, capable of classifying and stratifying real-world AML data. The Tazi calculator improves accuracy provided by the incorporation of clinical features and molecular data in predicting a patient's prognostic risk specific to each patient. Furthermore, online calculators such as the Tazi unified classification and risk-stratification model permit the introduction of molecular biomarkers into clinical algorithms for AML patient management.

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A CYTOGENETIC AND MINIMAL RESIDUAL DISEASE RISK ADAPTED STRATEGY IN THE MANAGEMENT OF ADULT ACUTE LYMPHOBLASTIC LEUKAEMIA: A SINGLE CENTRE 10 YEAR EXPERIENCE.

C Browne[1], S Toolan[1], I Hughes[1], A Polion[1], M Brennan[1], G Lee[1], D Waldron[1], M Regan[1], L Brennan[1], C Waldron[1], CM Flynn[1], E Conneally[1], PJ Hayden[1], R Henderson[1], E Vandenberghe[1], CL Bacon[1]
[1]Department of Haematology, St James' Hospital , Dublin, Ireland

Introduction: Adult acute lymphoblastic leukaemia (ALL) historically carries a poor prognosis with cure rates of less than 40%[1,2]. Advances in prognostic markers for high risk disease with cytogenetics and minimal residual disease (MRD) as a standard of care in ALL has guided therapeutic pathways and the role of allogeneic stem cell transplantation (AlloSCT) after induction-chemotherapy[3,4].

Methods: A retrospective analysis was performed of consecutive patients who underwent induction-chemotherapy for ALL in St James' Hospital from January 2012 to December 2021. Data was collected from patient records. Cytogenetics at diagnosis and MRD status post induction were used to stratify disease risk. Post-induction treatment with chemotherapy-only (chemo-only) or AlloSCT was assessed. Statistical analysis for progression free survival (PFS) and overall survival (OS) was performed via the Kaplan-Meier method.

Results: A total of 60 patients were included in the cohort. The median age at diagnosis was 37 years (range 14-79); 40 (67%) were male and 20 (33%) were female. 41 (68%) patients were diagnosed with B-ALL; 9 (22%) of whom had a WCC >30x10^9/L at diagnosis. 19 (32%) were diagnosed with T-ALL; 3 (16%) of whom had a WCC >100x10^9/L at diagnosis.

59 (98%) were treated with intensive induction-chemotherapy. 37 (62%) were treated with standard adult protocols; UKALL-14 (N=29), UKALL-12 (N=8). 15 (25%) were treated with paediatric/adolescent protocols; UKALL-11 (N=13), UKALL-03 (N=2). 7 (12%) were treated with UKALL 60+ and other protocols.

16 (27%) had high risk cytogenetics at diagnosis as per the UKALL-14 criteria; low hypodiploid (N=2), near-triploidy (N=3), complex karyotype (N=2), t(4;11) KMT2A rearrangement (N=5) and t(9;22) BCR-ABL1 (N=4).

52 (87%) achieved complete remission (CR) post induction-chemotherapy and 7 (12%) had primary refractory disease. Of those achieving CR (N=52), 38 (73%) were MRD negative and 5 (10%) were MRD positive; 9 (18%) had morphological or radiological remission without MRD results available.

The median follow up for the total cohort (N=60) was 49 months (1-134months). 23 (38%) patients were consolidated with AlloSCT while 37 (62%) followed chemo-only protocols. 23 (38%) patients experienced relapsed or refractory disease and 18 (30%) died during the follow up period.

In the transplant cohort (N=23), 5 (22%) relapsed post AlloSCT at a median time from diagnosis to relapse of 12 months (7-49months). 6 patients (26%) died; transplant-related mortality N=3, relapse-related mortality N=3.

In the chemo-only cohort (N=37), 14 (38%) relapsed at a median time from diagnosis to relapse of 24 months (4-88months). 12 (32%) patients died; relapse-related mortality N=11, non-relapse mortality N=1.

The 5 year OS across the cohort (N=60) was estimated at 68%. 5 year OS in the transplant cohort (N=23) was 72% versus 59% in the chemo-only cohort (N=37) (p value=0.73). 5 year PFS across the cohort (N=60) was estimated at 62%. 5 year PFS in the transplant cohort (N=23) was 67.5% versus 47.5% in the chemo-only cohort (N=37) (p value=0.52).

Conclusion: Cytogenetic risk and MRD status to select high risk patients for allogeneic stem cell transplantation in first complete remission was an effective strategy with favourable overall and progression free survivals compared to historical controls.

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ANALYSIS OF THE PLATELET PROTEOME REVEALS INSIGHTS INTO THE PRO-INFLAMMATORY AND PRO-THROMBOTIC STATE ASSOCIATED WITH THE PHILADELPHIA CHROMOSOME-NEGATIVE MYELOPROLIFERATIVE NEOPLASMS

S Kelliher[1,2,3], A Krishnan[4, 5], A Falanga[6, 7], A Fortune[1, 2], S Maung[1, 2], M Fay[1, 2], C Andrews[2, 8], L Smyth[2, 8], K Fadalla[2, 8], L Weiss[3, 9], K Bennett[10], S Macleod[8], R Power[1], E Conneally[11,12], MF McMullin[13], F Ní Áinle[1,2,3], P Maguire[3,9], B Kevane[1,2,3]

[1]Department of Haematology, Mater Misericordiae University Hospital, Dublin, [2]School of Medicine, University College Dublin, Dublin, [3]Conway SPHERE Research Group, University College Dublin, Dublin, [4]Department of Pathology, Stanford University School of Medicine, California, USA, [5]Stanford Cancer Institute, Stanford University, California, USA, [6]Department of Immunohematology and Transfusion Medicine, Hospital Papa Giovanni XXIII, Bergamo, Italy, [7]University of Milano-Bicocca, Department of Medicine and Surgery, Monza, Italy, [8]Department of Haematology, St Vincent's University Hospital, Dublin, [9]School of Biomolecular and Biomedical Science, University College Dublin , Dublin, [10]RCSI School of Population Health, RCSI University of Medicine and Health Sciences, Dublin, [11]Department of Haematology, St James's Hospital , Dublin, [12]School of Medicine, Trinity College Dublin, Dublin, [13]Centre for Medical Education, Queen's University Belfast, Belfast, United Kingdom, [14]Department of Haematology, Rotunda Hospital, Dublin, [15]UCD Institute for Discovery, University College Dublin, Dublin, Ireland

Introduction: Myeloproliferative neoplasms (MPN) are clonal haematopoietic stem cell malignancies characterised by myeloid proliferation and thrombocytosis. Patients with polycythaemia vera (PV) and essential thrombocythaemia (ET) have an increased risk of thrombosis and progression to secondary myelofibrosis and/or acute leukaemia. While vascular risk is highest around the time of initial diagnosis, it remains elevated despite cytoreductive/anti-thrombotic therapy and represents the predominant source of early mortality.

There is emerging evidence that platelets are phenotypically distinct in multiple disease states, playing critical roles in a myriad of biological processes. However, the contribution of the platelet proteome to pathologic sequalae in MPN has yet to be fully elucidated. We hypothesised that platelet proteomic analysis would provide a snapshot into the haemostatic, thrombotic, and inflammatory derangements which drive the clinical complications experienced by patients.

Methods: Platelet samples from patients with established MPN (ET, n= 59; PV, n= 41) were obtained from an MPN biobank (Bergamo, Italy). Additional prospective recruitment of individuals referred to the Mater Misericordiae University Hospital and St Vincent's University Hospital for investigation of thrombocytosis/erythrocytosis formed a second independent cohort of patients with newly diagnosed, untreated MPN (n= 31) and a control group with transient/reactive thrombocytosis (n= 23).

Platelets were isolated from whole blood to generate platelet lysate and platelet releasate. Differential proteomic signatures were established using label-free quantification (LFQ) mass spectrometry (MS). Identified peptides were searched using MaxQuant and bioinformatic analysis was performed using R.

Results: We evaluated the platelet proteome in 100 patients receiving treatment (anti-platelet/cytoreductive) for an established diagnosis of PV/ET and 40 healthy controls. 2594 proteins were quantified, with 227 and 166 proteins significantly differentially expressed (false discovery rate <0.05; fold change >1.5) in ET & PV respectively. Mediators of inflammation were upregulated such as LGALS1 and MMP1. Effectors of platelet pro-coagulant activity were overexpressed in MPN including FcγRIIA and HSP47. Functional analysis of platelets using gene set enrichment demonstrated that proteins from the MTOR signalling pathway and unfolded protein response were enriched in PV & ET cohorts.

Next, we aimed to capture the unique pattern of protein expression in a cohort of treatment-naive patients at the time of MPN diagnosis. Unsupervised principal component analysis of platelet proteins separated patients with MPN from those with reactive thrombocytosis. Proteomic analysis of lysate samples from newly diagnosed patients showed profound prothrombotic signatures with altered expression of the inflammatory S100A8 protein. Moreover, the platelet releasate profile revealed insights into the contribution of platelets to the circulating, hypercoagulable milieu, as demonstrated by increased levels of protein disulfide isomerases amongst other markers.

Conclusions: We describe the untargeted proteomic profile of platelets from two large, independent MPN cohorts, including the first such characterisation from newly diagnosed, treatment-naïve patients. We highlight the predominance of thromboinflammatory mediators in this treatment-naïve group, however in keeping with the observation that vascular risk remains elevated amongst chronically treated patients, we also demonstrate evidence of an altered platelet proteome in that group despite standard therapy. The precise functional implications remain to be established, however identified candidates may serve as future therapeutic targets.

AEBP2 IS A NOVEL GENETIC DEPENDENCY IN EZH2 MUTANT B-CELL NON-HODGKIN LYMPHOMA

J Nolan[1,2,3], D Angelov[1,2], D Nimmo[1], M Mucha[1], G Brien[1], CW Chen[4], E Vandenberghe[2,3], E Conway[1], AP Bracken[1,2]

[1]Cancer Chromatin Biology Laboratory, Smurfit Institute of Genetics, Trinity College Dublin, Dublin
[2]Trinity St James' Cancer Institute, St James' Hospital, Dublin 8, Ireland
[3]Department of Haematology, St James' Hospital, Dublin 8, Ireland
[4]Department of Systems Biology, City of Hope Comprehensive Cancer Centre, Duarte, California, USA

Background: The chromatin regulator EZH2 is the enzymatic engine of Polycomb Repressive Complex 2 (PRC2) and writes repressive methylation marks at H3K27 resulting in genomic silencing, playing an essential role in normal B-cell maturation. Recurrent hotspot hypermorphic mutations arising in the catalytic SET domain of EZH2, which dramatically increase the levels of tri-methylated H3K27 (H3K27me3) are present in up to one quarter of germinal centre-derived B-cell lymphomas and are targetable by enzymatic inhibitors including Tazemetostat[1,2]. The utility of EZH2 inhibitors is limited by inevitable disease progression amongst responders after a short period of time[3]. We sought to examine the mechanism of action of the oncogene EZH2 in B-cell lymphoma and to expose novel genetic vulnerabilities in lymphoma amongst other PRC2 core and substoichiometric components.

Materials and methods: We designed a CRISPR tiling library (3973 small guide RNAs) consisting of every possible sgRNA targeting exons encoding PRC2 components in addition to control sgRNAs and transduced this library using a lentiviral vector in three B-cell lymphoma cell lines (EZH2 mutant and EZH2 wild type). We quantified using high-throughput sequencing sgRNAs at an early and late timepoint such that sgRNAs decreasing in abundance reflected sgRNAs targeting essential PRC2 components or domains within these proteins. We validated using individual sgRNAs and shRNAs (short hairpin RNA) and phenotyping rescue constructs findings arising from the screen in additional cell lines and cellular contexts including a cell line engineered to harbour acquired resistance to Tazemetostat. We furthermore evaluated the mechanisms of action for genes of interest using ChIP-Rx (chromatin immunoprecipitation relative to exogenous reference genome) to determine the genomic localisation of H3K27 methylation marks and evaluated the effects of genetic perturbation of genes of interest on the transcriptome using RNA-sequencing.

Results: AEBP2, a PRC2 substoichiometric component, was highlighted in addition to PRC2 core components as a genetic dependency in EZH2 mutant B-cell lymphoma. This dependency phenotype was specific and rescuable using an exogenous AEBP2 construct non-targetable by AEBP2 sgRNAs and shRNAs. We demonstrated the AEBP2 is an essential gene only in B-cell lymphoma and not in other EZH2-dependent cancer contexts. AEBP2 depletion was able to overcome acquired resistance to Tazemetostat in a B-cell lymphoma cell line. Unlike other PRC2 substoichiometric components which have been shown the enhance and localise the catalytic activity of PRC2, the role of AEBP2 is poorly defined. By depleting AEBP2, we demonstrate a further dramatic genome-wide gain of the silencing mark H3K27me3, with a corresponding downregulation in mRNA abundance from already repressed Polycomb-target genes.

Conclusions: For the first time in a human cancer, we demonstrate in germinal centre B-cell lymphoma a genetic dependency on a PRC2 substoichiometric component. Although EZH2 mutant lymphomas harbour elevated tri-methylated H3K27, further elevation in H3K27me3 by AEBP2 depletion is deleterious. This novel mechanism is potentially targetable, subject to drug design, and may overcome acquired resistance to EZH2 inhibition in patients with B-cell lymphoma. Ongoing work will precisely determine the transcriptional effects of AEBP2 depletion and relevance in additional haematological neoplasms.

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Child and Young Adolescent *TLX3* rearranged T Acute Lymphoblastic Leukaemia (*TLX3r* T-ALL): A National cohort analysis

A Trinquand[1], DR Betts[2], S Rooney[3], L Storey[1], S Augustine[1], S McLoughlin[1], S Jacob[1], P McCarthy[1], N Barrett[1], V Broderick[1], P Evans[1], J Bond[1], A Malone[1], A O'Marcaigh[1], OP Smith[1]
[1]National Children's Cancer Service, Children's Health Ireland at Crumlin, Dublin, Ireland
[2]Department of Clinical Genetics , Children's Health Ireland at Crumlin, Dublin, Ireland
[3]Haematology Laboratory, Children's Health Ireland at Crumlin, Dublin, Ireland

Introduction: The survival of children and adolescents with B acute lymphoblastic leukaemia has dramatically improved over the last few decades, however, outcomes for young patients with T-ALL has lagged behind partly due to a lack of prognostic molecular markers to guide risk-adapted therapeutic interventions. T-ALL can be subdivided into molecular subgroups based on ectopic and mutually exclusive expression of transcription factors, such as TLX3. *TLX3* is a homeobox gene, aberrantly expressed in approximately 20% of T-ALL due to translocations. Studies have shown conflicting results on its prognostic impact. Here we describe the clinical, biological characteristics and outcomes of paediatric *TLX3* rearranged *(TLX3r)* T-ALL patients treated in Ireland from 2004 to 2023.

Methods*:* A retrospective review of paediatric T-ALL treated in UKALL protocols in the Irish National Children's Cancer Service in CHI at Crumlin from 2004 to 2023 was performed. Data extracted from chart review was cross referenced with laboratory results at diagnosis and relapse.

Results: Our paediatric T-ALL national cohort comprised 97 patients, 91 of whom had a TLX3 FISH performed. We identified 20/91 (22%) patients with a *TLX3r.* The median age at presentation was 7.1y (1.2-15.5y) with a 3:1 Male:Female ratio. Their median WBC count was lower compared with non-*TLX3r* patients (36.4 [4.2-1235] versus 104 $x10^9$/l [0.7-956]).

In patients who had ABL-class FISH and array Comparative Genomic Hybridization analysis performed, we identified 4/11 cases with an ABL-class fusion in addition to TLX3r (3 *NUP214::ABL1* and one *ETV6::ABL2,* 2 of which were identified at relapse). No ABL-class fusion was observed in the non-*TLX3r* cases (p=0.032). Immunophenotypic data showed *TLX3r* T-ALL were more often blocked at cortical stage of maturation compared with non-*TLX3r* cases (58% versus 30%, p=0.025), in line with the described role for TLX3 blockage of TRA gene rearrangement. *TLX3r* patients were included/treated in UKALL2003 (n=6), UKALL2011 (n=8) and UKALL2019 interim guidelines (n=6). All patients had TCR qPCR MRD assay performed (Day29 +/- Week12/14) for MRD-risk stratification. A trend to worse therapy response and refractory/relapse disease was observed in the *TLX3r* cohort (35% versus 20%, p=ns), but this did not reach statistical significance [5-year EFS of 70.3% versus 76.3% respectively, and 5-year OS of 78.8% versus 80.7% respectively (p=0.41 and p=0.98)]. All *TLX3r* patients with refractory/relapsed disease (7/20, 35%) underwent allogeneic HSCT (4 in CR1 for poor W14 response (n=2), or induction failure (n=2); 3 in CR2 after very-early/early relapse); whereas only 36% of non-*TLX3* patients with refractory/relapsed disease had HSCT (p=0.0071). All 4 patients with ABL-class fusion were transplanted (2 for poor MRD response, and 2 post-relapse).

Conclusion: Although slightly more refractory/relapsed disease is observed in *TLX3r* patients their 5-y OS is similar to the non-*TLX3r* group. Despite the improvement of current therapy, the prognosis of refractory/relapsed patients remains poor and identification of prognostic markers (including ABL-class fusions) to refine the stratification of the relapse risk is needed.

Inhibition of HUWE1 Results in Sensitivity to Bortezomib and an Impaired Replicative Stress Response in Multiple Myeloma

JJ Morgan[1], BG Kennedy[1], R Williams[1], KI Mills[1], LJ Crawford [1]
[1]The Patrick G Johnston Centre for Cancer Research , Queen's University Belfast, Belfast , Northern Ireland

Introduction

Despite continuous advances in therapies over the last few decades, Multiple Myeloma (MM) remains an incurable malignancy with almost all patients developing relapsed/refractory disease. This emphasizes the need for novel approaches that can improve the efficacy of current standard of care treatments. Previous work from our lab and others has identified dysregulation of the E3 ligase HUWE1 in MM and highlighted it's potential as a therapeutic target. Through its interaction with a diverse set of substrates, HUWE1 is implicated in many key cellular processes including stress responses and DNA replication and repair pathways and is being increasingly recognised as a major regulator of MYC activity. In this study, we uncover a novel role for HUWE1 in DNA replication and repair and assess the combination of HUWE1 and proteasome inhibition as a potential therapeutic strategy in MM.

Methods

MM cell lines were transfected with SMARTvector Inducible Human HUWE1 shRNA or a non-targeting control (NTC) shRNA (Dharmacon, USA). Replicative stress was induced by treatment with 2 mM Hydroxyurea (HU) and assessed using immunofluorescence staining and iPOND (isolation of proteins on nascent DNA) analysis. Viability was assessed using CellTiter® Glo and combination indices (CI) calculated using CompuSyn software. Commercially available HUWE1 inhibitor BI8622 (MedChemExpress) and novel HUWE1 inhibitors synthesised in house were used throughout the study.

Results

HUWE1 knockdown and/or inhibition in MM cell lines led to an accumulation of cells in S phase, consistent with previous studies indicating that HUWE1 is required for effective DNA replication. Using proteomic profiling and co-immunoprecipitation, we identified and validated Replication Protein A (RPA), as a novel substrate of HUWE1. RPA is a heterotrimeric subunit complex which plays a critical role in the recruitment of DNA repair proteins. We observed significantly less K63-linked ubiquitination of RPA ($p=0.00213$) in the absence of HUWE1, with an associated decrease in both phosphorylation ($p=0.0064$) and localisation of RPA to DNA following treatment with hydroxyurea (HU) to induce replicative stress. Subsequent iPOND analysis determined that this is associated with reduced recruitment of repair proteins, including RAD51, to DNA. Moreover, induced replicative stress in HUWE1 depleted/inhibited cells resulted in significantly higher levels of DNA damage at 6hrs ($p=0.00421$) and 24hrs ($p=0.0219$) post HU treatment. A recent study demonstrated that HUWE1 ubiquitination of MYC promotes the formation of MYC multimers that protect stalled replication forks to limit the formation of double strand breaks (DSB). In line with this we also observe decreased ubiquitination of MYC in the HUWE1 knockdown cell line compared to the NTC following HU treatment. Finally, we assessed the efficacy of combining HUWE1 inhibitors with bortezomib which is known to impair DSB repair. Dual inhibition of HUWE1 and proteasome activity resulted in synergistic effects (CI values < 1) and a corresponding increase in DNA damage compared to HUWE1 inhibitor or bortezomib alone as measured by levels of yH2AX.

Conclusion

We have identified RPA as a novel substrate for HUWE1 and demonstrate that targeting HUWE1 results in increased replication stress and a dampened DNA repair capacity, underpinned by reduced recruitment of repair proteins. This work outlines a clear role for HUWE1 in genome stability in MM cells and highlights that HUWE1 inhibitors represent a novel anti-myeloma strategy that acts in synergy with bortezomib to exacerbate DNA damage.

ISOLATED UTERINE CERVIX PLASMACYTOMA TREATMENT CONUNDRUM

K Samuel[1], W.R Huddleston[2], S Rajendran[2], **A Niblock[1,3]**
[1]Haematology department, Antrim Area Hospital, Northern Ireland
[2]Pathology department, Antrim Area Hospital, Northern Ireland
[3]School of Medicine, Ulster University, Northern Ireland

Solitary plasmacytoma is a type of plasma cell tumour that can either be present in the bone marrow as a Solitary Bone Plasmacytoma (SBP) or the soft tissue as an ExtraMedullary Plasmacytoma (EMP). In the case of both the distinction from other plasma cell dyscrasias such as multiple myeloma is based upon clinical, serological, histological and radiological studies. Solitary plasmacytoma is rare and accounts for 3-5% of all plasma cell malignancies[1]. They occur more in men than women (65% to 35%) with a median age of 55 years[2]. The axial skeleton is the most common site of SBP. However if the plasmacytoma is an EMP approximately 85% of these lesions occur in the head and neck mucosa.

We present a case of solitary extramedullary plasmacytoma confined to the cervix resulting in significant therapeutic and management implications owing to this unusual site of disease.

A 64 year old female presented with post-menopausal bleeding per vagina. Vaginal speculum examination revealed a 15 mm cervical polyp (0.1 g) which was excised at the time of colposcopy. Interestingly, histology reported a heavy infiltrate of plasmacytoid cells. Positivity was demonstrated with CD79a, CD138 and MUM1; there was kappa light chain restriction as seen on kappa in situ hybridisation.

On referral to the haematological services a multiple myeloma screen was carried out. Relevant blood tests revealed a normal haemoglobin, calcium and kidney function. Serum free kappa / lambda light chain ratio was normal at 0.94 and no paraprotein was detected. PET CT scan showed no evidence of systemic or localised bone or marrow abnormality and no significant lymphadenopathy. There was no uptake around the uterine cervix, suggesting no residual disease; these findings were later supported by a dedicated MRI of the pelvis. Bone marrow biopsy had no clonal plasma cells.

Thus the diagnosis of a solitary extramedullary plasmacytoma arising in the uterine cervix was made. This is a relatively rare diagnosis but involvement or the cervix is even more unusual. Imaging as part of work up suggested no evidence of residual disease following polypectomy, however the biopsy margins were not clear. The documented treatment of choice for Plasmacytomas is radiotherapy given with curative intent (>40 Gy) which can result in long term disease-free survival in approximately 65% of patients with EMP.[3]

Initial worked up for localised radiotherapy raised concerns of the risk of secondary malignancies at this highly sensitive site. This case was discussed at the radiotherapy oncologists, gynaecology and the haematology MDMs as well as expert opinions. However, it was a difficult decision weighing up the risk of radiotherapy verses proceeding to a hysterectomy in the long term. The patient was educated with regards the risk/benefit of both options. She decided to proceed with localised radiotherapy. The daily preparation and side effects experience by the patient for months during treatment was awful making the treatment decision on future cases even more difficult to decide.

For EMP up to 50% of patients will go on to develop Myeloma within 2 years and disease progression at this point is similar to patients diagnosed with de novo symptomatic myeloma.[4]

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A CASE OF COPPER DEFICIENCY ASSOCIATED CYTOPENIAS AND MYELOPATHY

J Fitzgerald[1], J Tan[1], SY Chai[1], S Ni Loingsigh[1,2]
[1]Haematology department, Galway University Hospital, Galway
[2]Haematology, Mayo University Hospital, Mayo

Abstract:
Copper, a trace element, plays a significant role as an enzyme cofactor in cell division and protein synthesis. Clinical copper deficiency is a rare from dietary intake alone and is usually associated with gastrointestinal surgeries, enteropathies with malabsorption or prolonged total parenteral nutrition. It can present with a variety of haematological and neurological sequelae. Copper deficiency can present with anaemia and neutropenia and can display dysplastic features in the bone marrow . Unlike the neurological manifestations of copper deficiency, these cytopenias can be reversed with prompt copper replacement.

We present an case of a 41 year old lady, Ms A, with longstanding Type 1 Diabetes Mellitus with end organ damage – dialysis dependent nephropathy, gastroparesis, retinopathy and suspected neuropathy. She developed anaemia following dialysis initiation but this became increasingly refractory to erythropoietin supplementation and she subsequently developed fluctuating but progressive neutropenia and thrombocytopenia.

Baseline investigations including haematinics, autoimmune profile, virology screen, serum protein electrophoresis and serum free light chains were unremarkable. CT TAP ruled out infiltrative cause. Initial bone marrow biopsy in January 2023 showed an essentially normal marrow. Due to worsening anaemia, her erythropoietin doses were increased and a hypoxia inducible factor-1 inhibitor was introduced but no improvement was observed.

Her cytopenias continued to worsen and a repeat bone marrow biopsy was performed in April 2023 which showed approximately marked erythroid hyperplasia with some subtle erythrodysplasia (occasional binucleate cells). Megakaryocytes were plentiful.

In view of her concurrent neurological symptoms and possible chronic malabsorption, copper levels were sent for investigation and she was found to profoundly copper deficient with levels of < 2 µmol / L (normal range: 11.0-25.0 µmol/ L). She was subsequently commenced on copper replacement via intravenous additrace and total parenteral nutrition as intravenous copper was difficult to obtain in Republic of Ireland. Following receipt of Additrace, Ms A's neutrophil count normalised, and her haemoglobin rose rapidly with corresponding reticulocytosis. Her platelet count remained low in the context of infection but it subsequently improved. Unfortunately, to date, there has been poor recovery of her neuropathy.

Conclusion:
This case highlights the importance of consideration and early recognition of copper deficiency and prompt initiation of copper replacement in patients presenting with unexplained cytopenias and/or neuropathies to prevent severe and potentially irreversible consequences. This individual was found to have had very poor nutritional intake over a long number of months prior to the documented low copper level and other nutritional deficiencies may have contributed. The challenge of obtaining intravenous copper replacement in Ireland is also highlighted.

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BING–NEEL SYNDROME WITH CHRONIC LYMPHOCYTIC LEUKAEMIA: A CASE OF COMPOSITE LYMPHOMA

K Chmielowiec[1], A Abladey[2], K Clarke[1], M Catherwood[2], M Moore[3], D Donaldson [1]
[1]Department of Clinical Haematology, Belfast City Hospital, Belfast, Northern Ireland
[2]Regional Molecular Diagnostics Service, Belfast City Hospital, Belfast, Northern Ireland
[3]Histopathology Department, Royal Victoria Hospital, Belfast, Northern Ireland

We are presenting an unusual case of co-existing Bing-Neel syndrome (BNS)/lymphoplasmacytic lymphoma (LPL) and chronic lymphocytic leukaemia or biclonal composite lymphoma, in a patient with a long history of an underlying neurological disorder. Although three previous cases of composite LPL and CLL have been published, this is the first where LPL presentation includes BNS. As such, it has presented a diagnostic, investigative and management challenge requiring additional investigations and collaboration with national experts to formulate an appropriate and individualized treatment plan. This patient had been under investigation with neurology for a 19-year history of essential tremor with dystonic features in his upper limbs. Over the course of 2 years, the patient's symptoms continued to progress resulting in significant deterioration in mobility, as a result patient underwent biochemical investigations that identified an IgM kappa paraprotein of 21 g/L and free kappa light chains of 199 mg/L with a kappa:lambda ratio of 10.94. Differential diagnoses included lymphoma (most likely LPL/WM) with associated CNS involvement in the form of BNS, paraneoplastic manifestation of possible malignancy or an incidental finding unrelated to his neurological symptoms. Initial investigations included computed tomography (CT) of the neck, chest, abdomen, and pelvis, magnetic resonance imaging (MRI) of head, whole spine and pelvis, bone marrow (BM) aspirate and trephine (BMT), cerebrospinal fluid (CSF) analysis, and lymph node (LN) biopsy.

The patient was mildly anaemic with a haemoglobin of 127 g/L with no other cytopenias; lactate dehydrogenase (LDH) and calcium were normal. CT of the neck, chest, abdomen, and pelvis had shown widespread lymphadenopathy, both above and below the diaphragm without splenomegaly. Initial MRI showed bilateral symmetrical thickening of multiple cranial nerves and postganglionic, lumbar and brachial nerve roots as well as cauda equina nerve roots. Flow cytometry of the BM identified an infiltrate of CD19+ B and two distinct clonal populations. Peripheral blood (PB) morphology was unremarkable and flow cytometry confirmed two distinct clonal populations identical to those in BM. Flow cytometry on the CSF sample identified the CD5−/CD10− kappa + population only. BMT histology showed normal trilineage haematopoiesis, several nodules co-expressing CD23 and the lymphoid enhancer binding factor 1 (LEF1) in B cells, which appeared to also stain positively with CD5 by immunohistochemistry. BMT also identified a co-existing second nodule, which was negative for CD5, CD23, and LEF1. Examination of the LN showed numerous small mature lymphocytes and flow cytometry again identified two distinct clonal populations. Molecular analyses for mutational status of *MYD88* L265P and the tumour suppressor gene *TP53* were performed on both BM and CSF samples, with the *MYD88* mutation present in both samples. BM and CSF were negative for *TP53* mutation.

The patient was discussed at regional lymphoma MDM and with a national expert at University College London. CLL was diagnosed concurrently with BNS at Binet stage B; however, did not meet criteria for treatment. He was treated with four cycles of modified MATRIX (methotrexate, cytarabine, rituximab but no thiopeta) chemotherapy regiment this achieved a very good partial response (VGPR) followed by consolidation with autologous stem cell transplant. More intensive treatment was chosen due to aggressive nature of initial presentation with plans for in first remission. This was thought to be preferable with ibrutinib reserved for relapsed disease, especially in view of its CNS penetrance.

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Rosai-Dorfman-Destombes Disease: A Rare Diagnosis in a Child with Massive Cervical Adenopathy.

J Harford[1], L Feeley[2], D Mullane[3], J Pears[4], R Leahy[5], C Ryan[1]
[1]Department of Paediatric Haematology, Mercy University Hospital, Cork, Ireland
[2]Department of Histopathology, Cork University Hospital, Cork, Ireland
[3]Department of Paediatric Medicine, Cork University Hospital, Cork, Ireland
[4]Department of Paediatric Oncology, Children's Health Ireland, Crumlin, Dublin, Ireland
[5]Department of Paediatric Immunology, Children's Health Ireland, Crumlin, Dublin, Ireland

Rosai-Dorfman-Destombes disease (RDD) is a rare, non-Langerhan's cell histocytosis, primarily seen in children and young adults, with an estimated prevalence of 1:200,000 globally[1]. It is characterised by the accumulation of large histocytes within both lymphoid and extra-nodal tissues, and can occur in isolation, or in association with malignant or autoimmune disease. RDD is a heterogenous entity, classified within the R group of revised histiocytic disorders, by WHO 2023 classification[2]. Clinical presentation usually involves massive painless cervical adenopathy, and extra-nodal disease is seen in 40%, mainly with cutaneous manifestations[1]. Diagnosis and therapeutic strategies remain challenging, given its rarity and variable disease progression. In our case report, we discuss a case of RDD in a young girl, the diagnostic work up and treatment to date, while also exploring potential targeted therapies.

In May 2023, a 10-year-old girl presented to the paediatric service with a four-week history of bilateral, painless cervical lymphadenopathy, malaise, and sore throat, initially managed as an infectious aetiology. There was no resolution with empirical antimicrobial therapy. Clinical examination was notable for massive, painless bilateral cervical lymphadenopathy. CT Thorax at presentation demonstrated extensive bilateral cervical and mediastinal lymphadenopathy, with no evidence of airway compromise. Laboratory investigations revealed a persistent neutrophilia, elevated inflammatory markers, LDH within normal limits, and negative septic, viral and autoimmune screen. Screening for ALPs was negative, serum immunoglobulins normal, and T/ B cell subsets showed significant suppression.

Lymph node biopsy revealed massive expansion of the lymph node sinuses and sinusoids, loss of normal architecture, with a distinct population displaying abundant, markedly eosinophilic cytoplasm, with indistinct cytoplasmic borders, consistent with a histiocytic infiltrate. Phagocytosis of apoptotic bodies, and classic emperipolesis was present. Immunohistochemistry demonstrated strong CD45 and S100 positivity, with weak CD68 positivity, and MPR/CD1a negativity, consistent with a diagnosis of RDD. Mutational analysis for BRAF was negative, with further NRAS, KRAS, and MAP2K1 awaited.

She developed constitutional symptoms, and increasing massive cervical adenopathy, confluent in areas, and new inguinal adenopathy. There were no cutaneous nodules. Staging CT TAP, one month post initial presentation to hospital, demonstrated progression, with extensive cervical, thoracic, pelvic and inguinal adenopathy, and asymmetric narrowing of the oropharynx by enlarged, conglomerate tonsillar lymphadenopathy, all FDG avid on PET. Following multidisciplinary discussion, we proceeded initially with high dose corticosteroid therapy, with tumour lysis prophylaxis on induction. Clinically, the patient has responded promptly to high dose steroids, with significant resolution of the adenopathy and symptoms, and will be monitored closely through steroid taper.

In summary, Rosai-Dorfman-Destombe's Disease presents a significant challenge both in terms of diagnosis and clinical management. At present, the exact standard of care therapy remains unclear, although clinical surveillance, corticosteroid therapy, systemic chemotherapy and immunomodulation have all been used in selected cases. With advances in molecular studies, the advent of targeted molecular agents may hold promise, with the potential for BRAF and MEK signalling pathway inhibitors in multi-refractory cases[1].

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Paediatric Non-Hodgkin's Lymphoma presenting in the oral cavity: a brief review of the literature and case series.

A Allen, K FitzGerald, Y MacAuley, A Cant, D Murray, A Beattie, A Malone, O Smith, L Storey, A O'Marcaigh, N Barrett, P McCarthy, P Evans, V Broderick
[1]Department of Haematology, CHI, Dublin, Ireland
[2]Department of Dentistry , CHI, Dublin, Ireland

Introduction: Non-Hodgkin's lymphoma (NHL) constitutes a diverse spectrum of lymphoid malignancies, with a minor subset manifesting within the oral cavity in the pediatric population. We present three cases from our centre and examine the current literature on this rare entity. Paediatric NHL comprises distinct subtypes, with Burkitt and Burkitt-like lymphomas, precursor T-cell lymphomas, diffuse large B-cell lymphomas, and anaplastic large cell lymphomas being the most common subtypes(1). Although rare, oral NHL constitutes about 2% to 3% of cases (2). The scarcity of reported cases of NHL with dental and intra-oral presentations, makes understanding its biological, behavior and treatment options challenging.

Case 1: An 11 year old male patient, presented to community dentist with left mandibular dental pain, associated with a loose primary molar. An uncomplicated extraction of the tooth was performed, however, he experienced persistent left jaw pain and development of an intra- oral swelling at the extraction site over the next three weeks. A biopsy of the mass was performed by an oral surgeon under local anaesthesia and found to be consistent with ALK+ anaplastic large cell lymphoma. Staging with CT TAP demonstrated locally advanced disease with invasion of left maxilla and left mandible. There was no evidence of involvement on bone marrow aspirate or CSF analysis. The patient was treated as per COG ANHL 12P1 protocol with complete response.

Case 2: A 12 year old male patient presented to his local hospital with a week-long history of jaw pain, paraesthesia in the distribution of the right mental nerve, loose permanent teeth and severe headache. A blood film was leucoerythroblastic with associated hypercalcemia and elevated LDH. Dental examination revealed pathologic mobility of his teeth. An orthopantomogram (OPG) revealed generalised increased radiolucency of the maxillary and mandibular alveolar processes, with "floating teeth". MRI imaging showed extensive uniform diffuse osseous enhancement throughout the visualized skeleton and dural enhancement. A bone marrow biopsy was consistent with Burkitt's lymphoma. The patient was treated as per inter-BNHL protocol with complete response. His treatment was complicated by grade 4 mucositis for which he received intra-oral and extra-oral photo-biomodulation therapy and opiate analgesia.

Case 3: An 11 year old male patient with a four week history ofincreased mobility of all his teeth, paresthesia of his lower lip and jaw painwas referredto a craniofacial surgeon.An OPG was performed which showed "floating teeth".He required extraction of all his mandibular teethand an intra-oral biopsy of soft tissue mass, which was consistent with Burkitt's Lymphoma. CT imaging showed local involvement of the mandible, nasopharynx, skull vault, appendicular skeleton and spinal cord compression at T7. The patient was treated as per inter-BNHL protocol with complete response. His therapy was complicated by grade 4 mucositismanaged in part by photo-biomodulation therapy. Post completion of therapy, he has hada supported dental prosthesis placed.

Conclusion: These cases illustrate the important role of the dental team in the haemato-oncology service, through the detection, diagnosis, provision of supportive oral care and restoration post treatment of patients with haematological malignancies.

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A rare case of polycythaemia vera driven by the JAK2 R564L mutation

A AL-BAGHDADI[1], A NEE[1]
[1]Haemtology, University hospital Limerick , Limerick ,

Polycythaemia vera (PV) is a myeloproliferative neoplasm driven in over 95% of cases by the gain-of-function JAK2 V617F mutation, and in almost all other cases by mutations in JAK2 exon12.

Diagnostic criteria for PV include an elevated haemoglobin concentration (Hb) of >16.5g/dL or haematocrit (Hct) >49% for males, or Hb >16.0g/dL or Hct >48% for females, the presence of a JAK2 mutation, and either a bone marrow biopsy showing hypercellularity and panmyelosis, or a subnormal serum erythropoietin.[1]

Here, we describe a case of polycythaemia vera driven by an uncommon JAK2 mutation on exon 13.

Our patient was referred to us in 2020 at the age of 55 by the Renal service in University Hospital Limerick with a Hb of 17.5g/dL and Hct of 51.8%, with the remaining full blood count parameters falling within reference range. He had a history of polycystic kidney disease, hypertension, dyslipidaemia, a mildly aneurysmal ascending aorta and mild concentric left ventricular hypertrophy on echocardiogram. He had no history of smoking or any respiratory comorbidities. He tested negative for the JAK2 V617F and exon 12 mutations known to drive the vast majority of cases of polycythaemia vera. His serum erythropoietin (Epo) was subnormal at 1.5mIU/ml (reference range 2.6-18.5). He proceeded to have further mutation testing by next generation sequencing (NGS) which identified a heterozygous JAK2 R564L variant [c.1691G>T; p. (Arg564Leu)].

Based on his laboratory parameters, the presence of a JAK2 mutation and subnormal serum Epo, a diagnosis of PV was made. As he was under 60 years of age, with no thrombotic history, his disease was categorised as low-risk and managed with once-daily low-dose aspirin and venesection to a target Hct of <45%.

We performed a literature review using PubMed and found only two publications describing the JAK2 R564L mutation in myeloproliferative neoplasms (MPNs). The first publication by Ma et al. in 2009 reported on reverse transcription-PCR analysis of peripheral blood RNA of approximately 20,000 cases of MPNs[2]. These analyses identified three cases of MPN with the JAK2 564L mutation, but did not detail the clinical phenotype.

The second publication by Benton et al. in 2019 reported on NGS of the coding region of JAK2 and 27 other genes on bone marrow DNA in patients with MPNs, MPNs transformed to acute myeloid leukaemia (AML) and de novo AML[3]. Analysis was performed on 2154 patients and the JAK2 R564L mutation was identified in one patient with secondary AML, transformed from an MPN, with acquisition of the mutation only becoming detectable at time of leukemic transformation.

Our case details a case of polycythaemia vera driven by the rare JAK2 R564L mutation. Our patient's phenotype of an uncomplicated low-risk polycythaemia vera disease course has, as yet, not been described elsewhere. Clearly there is paucity of available data on how best to manage cases with rarer JAK2 mutations. However, our patient's clinical course has been uncomplicated and is being managed as low-risk disease. Further studies into this mutation are required to determine its impact on disease phenotype and prognosis.

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VIRUS-INDUCED ENDOTHELIAL CELL 'MEMORY' ENHANCES PRO-INFLAMMATORY AND PRO-THROMBOTIC ACTIVITY TO SUBSEQUENT STIMULATION

Z Wang[1,3], AM Rehill[1,2], G Leon[1,2], P Deng[1,3], RJS Preston[1,2]
[1]Irish Centre for Vascular Biology, Royal College of Surgeons in Ireland, Dublin, Ireland
[2]National Children's Research Centre, Our Lady's Children's Hospital Crumlin, Dublin, Ireland
[3]Center for Drug Metabolism and Pharmacokinetics, Soochow University, Suzhou, China

Background: Viral infection, particularly COVID-19, is associated with prolonged endotheliopathy, characterised by enhanced blood vessel pro-inflammatory and prothrombotic activity. Nevertheless, how endothelial cells remain perturbed long after infection has been resolved is currently unknown. 'Trained immunity' is a non-specific immune memory in which innate immune cells exhibit exacerbated pro-inflammatory responses after prior exposure to pathogenic or inflammatory challenges. More recently, evidence has emerged that non-immune cells can also be 'trained' to confer long-term deleterious properties, which may have implications for chronic cardiovascular or inflammatory disease progression. Specifically, we hypothesised that virus-mediated 'trained immunity' in endothelial cells could generate a heightened pro-inflammatory, pro-adhesive endothelial cell phenotype when re-exposed to pro-inflammatory stimuli.

Aim: To investigate whether endothelial cells previously exposed to a virus mimetic retain cellular memory of exposure that promotes subsequent endothelial cell inflammation and immune cell adhesion.

Methods: Human umbilical vein endothelial cells (HUVECs) were trained with polyIC, a viral synthetic analogue, then washed and left unperturbed for 3 days, before restimulation with pro-inflammatory agonists, Pam3CSK4, LPS or TNFa. HUVECs gene expression and function were analysed by RT-qPCR, ELISA and flow cytometry.

Results: Surprisingly, polyIC-exposed endothelial cells exhibited enhanced pro-inflammatory and cell adhesion gene expression compared to cells not previously exposed to polyIC. In particular, polyIC-trained endothelial cells exhibited significantly increased PAM3CSK4-induced pro-inflammatory cytokine IL-6 and IL-8 gene expression and release. Furthermore, polyIC-trained endothelial cells exhibited significantly greater expression of surface adhesion molecules ICAM-1 and VCAM-1, respectively, compared to Pam3CSK4-treated cells alone, demonstrating that prior polyIC-mediated endothelial cell training enhances the generation of a more pro-inflammatory, pro-adhesive surface. This phenomenon was not unique to Pam3CSK4 re-stimulation, as similar results were observed in the presence of other pro-inflammatory agents (LPS, TNFa).

Conclusions: This study demonstrates, for the first time, that endothelial cells can retain 'memory' of prior infection that promotes a subsequent exaggerated pro-inflammatory and pro-adhesive response upon restimulation. Targeted intervention in the pathways underlying endothelial cell memory represents a potential therapeutic target to mitigate persistent endotheliopathy occurring post-infection.

THE RELATIONSHIP BETWEEN LOW VON WILLEBRAND FACTOR, TYPE 1 VON WILLEBRAND DISEASE AND AGEING - NOVEL INSIGHTS FROM THE LOVIC AND WIN COHORT STUDIES

F Atiq[1, 2], R Blok[2], CB van Kwawegen[2], **D Doherty[1]**, M Lavin[1, 3], JG van der Bom[4], NM O'Connell[3], J de Meris[5], K Ryan[3], SEM Schols[6], M Byrne[3], FCJI Heubel-Moenen[7], KPM van Galen[8], RJS Preston[1], CJ Fijnvandraat[9], RI Baker[10,11], K Meijer[12], P James[13], J Di Paola[14], HCJ Eikenboom[15]

[1]Irish Centre for Vascular Biology, Royal College of Surgeons in Ireland, Dublin, [2]Department of Haematology, Erasmus University Medical Center-Erasmus MC, Rotterdam, The Netherlands
[3]National Coagulation Centre, St James's Hospital, Dublin, [4]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands, [5]Netherlands Hemophilia Society, Leiden, The Netherlands, [6]Department of Hematology, Radboud university medical center, Nijmegen, The Netherlands, [7]Department of Hematology, Maastricht University Medical Center, Maastricht, The Netherlands, [8]Van Creveldkliniek, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands, [9]Department of Pediatric Hematology, Emma Children's Hospital, Amsterdam University Medical Centres, University , Amsterdam, The Netherlands, [10]Western Australia Centre for Thrombosis and Haemostasis, Perth Blood Institute, Murdoch University, Perth, Australia,[11]Irish-Australian Blood Collaborative (IABC) Network, [12]Department of Hematology, University Medical Center Groningen, Groningen, The Netherlands, [13]Department of Medicine, Queen's University, Kingston, Canada, [14]Department of Pediatrics, School of Medicine, Washington University in St. Louis, St. Louis, USA, [15]Department of Internal Medicine, Division of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands

Introduction: For many years, there has been debate about how to optimally diagnose type 1 VWD. Initial guidelines proposed that only individuals with VWF levels < 30 IU/dL should be diagnosed with 'type 1 VWD'. This was revised in recent ASH/ISTH/WFH/NHF panel which recommended that patients with a significant bleeding history and plasma VWF of 30-50 IU/dL should also be diagnosed with type 1 VWD, as opposed to the discrete 'Low VWF' entity proposed previously. In this study, we investigated whether Low VWF is a discrete clinical entity, or whether it is instead part of an age-dependent type 1 VWD evolving phenotype.

Methods: We utilized datasets from two renowned national cohort studies - the Low VWF in Ireland Cohort (LoVIC) and Willebrand in the Netherlands (WiN) studies. In the LoVIC study, patients had historically lowest VWF levels of 30-50 IU/dL. In the WiN study, patients had either a personal bleeding history or positive family history, combined with historically lowest VWF levels ≤ 30 IU/dL.
The FVIII:C/VWF:Ag ratio was used to assess the synthesis/secretion of VWF and the VWFpp/VWF:Ag ratio was used to assess the clearance of VWF.

Results: In total, 565 patients were included (403 WiN patients with type 1 VWD and 162 LoVIC patients with Low VWF). Mean age at diagnosis was significantly higher in the LoVIC cohort compared to the three WiN subgroups (32.5 years versus 23.3 years, 26.5 years and 25 years respectively; p<0.001). Conversely, there was no difference in age at time of enrollment into both studies (p=0.532). Among the total WiN cohort (with initial VWF levels < 30 IU/dL), 47% of subjects (n=188) had VWF levels that remained < 30 IU/dL despite advancing age. Conversely, 30% of type 1 VWD patients (n=121) increased their plasma VWF levels into the Low VWF range (30-50 IU/dL) over time, whereas 23% (n=94) had age-dependent increments that led to complete normalization in VWF levels > 50 IU/dL. Similarly, 39% (n=63) of patients from the LoVIC study had normalization of VWF levels over time.

Crucially, we observed that VWF:Ag in Low VWF patients clearly overlapped with those in normalized (> 50 IU/dL) type 1 VWD subjects, indicating that the LoVIC cohort is a subgroup within the WiN normalized subgroup. Indeed, multiple regression analysis confirmed that plasma VWF:Ag in the LoVIC cohort and the WiN normalized (> 50 IU/dL) subgroup would have not been different had they been diagnosed at the same age (difference of β=0.00 (95% CI -0.03 to 0.04)).

Consistently, no difference in prevalence of *VWF* mutation (36.4% vs 22.6% respectively, p=1.000), FVIII:C/VWF:Ag ratio (1.24 ±0.24 vs 1.46 ±0.27 respectively, p=0.444) or VWFpp/VWF:Ag ratio (1.36 ±0.99 vs 1.75 ±0.38 respectively, p=1.000) was found between LoVIC and normalized WiN patients.

Conclusion
Our findings clearly demonstrate that Low VWF does not constitute a discrete clinical or pathological entity. Rather, it is part of an age-dependent type 1 VWD evolving phenotype. This study has direct consequences for VWD diagnosis and for patients with low VWF/type 1 VWD.

EXPLORING THE METABOLIC PROFILING OF MULTIPLE MYELOMA: IMPLICATIONS FOR TARGETED THERAPIES

LDM DI MARTINO[1], SG GILMORE[1], YW WANG[1], SG GLAVEY[2], TNC NI CHONGHAILE[1]
[1]1. Department of Physiology and Medical Physics, Royal College of Surgeons in Ireland, Dublin,
[2]2. Department of Haematology, Beaumont Hospital, Dublin,

Introduction

Multiple myeloma (MM) is a hematologic malignancy characterised by the clonal expansion of plasma cells (PCs) within the bone marrow (BM). Despite significant advances in treatment options, most of elderly MM patients experience relapse and resistance. A better understanding of the unique vulnerabilities faced by older MM patients is essential to improve outcomes for these patients. The bone marrow microenvironment is critical for MM progression and undergoes age-related changes, which may impact MM cell resistance to therapy. In particular, MM cells undergo substantial alterations in their metabolism to meet the high energy and biosynthetic demands associated with uncontrolled proliferation and survival within the BM microenvironment. Therefore, our project aims to study the complex interaction between BM and MM cells by profiling the metabolic phenotype in both cell lines and MM patient samples.

Methods

To understand the metabolic dependencies and vulnerabilities of MM patient samples we assessed the single cell metabolism using SCENITH profiling. This innovative technology, performed at flow cytometry, uses protein translation as a functional read-out of metabolism following 2-deoxy-D-glucose (2DG) treatment to inhibit glycolysis or oligomycin to inhibit OXPHOS. Firstly, to study how the BM microenvironment alters the metabolic profile of MM, we co-cultured MM cell lines (MM1S and JJN3) with bone-marrow stromal cells (BMSCs) and we used SCENITH and Seahorse assays to ensure they are comparable. Using the Seahorse XFe96 we measured glycolysis as the extra cellular acidification rate along with the oxygen consumption rate (OXPHOS). Glycolysis, glycolytic capacity, and glycolytic reserve have been calculated from the ECAR measurements.

Results and Conclusion

Our preliminary data showed that *in vitro* MM cells following co-culture with bone marrow fibroblasts shift their metabolism from a high energy demanding status using mitochondria respiration to a glycolytic based rapid ATP production. More specifically, MM1S cells reduced their glycolytic capacity when co-cultured with BMSCs as compared to MM1S cultured alone. This phenotype was further confirmed using SCENITH assay, which early results showed that in MM1S co-cultured with BMSCs there was a more mitochondrial dependency compared to MM1S cultured alone. These preliminary data suggested that the results of Seahorse assay and SCENITH profiling were highly comparable. Furthermore, in order to analyse the metabolic phenotype of primary plasma cells obtained from the bone marrow of MM patients we used the *in vitro*-optimized SCENITH conditions to profiled them. The results showed that primary samples reliant on BCL-2 for survival are more sensitive to oligomycin inhibition leading us to hypothesize a possible link between oxidative phosphorylation (OXPHOS) and BCL-2 dependency within MM cells, unveiling new avenues for targeted therapies. Given these early results, it will be interesting to investigate the impact of BM microenvironment on MM cells with respect to anti-apoptotic dependency. By using BH3 profiling on MM cells in the co-culture system we will able to correlate the anti-apoptotic dependency and metabolic vulnerabilities.

In conclusion, by elucidating the metabolic dependencies of MM samples, these assays hold the potential to identify metabolic vulnerabilities in order to develop personalised targeted therapies.

EXTRACELLULAR VESICLE-MEDIATED MOLECULAR MECHANISMS IN THE PROGRESSION OF MULTIPLE MYELOMA.

C Wylie[1], D Malinova[2], L Crawford[1]
[1]Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, Belfast, Northern Ireland
[2]Wellcome Wolfson Institute for Experimental Medicine, Queen's University Belfast, Belfast, Northern Ireland

Introduction/Background:
Despite treatment advances, MM remains incurable due to inevitable relapse and drug resistance (DR) to available therapeutics, highlighting the necessity for identification of new therapeutic targets. Complex interactions within the BM microenvironment (BMM) contribute to DR and extracellular vesicles have been recently identified as a key player in establishing a resistant phenotype. Extracellular vesicles are formed by the majority of cell types and are utilised in local and systemic cell-to-cell communication. A genome wide CRISPR screen identified extracellular vesicle biogenesis as an essential pathway for MM. This research hypothesises that targeting extracellular vesicle biogenesis will explicate their role in DR,and could aid in sensitisation of resistant MM cell lines.

Materials and methods:
Two MM cell line models (AMO-1 and RPMI-8266) reflecting proteasome inhibitor (PI) sensitive and resistant disease were used; both parental cell lines have isogenic cell lines with bortezomib resistance (BR) and carfilzomib resistance (CR). AMO-1 and RPMI parental and resistant cell lines were cultured in RPMI supplemented with 10% extracellular vesicle-free FCS and 5% Pen-Strep for 24H. To isolate extracellular vesicles, cells were removed, and media centrifuged at 10,000g for 30 minutes to remove cell debris. Conditioned media was concentrated to ~1mL (10,000 MWCO, Merck, Z614661-12EA). Extracellular vesicles were pelleted utilising the Total Exosome Isolation Kit from culture media (Thermo Fisher). Pharmacological inhibition of extracellular vesicle biogenesis was conducted using single agent 10µM GW4869 (Sigma). Proteasome inhibitors were used at a concentration of 1.25 or 2.5nM. Cell viability was measured using Cell Titer Glo (Promega).

Results:
Treatment of MM cell lines with the extracellular vesicle biogenesis inhibitor GW4869 led to a dose-dependent decrease in viability. PI resistant AMO-1 cell lines displayed increased sensitivity to GW4896 with a half-maximal inhibitory concentration (IC50) of approximately 5µM by 72H in comparison to 7µM in the PI sensitive cell line, suggesting that extracellular vesicles may contribute to the resistant phenotype. Combination studies utilising GW4869 and PIs demonstrated a synergistic effect in the AMO-1 BR cell line with combination index (CI) values between 0.495 – 0.788, while there was no synergy observed in PI-sensitive AMO-1 or AMO-1 CR cells (CI >). Analysis of publicly available patient data found that MM patients at relapse with a higher expression of some extracellular vesicle biogenesis genes had a poorer prognosis. Extracellular vesicles have been isolated from cell lines and confirmed via Western blot using extracellular vesicle markers such as TSG101, HSP70, Alix, and CD9. Future studies will quantify and profile the RNA and protein content of extracellular vesicles derived from sensitive vs resistant cell lines to elucidate targetable pathways and biomarkers which can be translated to patients.

Conclusions:
The differential response of PI resistant cell lines to GW4869 suggests a role for extracellular vesicle biogenesis in the development of drug resistance. Characterisation of extracellular vesicle cargo in PI resistant and sensitive cells could identify key biomarkers and provide a new molecular target to overcome resistance.

Clinical Features and Outcomes of Adults Diagnosed with Haemophagocytic Lymphohistiocytosis (HLH) over a Five Year Period from 2018 – 2023 in a Tertiary Referral Hospital : A Single Centre Study

CJ Jennings[1], K Fadalla[1,2], K Murphy[1,2], C Andrews[1,2], M Coyne[1,2], DG Connaghan[1,2], J Fitzgerald[1,2], M Power[1,2], N Swan[2,3], E Feeney[2,5], E Molloy[2,6], R Hughes[2,7], O Solymus[2,8], C Collins[2,4], J Wade[1], L Smyth[1,2]
[1]Department of Haematology, St Vincents University Hospital, Dublin, [2]School of Medicine, University College Dublin, Dublin, [3]Histopathology Department, St Vincents University Hospital, Dublin, [4]Department of Radiology, St Vincents University Hospital, Dublin, [5]Infectious Disease Department, St Vincents University Hospital, Dublin, [6]Department of Rheumatology, St Vincents University Hospital, Dublin, [7]Department of Dermatology, St Vincents University Hospital, Dublin, [8]Department of Anaesthetics, St Vincents University Hospital, Dublin,

Introduction: Haemophagocytic Lymphohistiocytosis (HLH) is a disorder of uncontrolled immune activation, characterised by clinical signs and symptoms of extreme inflammation (1). HLH is classified as either primary (familial) or secondary (acquired), with primary HLH predominantly presenting in children and secondary HLH occurring in the setting of an inciting event such as infection, rheumatological disorders or malignancy (2). HLH has been attracting increasing attention over recent years due to a rise in incidence of this potentially devastating disorder, which may be due to improved recognition by clinicians but also an increasing incidence of associated “drivers” such as haematological malignancies (3)

Aims: The aim of this retrospective study was to evaluate clinical and biological characteristics of adult HLH patients, diagnosed and treated in a tertiary referral hospital over a five-year period between 2018 -2023.

Methods: Patients were diagnosed with HLH using the HLH-2004 diagnostic criteria and HScore. The HLH-2004 is defined by either a confirmed molecular study, or a patient fulfilling 5 out of 8 diagnostic criteria which include: fever, splenomegaly, cytopenias, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis visualised in bone marrow/spleen/lymph node biopsy, low/absent NK cell activity, hyperferritinemia, or raised sCD25. The HScore, which comprises additional diagnostic features including hyperbilirubinemia, hepatomegaly, transaminitis, raised LDH and D-dimers, was also included as part of the overall evaluation to distinguish a diagnosis of HLH.

Results: Twelve cases of HLH were identified during the study period, confirmed by HScore and HLH-2004 diagnostic criteria. Patients ranged in age from 19 to 49, with seventy-five of cases (9/12) occurring in men. Fifty percent (6/12) of patients had known underlying immunosuppression, including adult onset stills disease, Crohns disease, psoriatic arthritis, mixed connective tissue disease and Kartageners. All cases (12/12) were secondary with a wide range of primary drivers identified. Infectious drivers were identified in 58% (n=7) including EBV (4/12), Dengue Virus (1/12), Murine Typhus (1/12) and Leishmaniasis Donovani Complex (1/12). Five cases had a malignant driver identified at presentation or as a paraneoplastic phenomenon, including Peripheral T-Cell Lymphoma (n=1), Nodular Lymphocyte-Predominant Hodgkin Lymphoma (n=1), Histiocytic Sarcoma (n=1), T cell / Histiocyte -rich large B-cell lymphoma (n=1) and Hodgkin lymphoma (n=1). Patients were treated with modified HLH-94 protocol in 33% (n=4). Remaining patients were treated with combination of anticytokine therapy and therapy targeting primary driver. Seventy-five percent (n=9) of patients were alive post HLH treatment.

Conclusion: We identified 12 cases of HLH in our Centre over a 5-year period. Primary drivers in our cohort of patients included infection (n=7; 58%), haematological malignancy (n=5; 42%) and underlying rheumatological disorders (n=4; 33%), in keeping with previous published reports (4). Preceding immunosuppression was present in half the cohort. There was no standard management for all patients and treatment varied based on the HLH trigger, functional capacity and treating clinicians' preference. The 30-day mortality from time of HLH diagnosis in our cohort was 25%. This study highlights the importance of recognition of HLH and its driver, thus facilitating early targeted treatment, with the ultimate aim of improving overall survival in patients with this potentially devastating disorder.

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AUDIT ON THE SCREENING AND MANAGEMENT OF LATE AND LONG-TERM CONSEQUENCES OF MYELOMA AND ITS TREATMENT.

K Sweeney[1], P Copeland[1], G Brown[1], A Niblock[1,2]
[1]Haematology department, Antrim Area Hospital, N. Ireland
[2]School of Medicine, Ulster University, N. Ireland

Advances in myeloma treatment have resulted in improved outcomes and prognosis for patients, with some now living with their condition for up to 20 years (National Institute for Health and Care Excellence, 2022). However complications from the disease, alongside toxicity from multiple lines of therapy, further impacted by increasing frailty, comorbidities and the psychosocial impact of living with myeloma, puts patients at risk of specific long-term consequences (Snowden *et al.*, 2017).

Research is limited in relation to 'late effects' of myeloma, however there are studies that demonstrate myeloma patients face a wide range of long-term consequences, including cardiovascular and pulmonary toxicity, skeletal related events, renal failure, endocrine and nutritional abnormalities, increased susceptibility to infections, secondary malignancies, and psychosocial concerns.

It is recommended that screening to identify long-term consequences and allow for appropriate management is established. The British Society for Haematology (BSH) published 'Guidelines for screening and management of late and long-term consequences of myeloma and its treatment' (Snowden et al., 2017). However some studies suggest that levels of adherence to such guidance is suboptimal (Thompson *et al*., 2023; George *et al.*, 2020; Giri *et al*., 2019; Olszewski *et al*., 2019; Alemu *et al*., 2017).

An audit tool was developed, which was adapted from an existing tool published by the Royal College of Pathologists (2017), to assess compliance with BSH recommendations within a sample of 30 patients, in the Northern Health and Social Care, Northern Ireland. Following baseline audit, a screening checklist was developed and completed with each patient, to be used as an aide memoire for implementation of the screening recommendations. A re-audit, after three months was carried out to assess the effectiveness of the checklist.

Audit findings demonstrated several areas of good baseline practice: appropriate vaccinations; herpes prophylaxis; education of infection risk, dental assessment; regular bisphosphonate, calcium and vitamin D supplementation; and holistic needs assessments. However, others areas demonstrated gaps in practice including: monitoring of lipids; HBA1C; NT-proBNP; weight, height, BMI; endocrine screening post-transplant; calcium, vitamin D and parathyroid hormone in chronic kidney disease; education regarding secondary malignancy, and offers of a geriatric assessment in individuals aged over 75.

Findings from re-audit, after three months, following implementation of the screening tool, demonstrated that whilst offers of a geriatric assessment for appropriate patients still remains a gap in practice, all other remaining standards demonstrated high levels of compliance to the guidance, now ranging between 80 to 100% compliance.

Gaps were identified in meeting the recommendations for screening and management of long-term consequences of myeloma, however, utilisation of a screening checklist, as an aide memoire, has the potential to significantly increase compliance with recommendations. Early recognition of potentially reversible or manageable abnormities alongside education of patients and professionals on the importance of this key element of myeloma care is crucial to help improve outcomes for these individuals, and should be embedded into routine practice when caring for this patient group.

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WHAT IS THE IMPACT OF A MINDFULNESS-BASED INTERVENTION ON DEPRESSION AND BIOPSYCHOSOCIAL VARIABLES AMONG HAEMATOPOIETIC STEM CELL TRANSPLANT PATIENTS DURING HOSPITALISATION.

M Roche
[1]Denis Burkitt Ward , RCSI, Dublin 2,

Aim: To determine the impact of a mindfulness-based intervention on depression and biopsychosocial variables among haematopoietic stem cell transplant patients during hospitalisation.

Background: Hematopoietic stem cell transplant is an entrenched potentially lifesaving treatment option for haematological malignancies and bone marrow disorders. Psychological distress is identified as a major side effect of this treatment. Depression being the most prevalent symptom. Anxiety, diminished quality of life, physiological symptoms, fatigue, and poor concentration are also commonly experienced. Debilitating physical side effects that develop also during lengthy hospital stays in isolation can exacerbate these. Research studies suggest using alternative mental health options such as mindfulness-based interventions to help psychological anguish. Mindfulness-based interventions can help to combat depression, anxiety and overall emotional turmoil encountered during haematopoietic stem cell transplant. As treatments advance and expand in transplant, research suggests so too must the level of psychological care.

Design: Systematic review using narrative analysis.

Data Sources: Databases CINAHL, Medline, PubMed, Embase and PsycInfo were all searched between 12th of December and 4th of January 2023 for available evidence to answer the aim. Relevant reference lists of studies and relevant journals were hand searched and grey literature also searched for potential studies in January 2023.

Review Methods: The PICO (Population, Intervention, Comparison, and Outcome) mnemonic was used to formulate the review question. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to conduct the review. Out of 238 potential studies identified, six studies met the inclusion criteria. Within the six studies, a total of 270 patients were examined at different timelines during the haematopoietic stem cell transplant process. Quality appraisal of the included studies was carried out by using the evidence-based librarian critical appraisal checklist.

Results: Psychological distress was noted in all six studies as a harrowing side effect of haematopoietic stem cell transplant. Significantly a reduction in depression levels was reported in all six studies after the use of a mindfulness-based intervention. Notably, the response was higher with healing touch ($p=0.039$), and interventions based on mindfulness-based stress reduction ($p=0.04$) than with relaxation therapy ($p=0.824$). Timing was significant, noting an increase in psychological suffering at various points in the transplant process, questioning the need for intervention sooner. Mixed results were noted on biopsychosocial variables. By using elements of mindfulness, some significant responses were reported with anxiety ($p= <.05$) and conflicting results for fatigue.

Conclusion: Haematopoietic stem cell transplant, though lifesaving clearly comes with psychological risks. Mindfulness-based interventions appear to play a crucial role in assisting to cope and improve depression and biopsychosocial variables. Given the different types of hematopoietic transplant and accompanied side effects, further research is warranted in this area.

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LYMPHOMA FOLLOW-UP IN THE MID-WEST: A 10 YEAR RETROSPECTIVE REVIEW TO GUIDE PRACTICE

C. Ryan, S. Baker, R.K. Gupta, H. O Leary, R. Clifford, D. Kelly, F. McKenna Beattie, A. Sheikhi, **F. Hackett**
Cancer Services University Hospital Limerick, University of Limerick

Background: Lymphoma survivors who have received curative intent treatment are currently followed up in medical and nurse- led clinics often indefinitely. Surveillance is important to detect relapse quickly and includes radiological imaging, biochemical analysis, physical examination and focused patient clinical history at defined time points. Due to limited evidence, the follow up protocol is at the discretion of the treating physician. The purpose of this study was to analyse the biochemical, radiological and clinical findings at relapse to evaluate their significance when detecting recurrence in patients post curative intent treatment. This information can be used to guide optimal follow up.

Aim:

1. To explore the clinical, biochemical and radiological presentation of patients with Diffuse Large B-cell Lymphoma (DLBCL) & Classical Hodgkin Lymphoma (CHL) treated with curative intent at the point of recurrence from first remission.
2. To identify the number of these patients attending for follow up, the percentage who recurred, the time to recurrence and if recurrence was detected at scheduled follow up.

Methods: Ethical approval was sought and granted from the Research Ethics Committee, University Hospital Limerick. A retrospective review of all patients with DLBCL and CHL who attended the Mid-Western cancer Centre over a 10 year period on a surveillance schedule was performed. Patients treated with curative intent treatment who achieved remission and subsequently relapsed were identified. Data collected related to diagnosis, treatment type, confirmation of remission and recurrence event information. Statistical analysis was performed.

Results: There was a substantial number of patients with DLBCL & CHL treated with curative intent on a surveillance programme (N=226). Small numbers of this patient group relapsed (17% DLBCL and 7% CHL). The majority recurred between scheduled visits (93%). Clinically, the majority reported a symptom at recurrence (97%). Radiologically, a small number showed abnormality on CXR at recurrence (10%). Biochemically, 47% had an abnormal ESR and 70% had an abnormal LDH at recurrence. The majority relapsed within 5 years (67% DLBCL & 66% CHL).

Conclusions: The benefit of routine follow-up, particularly longer term follow up > 5 years, for detecting recurrence is not supported. The resources utilised for routine follow-up must be balanced with the requirement for access for new patients and acute relapses.

Stratified follow-up with direct access for patients with red flag signs & symptoms is recommended. The multiple survivorship aspects of follow-up visits are acknowledged. Provision of an End of treatment Patient Treatment Summary and Care plan, Patient Passport and signposting to survivorship services should be considered in addition.

Next Steps: To present the study findings to Lymphoma clinicians at the Lymphoma Forum of Ireland Annual Conference & to establish a working group of Lymphoma nurses to develop survivorship services in collaboration with NCCP.

Empowering Care: Advanced Nurse Practitioner led Oral Anti-Cancer Medication (OAMs) clinics leading the way in expansion of cancer care.

GW Walpole, Sligo University Hospital, Sligo

Introduction/Background: The use of SACT (systemic anti-cancer treatment) has increased significantly over the past 10yrs, with a variety of new therapeutic treatments which has led to improved cure rates, long term remission rates, better quality of life and longer survival (DOH, NCS 2017-2026). NCRI (2019) reports have projected increase by 51-81% demand for treatments nationally up to 2045.
National Cancer Control Programme recommended a model of care for the delivery of OAMS in 2018 and the need was identified locally. The Advanced Nurse Practitioners (ANP's) are central in the role of delivery of a service that sees a shift from IV SACT to oral drug treatments. This abstract discusses the evolution of an established nurse-led OAM in a Saolta Hospital.

Materials and methods: A service needs analysis was undertaken in 2017, which led to the development of an ANP-led OAM clinic. This was developed in a step-wise approach involving the relevant stakeholders and policy makers to ensure quality, safety and value for the service and patients.
Under agreed guidelines, patients are seen by the same person in a designated clinic at an agreed time which providing continuity of care. While managing the delivery of oral treatment and its complex side effects, the ANP provides holistic care, emotional support and education to patients, while liaising with consultant/nurse colleagues and other allied health professionals.
The OAM nurse led clinic has developed from 4 drug regimens to now encompassing all oral SACT up to 10 regimens, each with varying complexities. This is in line with the shift seen from IV to oral in the haematology setting.

Results: Feedback expressed from the clinic has been very positive, patient report feeling safe and supported, they enjoy the continuity of care received under this type of clinic, reports of time-saving for patients means greater quality of life overall. In liaising with the larger Haematology service improved adherence and early detection of relapse have been observed.
The complexities of running an OAM clinic, are not without challenge. The clinic has grown 4 fold in numbers. No additional resources have been put in place which restricts the addition of new patients. Additionally adding to this burden is a dearth of space and administrative support which provides a demanding environment for the haematology staff and patient which despite its demand has further potential to grow.

Conclusion: OAMs have the same potential for risk as parenteral SACT in terms of treatment-related toxicities and potential for serious medication errors leading to patient harm.
The growth of oral anti-cancer medications and the evolution of ANP led clinics for haematology patients is a positive step forward in enhancing patient care and provides a cost effective, holistic, patient centred service. The provision of necessary additional supports is required and will further enhance this service.

The future of oral anti-cancer medicines and ANP led clinics is promising. As drug therapies expand and increase, ANP's will continue to play a pivotal role in managing this patient cohort.

MEDICAL/SCIENTIFIC DISPLAY POSTER BOARD LISTING

(Listed by Category and then alphabetically within each category. Where an author has multiple submissions in different categories, these are listed together under presenting author name)

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WALDENSTROM HAS A HIGHER THAN EXPECTED INCIDENCE OF ASYMPTOMATIC CRYOGLOBULIN BUT DESPITE CURRENT GUIDANCE CAN BE CLINICALLY SIGNIFICANT.

A Niblock[1,2], P Logue[3]
[1]Haematology department, Antrim Area Hospital, N. Ireland, [2]School of Medicine, Ulster University, N. Ireland, [3]Biochemistry department, Antrim Area Hospital, N. Ireland

Background: When monitoring a patient with Waldenstroms it was noted the IgM paraprotein was fluctuating between visits making their disease difficult to predict. Interrogation of the sample found the patient to have a type 1 cryoglobulin that was interfering with the quantification of the paraprotein. The patient had no clinical features of cryoglobulin. Some studies have found it in up to 20% of patients with Waldenstroms but they are generally asymptomatic[1]. Only 16% of patients with a type 1 cryoglobulin have symptoms. Worryingly this patients cryoglobulin was measured and when combined with the paraprotein in the cryoglobulin was 10g/l higher than reported. This raised concern and all patients with an IgM paraprotein were screened for the presence of a cryoglobulin.[2]

Method: Business Services Organisation Laboratory Information Management System was used to extract patients with IgM paraproteins from the 1/1/2021 to 1/1/2022. 41 Patients were obtained of which 18 were excluded.

23 patients were recruited with a statistical power of 87%. These 23 patients attended to have temperature-controlled venepuncture allowing assessment of paraprotein and cryoglobulin at body temperature. The samples were retested at room temperature and at 5^0C to demonstrate possible temperatures paraproteins are routinely checked in the laboratory.

Statistical analysis of results was carried out on MedCalc. Numerical variables were first assessed for normality distribution using Shapiro-Wilk test of normality. Wilcoxon signed-rank test was used as the data did not meet parametric assumptions. Kruskal-Wallis test was used to determine the significance between paraprotein levels and related IgM disease. Analysis of the temperature data was assessed using Prism GraphPad and results analysed using paired t-test.

Results: Waldenstrom was seen in 70% (n=16) of patients within this study, the remainder had IgM MGUS 13% (n=13), 9% (n=2) IgM related disease and 9% with other lymphomas (CLL, MZL). 26% of patients tested positive for cryoglobulinemia (n=6. Sub-analysis of the patients with a detectable cryoglobulin worryingly found 5 of 6 had an underestimation of their paraprotein. Although overall the change was not statistically significant (p=0.71) given sample population size, this did result in a clinical change in management for these patients. in the patients with cryoglobulins the difference in paraprotein quantification between the extreme of temperatures becomes more evident as the protein size increased.[2]

Clinical Implication: Current British Society of Haematology guidelines on the diagnosis of Waldenstrom macroglobulinaemia state if clinically indicated for example renal impairment, skin rash/ulceration consider testing for the presence of cryoglobulin.

The high frequently of cryoglobulins is interesting in IgM paraproteins and concerning given their potential to interfere with paraprotein quantification. Accurate paraproteins are crucial in the diagnosis of IgM disorders, monitoring disease progression, relapse, guiding treatment initiation and response.

A change in clinical practice would be appropriate initially to test all high IgM paraproteins at body temperature and allowing to cool and re-quantifying their paraprotein. This would ensure in vivo paraproteins are being accurately assessed and may also act as an indirect test for cryoglobulin if a discrepancy is found.+

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THE UTILITY OF IMMATURE PLATELET FRACTION MONITORING DURING A CASE OF LIFE THREATENING ITP PREDICTED HAEMORRHAGIC RISK

A Niblock[1,2], C Gore[1], J sin[1]
[1]Department of Haematology , Antrim Area Hospital, Antrim, Northern Ireland
[2]School of Medicine, Ulster University, Derry / Londonderry, Northern Ireland

A severe case of immune thrombocytopenia purpura ITP presented with widespread petechiae haemorrhages and gum bleeding. Despite first line steroids and intravenous immunoglobulin IVIg this patient continued to deteriorate requiring full dose elthrombopag, romiplostim, cyclophosphamide, vincristine, anti D, mycophenolate mofetil MMF, 31 units of platelets and 14 units of packed red cells.[1,2] It took 3 weeks before the platelets responded, and the patient went on to make a full functional recovery despite severe pulmonary haemorrhages and a pneumothorax.

Immature platelet fraction IPF measurements are now more readily available in routine laboratories given the ability of high-end full blood count analysers to perform them. Although techniques vary and there are no standard ranges, a high percentage would correlate with increased megakaryopoiesis in the bone marrow.[3] When combined with a thrombocytopenia it would favour a consumptive process like ITP as the underlying aetiology.[4]

In this case the IPF was monitored concurrently with the absolute platelet count. Its high percentage at diagnosis was in keeping with a consumptive process but in this case,it did not guide interventions nor predict platelet recovery in a timely manner. Interestingly when the severe thrombocytopenia had an IPF<10% the patient demonstrated overt bleeding requiring intensive blood product support.

The combined use of IPF and thrombocytopenia in ITP may identify the haemorrhagic patient. On the other hand if the IPF remains high it is more likely the patient may not be haemorrhagic possibly identifying patients more suitable to outpatient management.

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A RARE CASE OF ADULT MULTISYSTEM LANGERHANS CELL HISTIOCYTOSIS AND THE ADVENT OF TARGETED THERAPY

R O'Brien , D Swan, R Turner
[1]Haematology Department, Beaumont Hospital , Dublin 9 ,
[2]Haematology Department, Connolly Hospital Blanchardstown, Dublin 15 ,
[3]Intensive Care Unit, Beaumont Hospital, Dublin 9 ,

Langerhans Cell Histiocytosis (LCH) is a rare hematologic disorder that can affect adults and children with a wide variety of clinical manifestations. This can include unifocal, single- system multifocal, single- system pulmonary (smoking- associated) and multisystem disease. Most of our current understanding of LCH and treatment paradigms are derived from paediatric literature, with a relative paucity of data in the management of adult patients[1]. The discovery of clonality and MAPK-ERK pathway mutations has solidified the classification of LCH as a neoplastic disease. This has also opened up the possibility of the use of targeted therapies as part of clinical management. Current guidelines for systemic treatment in adult patients with LCH includes chemotherapy (cladribine or cytarabine) and targeted therapies (MEK, BRAF) inhibitors) [1].

Our case documents the diagnostic workup and clinical management of a 34 year old lady with a new diagnosis of multisystem LCH. The patient presented acutely unwell with respiratory distress and jaundice. She had no significant past medical history. Investigations revealed a large right sided pneumothorax, hepatosplenomegaly with multiple hepatic lesions, a large retroperitoneal mass and a diffusely enlarged thyroid affecting both lobes with associated tracheal compression. Liver function tests were grossly abnormal. Electrolyte abnormalities raised the suspicion of diabetes insipidus. The patient subsequently underwent a hemi- thyroidectomy. Histological examination of the thyroid revealed a dense cellular infiltrate including lymphoid aggregates, histiocytes and eosinophils. Immunohistochemistry demonstrated positivity for S100, CD68, CD1a and cyclin D1. Morphology and immunophenotype were consistent with LCH. MRI Brain revealed thickening and enhancement of the infundibulum, consistent with pituitary involvement. The patient was commenced on high dose steroids as part of initial management of LCH. Systemic treatment plan for this patient included chemotherapy (cladribine, due to more favourable liver side effect profile than cytarabine) and a MEK- inhibitor (cobimetinib), with plan for addition of a BRAF- inhibitor (vemurafenib) once BRAF status established.

This case is of unique scientific and clinical value on many fronts. It involves the diagnostic work up and clinical management of an adult patient with multisystem LCH, a very rare hematologic disorder. Most of our understanding and subsequently our treatment protocols for LCH are derived from paediatric data[1]. This creates a dilemma when trying to decide optimal treatment for the adult patient. The establishment of LCH as a clonal disease with MAPK-ERK pathway mutations, has led to the advent of targeted therapy use in its management. Management of LCH remains challenging due to lack of data in adult patients, rate of disease recurrence, lack of robustly tested salvage treatment options and significant disease morbidity[2]. Further studies are required to elucidate the optimum treatment regimen for the adult patient with multisystem LCH. Recent redefinition of LCH as a clonal haematological disorder and discovery of recurrent somatic mutations in MAPK- ERK pathway genes has provided opportunities to develop novel approaches to both diagnosis and therapy[2].

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A CASE DEMONSTRATING THE DIAGNOSTIC DILEMMA WHEN MOLECULAR MUTATIONS DO NOT FIT THE MORPHOLOGY IN THE CLASSIFICATION OF AN MPN.

D Waddell[1], A Niblock[1,2]
[1]Haematology department, Antrim Area Hospital, N. Ireland
[2]School of Medicine, Ulster University, N. Ireland

Myeloproliferative Neoplasms (MPN) classification has been revolutionised by mutational analysis. This broad category of disorders still can cause diagnostic difficulty's especially when morphology doesn't fit with the mutations found.

We report a case of a 67-year-old Caucasian male presenting with night sweats and headache. He had a past medical history of type 2 diabetes. A full blood count (FBC) was performed, and results showed a Haemoglobin (Hb) 133g/L (normal 130-170g/L), Total White Cell Count (WCC) $107.7x10^9$/L (normal 4-$10x10^9$/L), Platelet count (PLT) $83x10^9$/L (normal 150-$410x10^9$/L), Absolute Neutrophil Count (ANC) $57x10^9$/L (normal 2-$7x10^9$/L). A blood film was reviewed which showed a significant neutrophilia with no blasts, no basophils and no dysplastic features seen. A diagnosis of CML was excluded with the absence of BCR ABL.

Bone marrow aspirate showed predominantly neutrophils (>90% of nucleated cells) with no excess of blasts or any dysplastic features. Cytogenetics showed a normal karyotype (46XY) and no clonal abnormality or evidence of the Philadelphia chromosome. Bone marrow trephine was hypercellular and also showed mainly mature neutrophils with no excess of blasts. The morphological features were suggestive of chronic neutrophilic leukaemia.

Interestingly his NGS bloods returned and was negative for CSF3R but positive for ASXL1, KRAS, SRSF2 and TET2. NGS also found CUX1 of unknown significance.
Despite being negative for CSF3R he fulfilled the rest of the criteria for Chronic Neutrophilic Leukaemia as his peripheral blood and bone marrow aspirate/trephine have shown mainly mature neutrophils with no excess of blasts with no evidence of dysplasia and no other cause found.

CNL can be difficult to diagnosis as it has many overlying features with other myeloproliferative disorders such as atypical Chronic Myeloid Leukaemia (aCML). Recent developments with molecular sequencing have aided the diagnosis of CNL with most cases displaying a mutation in colony stimulating factor 3 receptor (CSF3R).[1,2] The two main mutations are T618I and more rarely T615A. Colony stimulating factor stimulates granulopoiesis and encourages differentiation of granulocytes to mature neutrophils which are characteristic of CNL. Despite being present in the majority (~80%) of cases, CSF3R is not the only driver mutation in CNL and many others can also be present adding to the complexity of the condition such as in this case where ASXL1, KRAS, SRSF2, TET2 and CUX1 are positive.[3]

The CUX1 gene is a tumour suppressor gene that is located on chromosome 7. It has been identified in myeloid neoplasms (AML, MPN) and are common in Myelodysplastic Syndrome. It has been noted that CUX1 mutations have been described in low risk MDS or AML whereas CUX1 deletions have been described in high-risk AML and MDS.[4,5] It has been noted that CUX1 mutations can occur in MPN however there are currently no cases describing CUX1 mutations in CNL. This case was labelled as an MPN-U and demonstrates the difficulty with the classification of myeloid malignancies when the mutations do not match the morphology.

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CASE REPORT: NEW DIAGNOSIS OF G6PD DEFICIENCY IN AN ELDERLY FEMALE ON COMMENCING MYELOMA TREATMENT

D WADDELL, R FORSYTHE, S LAWLESS
[1]DEPARTMENT OF HAEMATOLOGY, BELFAST CITY HOSPITAL, BELFAST, NI

Introduction: Glucose 6 phosphate dehydrogenase (G6PD) Deficiency is the most common enzyme deficiency in humans, affecting more than 400 million people worldwide[1]. It is usually an X-linked recessive disorder caused by mutations in the G6PD gene on X q28, and over 300 mutations have been identified[1]. Disease severity is usually linked to the degree of enzyme deficiency. It is most common around the Mediterranean, in parts of Africa, India and South-East Asia. It is usually asymptomatic but can present with neonatal jaundice, or haemolysis after exposure to a stressor (medications, certain foods, infections etc)[2]. We report a case of G6PD presenting during the commencement of myeloma therapy in an elderly female.

Case: A 77 year old lady, originally from Switzerland but living in Northern Ireland for many years, was initially referred to the Haematology outpatient Clinic with normocytic anaemia (Hb 105g/L normal 115-165), new renal dysfunction (creatinine 338umol/L) and raised Serum Free Lambda (5883mg/L). She has a past medical history of type 2 diabetes mellitus and atrial fibrillation. Given her worsening renal function, increased back pain and decreased mobility she was admitted for further investigation.

Due to these symptoms as well as right iliac bone lesion seen on MRI she was commenced on oral Dexamethasone 8mg twice daily and received one dose of Rasburicase 3mg intravenously to prevent tumour lysis syndrome.

On day two of admission her Haemoglobin (Hb) had dropped to 92g/L and Total Bilirubin had risen to 46umol/L (5umol/L on admission). Her oxygen saturation decreased to 84% on room air and an arterial blood gas was performed, showing an increase in methaemoglobinaemia (10.4%). Due to this a G6PD screen was sent. On day three of admission her Hb had dropped to 70g/L and Total Bilirubin risen to 60umol/L (Direct Bilirubin 18umol/L). Her reticulocyte count was $47x10^9$/L (normal 50-100) and Coomb's test was negative.

A blood film was reviewed (see image one) which demonstrated oxidative haemolysis with bite cells, hemighosts, blister cells and spherocytes. A G6PD screen proved reduced enzyme activity, the sample has been forwarded for molecular characterisation.

She was managed with red cell transfusion and Rasburicase was discontinued. A bone marrow biopsy confirmed the diagnosis of plasma cell myeloma which is likely the cause of her presenting anaemia as there were no features of haemolysis on her initial investigations.

Conclusion: In certain demographics G6PD deficiency is an important cause of haemolysis and can be diagnosed after common precipitating events and demonstrates characteristic morphology. We here demonstrate the importance of considering this possibility in other populations as it would not be expected that an elderly female from Central Europe without history of haemolysis proves to have G6PD deficiency.

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ACTIVELY TARGETING NATURAL KILLER CELL-MIMIC NANOPARTICLES TO ELIMINATE ACUTE MYELOID LEUKEMIA CELLS

HA Zeinabad[1, 2], WJ Yeoh[3, 4], **M Arif[1]**, M Lomora[5, 6], Y Banz[3], C Reither[7], P Krebs[3], E Szegezdi[1]
[1]Apoptosis Research Centre, School of Biological and Chemical Sciences, University of Galway, Galway, Ireland
[3]Institute of Pathology, University of Bern, Bern, Switzerland
[4]Graduate School for Cellular and Biomedical Sciences, University of Bern, Bern, Switzerland
[5]School of Biological and Chemical Sciences, University of Galway, Galway, Ireland
[6]CÚRAM, Science Foundation Ireland Research Centre for Medical Devices, University of Galway, Galway, Ireland
[7]Department of Medical Oncology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

Statement of the Problem: Natural killer (NK) cells are effector immune cells. The potency of NK cells to target and eliminate emerging tumour cells is increasingly recognised, however, fully-established tumours can inactivate NK cells or hide from them. Here we describe a nanoparticle (NP) functionalised with cytotoxic and tumour-recognising components of NK cells to overcome this problem and develop a therapeutic strategy simulating NK cell functionality.

Methodology & Theoretical Orientation: The NPs were generated as 100 nm liposomes. The death ligand, tumour necrosis factor-related apoptosis-inducing ligand (TRAIL), immunoglobulin binding peptide and therapeutic antibodies targeting acute myeloid leukaemia (AML) were immobilised on the liposome surface in their native orientation and conformation to create NK cell-mimic NPs (NK.NPs). Functionalisation of the liposomes was confirmed by immunofluorescent labelling of TRAIL and antibodies detected with flow cytometry. The morphology and size of liposomes in different steps of modification were monitored via transmission electron microscopy and dynamic light scattering. The ability of NK.NPs to target and kill AML were investigated in vitro and in vivo, in AML xenografts. Findings: Cytotoxicity assays on primary AML blasts showed NK cell-mimic NPs have a superior cytotoxic potential than soluble TRAIL protein (sTRAIL), TRAIL-conjugated liposomes (LP/TRAIL) and the NK cell line, KHYG-1. NK.NPs were also more effective in targeting and eliminating AML cells in vivo from peripheral blood, spleen and bone marrow than sTRAIL and LP/TRAIL in a disseminated AML mouse model. Notably, NK.NPs did not show any detectable systemic or organ toxicity.

Conclusion & Significance: Here we report the successful development of a cell-mimic NP that carries NK cell properties. One of the unique features of this cell-mimic NP is its modular built that can easily be functionalised with any tumour-targeting antibody through an immunoglobulin-binding peptide, enabling personalised therapy.

EXPERIENCES WITH BISPECIFIC T-CELL ENGAGER (BITE) ANTIBODIES THERAPY IN GALWAY UNIVERSITY HOSPITAL

S.Y. Chai[1], D.E. Zahra[1], Y.P. Nunez[1], A. Hayat[1], S. NiLoingsigh[1], N. Keane[1], R. Morrell[2], M. Papanikolaou [2], A. Burke[3], A. Hodgson[3], J. Krawczyk [1]
[1]Department of Haematology, Galway University Hospital, Galway , Ireland
[2]Department of Haematology, Letterkenny University Hospital, Letterkenny, Donegal
[3]Department of Haematology, Sligo University Hospital, Sligo, Ireland

Background: Bispecific T-cell engager (BiTE) antibodies has shown clinical benefits in patient with relapsed/ refractory multiple myeloma (MM) in many clinical trials[1, 2].

Method: We aim to look at the experiences of BiTE therapy in our cohort of relapsed and refractory multiple myeloma patients who were at least triple exposed MM (Proteasome inhibitors, IMiDs and Anti-CD38). Here specifically explore two keys aspect: the overall response (response or better) and the safety profile of BiTE therapy. There are three BiTE antibodies therapy that are used here in West of Ireland (Compassionate access programs) including, Teclistamab, Elranatamab and Talquetamab.

Results: A total of 13 patients have received or receiving BiTE therapy in West of Ireland. The median age of patient was 75 (range, 55 to 89) and mean time since diagnosis was 6.7 years. Most patient (76%) had ECOG status of 0 at baseline prior starting BiTE therapy. In terms of cytogenetics, 1 patient (7%) had high risk cytogenetic abnormality of Tp53, 7 (53%) had a cytogenetic aberration of 1q gain, 3 (23%) had IgH aberration and 3 (23%) had monosmy 13. The 13 patients had received median of 5 previous antimyeloma regimen (range, 2 to 9) and 8 (61%) had received previous autologous stem cell transplant.

At a median follow-up of 3 months with longest follow up of one patient of 10.5 months, 9 of 13 (69%) had response; 8 out of 9 (88%) are in complete remission and 1 (12%) is in very good partial response (VGPR) with the median time to first response was 7 days week (ranges, 4 to 21 days). A median progression free survival of 4 months. Cytokine release syndrome (CRS) was reported in 8 patients (61%), with mostly 4 patients who had grade 1 (50%) and 4other 4 patients had grade 2 (50%) which required antidote, Tocilizumab, which is an anti-IL6 antibodies; only 1 patient out of 13 (7%) developed neurotoxic effects and was grade 1 with no CRS or neurotoxic effects higher than grade 3 occurred. Infections rate was 39% occurred in 5 patients, including 1 who had grade 3 infection which required multiple admission for cavitating Pseudomonal pneumonia. None of our patients required admission to high dependency unit (HDU)/ Intensive care unit (ICU).

Conclusion: The experience of BiTE therapy in our cohort of heavily pre-treated patients without other therapeutic options, is very promising with BiTE induced response in 69% of patients. Common side effects not limited to infection rate, CRS and neurotoxicity events are generally reasonable with no events greater than 3 or higher. Medical staff and nursing colleagues were given educations and information of the therapy and management guidelines in the setting of adverse effects. Although the follow up periods and the impact on quality of life and survival are still at its infancy state to draw any definite conclusion, our findings up to this point have shown some promising result as these data reflects efficacy and safety of BiTE therapy in relapsed and refractory multiple myeloma in a real-life setting.

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AL AMYLOIDOSIS – AN AUDIT OF MANAGEMENT AND OUTCOMES IN BEAUMONT HOSPITAL BETWEEN 2008 AND 2023.

J Costello[1], C Kearns [1], P Murphy [2], D Swan[2], P Thornton[2], J Sargent[2], S Glavey [2], J Quinn[2]
[1]School of Medicine , Royal College of Surgeons in Ireland, Dublin , Ireland
[2]Department of Haematology, Beaumont Hospital, Dublin, Ireland

BACKGROUND: AL (light chain) amyloidosis is a rare disease involving systemic deposition of misfolded light chain immunoglobulins in tissues. Cardiac involvement is the main predictor of mortality and cardiac-based staging systems are powerful prognostic tools (1). Promising therapeutic developments for AL amyloidosis include daratumumab, an anti-CD38 monoclonal antibody, which has demonstrated low toxicity and deep haematological responses in pre-treated and de novo disease (2). The aims of this study were to audit patient demographics, management pathways, and overall survival of patients diagnosed with AL amyloidosis in Beaumont Hospital 2008-2023.

METHODS: Retrospective audit of the management of patients diagnosed with AL amyloidosis between 2008 and 2023 at Beaumont Hospital. Baseline stage was determined according to Mayo 2012 staging model. Treatment response was determined based on criteria established by Palladini et.al. (3).

RESULTS: Our audit included 36 patients. 94% (n=34) of patients had treatment data available. Of these, 50% (n=17) of patients received daratumumab during the course of their treatment. Response to induction treatment was documented for 86% (n=31). 67.5% (n=21) achieved complete response (CR) or a very good partial response (VGPR). Cyclophosphamide-bortezomib-dexamethasone (CyBorD) was the most common 1st line treatment with 72.5% (n=16) achieving CR or VGPR. 68% of patients (n=21) progressed to 2nd line therapy, 43% (n=9) with lenalidomide-dexamethasone and 33% (n=7) with daratumumab. Daratumumab usage as 2nd line agent has increased from 14% (n=1) pre-2017 to 43% (n=6) post-2017. 36% (n=11) of patients advanced to 3rd line therapy, 64% (n=7) of which received daratumumab. 73% (n=8) of patients that received daratumumab achieved CR or VGPR. Haematological response to daratumumab therapy did not correspond to disease stage or line of treatment. 72% (n=26) of patients had ≥ 2 organs involved and 42% (n=15) had ≥ 3 organ involvement at diagnosis. At 5 years, overall survival (OS) for our patient cohort is 74% and at 10 years it is 62%. Elevated NTProBNP and cTNT at diagnosis were both independently associated with a trend towards reduced OS, however less so with cTNT (p=0.063, p=0.154 respectively). 41% (n=15) of patients were staged using the Mayo 2012 system. Advanced stage at diagnosis was associated with a reduced survival probability (p=0.001).

CONCLUSION: Novel therapies used in Beaumont Hospital have demonstrated favourable haematological responses for the majority of patients. In our patients, daratumumab-based therapy was well tolerated and effective and is increasingly becoming standard of care in the treatment of AL amyloidosis. In keeping with published data, advanced stage at diagnosis was associated with reduced OS. Therapies achieving early and deep haematologic response have proven most successful at prolonging survival in advanced staged patients at diagnosis (4). It is likely that earlier diagnosis and increased access to novel and effective therapies will contribute to the continued improvement in the overall survival of patients with AL amyloidosis in Ireland.

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UNCOVERING METABOLIC AND APOPTOTIC VULNERABLILITIES IN MULTIPLE MYELOMA

S Gilmore[1], Y WANG[1], L DI Martino[1], S Glavey[2], T Ni Chonghaile[1]
[1] Department of Physiology and Medical Physics, Royal College of Surgeons in Ireland, Dublin,
[2]Department of Pathology, Royal College of Surgeons in Ireland, Dublin,
[3]Department of Haematology, Beaumont Hospital, , Dublin,

Multiple myeloma (MM) is an incurable type of B cell haematological cancer that is characterised by the accumulation of neoplastic plasma cells in the bone marrow. The prevalence of the disease is increasing due to a rise in the ageing population, with a median age of 73 at diagnosis. MM is estimated to increase by 80% in the next 20 years. There have been little improvements in the survival of elderly MM patients over the age of 65 with relapse and resistance proving major obstacles, despite the addition of novel therapeutic agents.

Metabolic rewiring and apoptotic resistance are mechanisms described for driving therapeutic resistance. Our aim was to assess if BCL-2 dependence is associated with metabolic phenotypes in MM and to determine if this association can be harnessed for therapeutic treatment options.

Methods: Metabolic and BCL-2 dependencies in a panel of MM cell lines (JJN3, KMS12BM and KMS27) and patient samples were investigated. Metabolic phenotypes were investigatedusing the single-cell puromycin assay SCENITH or the seahorse assays using oxygen consumption rate. Apoptotic vulnerabilities were determined by sensitivity to BH3 mimetics (BCL-2 inhibitor: venetoclax; MCL-1: AMG-176 and BCL-XL: A-1331852) by annexin v/propidium iodide staining. BCL-2 dependence was also assessed by BH3 profiling, BH3 peptides are added to cells and mitochondrial permeabilisation was measured.

Results: First, I assessed the BCL-2 dependence of the cell lines using BH3 profiling and sensitivity to BH3 mimetics. The KMS12BM were sensitive to venetoclax (BCL-2 inhibitor) and AMG-176 (MCL-1 inhibitor), suggesting a BCL-2/MCL-1 dependence. The JJN3 cell line was most sensitive to AMG-176 indicating MCL-1 dependence, with a strong response from the A12 BH3 peptide by BH3 profiling. While the KMS27 were most sensitive to venetoclax and showed a high response to the BAD BH3 peptide by BH3 profiling, indicating a BCL-2 dependence.

Next, I compared the utility of using seahorse versus the SCENITH assay and found that the seahorse gave a more reliable readout. The JJN3 and KMS27 showed a reliance on OXPHOS metabolism, while KMS12BM appeared to be the least dependent on OXPHOS.

As two of the cell lines seemed reliant on OXPHOS, I assessed the sensitivity of MM cells to to IACS-010759, the complex I inhibitor. While IACS-010759 alone did not cause cell death in the MM cell lines. Interesting, it induced a reliance on BCL-XL that was identified by dynamic BH3 profiling. Lastly, co-treatment of the KMS12BM, KMS27 and patient samples with IACS-010759 and the BCLXL inhibitor (A-1331852) enhanced cell killing.

In conclusion, there was a difference in BCL-2 dependence across the three MM cell lines. In addition, two of the cell lines relied more on OXPHOS, however they were not sensitive to an OXPHOS inhibitor alone. Of interest the OXPHOS inhibitor IACS-010759 induced BCL-XL dependence in two cell lines next we aim to uncover how this increase in reliance on BCL-XL occurs. Through these innovative assays, we hope to uncover the metabolic and apoptotic vulnerabilities in MM patient samples, with the goal of potentially identifying personalised targeted therapies for enhanced survival.

PAROXYSMAL NOCTURAL HAEMOGLOBINURIA: Presenting with Acute Liver Injury

M. Griffin, H Enright, C Flynn, C. Andrews, A. Dillon, J. Falco, L. Smyth

Paroxysmal Nocturnal Haemaglobinuria (PNH) is a rare clonal disorder of hematopoietic stem cells characterized by both intra- and extravascular haemolysis and venous thrombosis. It is caused by mutations in the PIG-A gene, resulting in the loss of GPI anchor proteins, manifesting as haemolytic anaemia, thrombosis and smooth muscle dystonias. It can present de novo or in the context of other haematological disorders including Aplastic Anaemia and Myelodysplastic syndrome. Terminal compliment inhibition results in significant improvement in intravascular haemolysis and marked reduction in thrombotic complications. We review two cases that were referred to the Hepatology team for assessment and management of hepatic failure and consideration for emergency liver transplantation.

A forty-three year old female was referred to the liver transplant service. She had a background history of aplastic anaemia treated with immunosuppressive therapy. She presented to her local hospital with a five-day history of viral illness and sudden collapse. She developed an Acute Kidney Injury and Acute Liver failure. She was transferred to ICU with multi-organ failure. A four-phase liver CT showed flow stasis in her portal vein. Unfortunately, she died of progressive muti-organ failure shortly after transfer. Post mortem examination confirmed cause of death due to multi-organ failure secondary to Budd-Chiari syndrome as a thrombotic complication of PNH, her PNH clone size measuring 96.6%.

A nineteen year old male was referred to the hepatology services with significantly deranged liver enzymes and for consideration for liver transplant. Hus background history was significant for aplastic anaemia, treated with ATG, ciclosporine and eltrombopag. He reported episodic abdominal pain over the previous 8 weeks. Our care with a short history of abdominal pain and deranged LFTs on a background of PNH and AA. His PNH clone size increased significantly to 80.9%, from his baseline of 36.5%.

On admission, a Liver four-phase CT confirming Budd Chiari Syndrome. He was commenced on emergency eculizumab and unfractionated heparin. He responded well, with improvement in transaminases and synthetic function. He was transferred back to his primary haematology service on eculizumab and therapeutic low molecular weight heparin.

Budd Chiari Syndrome is a complication of PNH that occurs in 12-20% % of cases. It is characterized by hepatic venous outflow obstruction, and can be thrombotic or non-thrombotic. It should always be considered in cases of PNH with liver involvement or ascites. Serum transferase levels are often markedly increased, and Hepatic ultrasound is diagnostic, or a spider-web appearance of collateral hepatic venous circulation. Treatment options include Transjugular intrahepatic portosystemic stent-shunting (TIPSS).

Both cases highlight the need to identify and treat BCS as a serious complication of PNH. Though a relatively rare complication, BCS has a high associated mortality. The HSE has recently approved funding for Eculizumab and it is important that we recognise BCS and treat promptly.

Health professionals' perceptions of prehabilitation BEFORE haematopoietic cell transplantation to optimise candidacy in older adults

C Heuston[1], G Sheill[2, 3], M NÍ Chongaile [3, 4], N Orfali[3, 4], E Guinan[3, 5]
[1]Department of Physiology, Trinity College Dublin, Dublin, Ireland
[2]Department of Physiotherapy, St James's Hospital, Dublin, Ireland
[4]Stem Cell Transplant Unit , St James's Hospital , Dublin, Ireland
[5]Discipline of Physiotherapy, Trinity College Dublin, Dublin, Ireland

Introduction/Background: Haematologic malignancies for the most part, are diseases of the elderly. Haematopoietic stem cell transplantation (HSCT) remains the only potentially curative strategy for many patients, but carries substantial morbidity and mortality risks particularly in frail or co-morbid patients. Modified transplant platforms and improved supportive care now enable older patients to be increasingly considered for transplantation. Multi-disciplinary strategies to optimize patient function before and after-transplant may benefit both objective and patient-reported outcomes. Prehabilitation is defined as a process on the continuum of care that occurs between the time of cancer diagnosis and the beginning of treatment, includes physical and psychological assessments that establish a baseline functional level, identifies impairments, and provides targeted interventions that improve a patient's health to reduce the incidence and the severity of current and future impairments. Prehabilitation is widely used in oncology care, particularly for pre-operative optimisation of physical, nutritional, and psychological indices, however the role of prehabilitation in haematological malignancies is under-investigated. Pre-transplant optimisation of key targets through prehabilitation may have significant clinical impact.

Materials and methods: We utilised qualitative methodology (semi-structured interviews) to gain insights and understanding of the perceptions of medical, nursing and allied health professionals towards prehabilitation before hematopoietic cell transplantation to optimise candidacy in older adults. Participants were recruited using purposive sampling methods targeting medical, nursing and allied health professionals working in cancer centres across Ireland and caring for older adults preparing for or undergoing hematopoietic cell transplant. Sociodemographic information and details pertaining to professional grade, experience with hematopoietic cell transplantation and understanding of prehabilitation were captured. Data will be collected through semi-structured interviews which will follow a flexible interview guide.

Results: Eight interviews have been completed to date (n=2 consultant haematologists, n=5 nurses and n=1 physiotherapist) from three major cancer centres. Two more interviews are scheduled, and recruitment is ongoing. Data analysis will be completed in September 2023 for presentation. Reflexive thematic analysis will be performed using a qualitative descriptive approach according to the standardised process described by Braun and Clark completed in duplicate by two independent researchers. Interviews to date have highlighted the unique challenges, particularly for post-transplant nursing management, of older adults who are receive HSCT, and indicated strong support for prehabilitation in the HSCT pathway to optimise functional and psychological wellbeing in advance of transplant. Challenges to prehabilitation may include concurrent intensive chemotherapy regimens with associated patient fatigue, anaemia and thrombocytopenia. Implementation may be complicated by the heterogeneity of treatment pathways across different sites and across a range of diseases. Individualized approaches will be necessary.

Conclusions: Geriatric haematology is a growing field and chronologic age alone is no longer a barrier to potentially curative HSCT. There is broad national multi-disciplinary interest in the development of prehabilitation programmes for patients being considered for transplant. Our results will inform the development of services in this area in consideration of national reach, malignancy-specific pathways and the unique factors associated with older patient age.

Frailty in haematopoietic cell transplantation: A systematic review exploring the role of physical frailty assessments IN ASsessing candidacy and predicting post-transplant outcomes.

C Heusont[1], G Sheill[2, 3], D Mockler[4], M Ni Chonghaile [3, 5], N Orfali[3, 5], E Guinan[3, 6]
[1]Department of Physiology, Trinity College Dublin, Dublin, Ireland
[2]Department of Physiotherapy, St James's Hospital, Dublin, Ireland
[3]Trinity St James's Cancer Institute, Dublin, Ireland
[4]John Sterne Medical Library, Trinity Centre for Health Sciences, St James's Hospital, Dublin, Ireland
[5]Stem Cell Transplant Unit, St James's Hospital, Dublin, Ireland
[6]Discipline of Physiotherapy, Trinity College Dublin, Dublin, Ireland

Introduction/Background: Haematologic malignancies are most comment in people aged 65 years and older. Haematopoietic cell transplantation (HSCT) offers a potentially curative option in high risk or relapsed/refractory disease. However, transplant remains a high-toxicity treatment with a high risk of severe complications including death. Older chronologic age has until recently precluded transplantation. However, treatment advances have reduced treatment-related morbidity and mortality and transplant rates amongst older patients have increased significantly over the past decade. Older age at diagnosis coincides with accumulation of geriatric conditions and co-morbidity, presenting unique challenges for those who may benefit from transplant. Pre-transplant assessments incorporating validated measures of physical frailty may help in assessing patient candidacy, predicting prognosis and identifying amenable targets for pre-transplant optimisation through prehabilitation. However, for frailty assessments to be broadly implemented in busy resource-limited environments, they should be easy and reasonably quick for an assessor to perform.

Materials and methods: We undertook a systematic review to examine if pre-transplant physical frailty assessments help in the selection of transplant candidates and determine if they are predictive of post-transplant outcomes in patients scheduled for HSCT. A core search strategy was developed to reflect the pillars of the review (HSCT, frailty assessment) and adapted for each database. The following databases were searched: EMBASE, MEDLINE, CINAHL, Web of Science and Google Scholar in June 2023. No restrictions were placed on publication period. Only articles available in English were included. Data extraction (selection and coding) was performed using the Covidence systematic review software. Titles, abstract and full text screening were completed independently by two reviewers in line with inclusion/exclusion criteria. Data extraction was completed using a standardised template and included author, patient characteristics, haematological malignancy, description of physical frailty assessments, transplant candidacy and post-transplant outcomes. Risk of bias assessment was performed using the validated Quality in Prognostic Studies tool.

Results: After the removal of duplicates, 1981 titles were identified for screening and 21 full-text articles were included in the review. Pre-transplant, the most utilised measures were Fried Frailty Index, the Timed Up and Go (TUG), handgrip strength (HGS), six-minute walking distance and weight loss or falls in the past 6 months. Patient frailty did not influence decision on transplant candidacy or intensity of the treatment in any of the studies reviewed. There was a significant difference in 1-year mortality in frail vs non-frail patients, particularly among allogeneic HSCT patients. Pre-transplant impairments in HGS (female only), the short physical performance battery and aerobic fitness were associated with longer length of hospital stay. Frailty was not associated with readmission post-transplant, though falls in the 6-months prior to transplant were associated with increased readmissions. Impairments in TUG, Medical Outcomes Study Physical Health score, quality of life, fatigue and lower extremity muscle strength were associated with overall survival.

Conclusions: Results suggest that select measures of physical frailty are associated with adverse transplant outcomes. Easy to perform and easy to standardize assessments such as HGS and TUG combined with patient-reported falls and functionality assessments are practical to implement in busy national clinics.

Understanding the mechanism of natural killer cell exhaustion in multiple myeloma

WS Hu[1], JU Verga[1,2], E Szegezdi[1]
[1]Apoptosis Research Centre, School of Biological and Chemical Sciences, University of Galway, Galway, Ireland
[2]Centre for Research Training in Genomics Data Science, School of Biological, University of Galway, Galway, Ireland

Introduction:

Multiple myeloma, an arduous hematological malignancy, is characterized by the involvement of immune suppression, which play a significant role in disease progression. Research has demonstrated. In our previous investigation, we employed a comprehensive analysis of single-cell RNA-Sequence data from multiple myeloma samples, which revealed a positive correlation between the proportion of exhausted NK cells and the advancement of multiple myeloma. With further gene-regulatory network analysis potential transcription factors driving the development of exhausted NK cells were identified. Through knock-in or knock-out experiments targeting these transcription factors, we aim to determine their significance in the generation of exhausted NK cells and assess changes in NK cell cytotoxicity and phenotype. This study endeavors to identify the principal transcription factor responsible for NK cell exhaustion in multiple myeloma, with the ultimate goal of targeting this transcription factor to mitigate or reverse NK cell exhaustion.

Methods:

For functional and mechanistic analysis of drivers of NK cell exhaustion in multiple myeloma, are developing an are developing NK cell exhaustion assay. Identification of key transcription factors likely to determine exhausted NK cells by single-cell sequencing. By knocking out the corresponding transcription factors, observing their phenotypic changes in long-term cytotoxicity experiments to verify their functions.

Results and Conclusion:

We identify novel key transcription factors for exhausted NK cells, whose expression levels can be altered to reverse the NK cell exhausted phenotype.

ISOLATING EXTRACELLULAR VESICLES FROM BONE MARROW ASPIRATE: A HUMAN OPTIMISATION PROTOCOL

D Kasianenko[1,2], S Kelliher[1,2,3], S Maung[2,3], M Fay[2,3], A Fortune[2,3], F NÍ Áinle[1,2,3], P Maguire[1,4], B Kevane[1,2,3]
[1]Conway SPHERE Research Group, University College Dublin, Ireland
[2]School of Medicine, University College Dublin, Ireland
[3]Department of Haematology, Mater Misericordiae University Hospital, Ireland
[4]School of Biomedical and Biomolecular Science, University College Dublin, Ireland

Introduction: Extracellular vesicles (EVs) are small, cellular derived membrane bound nanoparticles. EVs are increasingly recognised as effectors of important biological processes by delivering their cargo (including nucleic acids, proteins, and lipids) from their cell of origin to recipient cells, often at distant sites. To standardise the approach to EV research, and accurately characterise their physiological and pathobiological functions the Minimal Information for Studies of Extracellular Vesicles (MISEV) framework was published in 2018. EVs are abundant in many biological fluids however their separation from plasma is described most comprehensively. Bone marrow derived EVs have been shown to be phenotypically distinct in haematological malignancies, yet the optimal approach for isolating EVs from bone marrow aspirate remains unknown. The aim of this study was to separate EVs from bone marrow aspirate according to the MISEV guidelines.

Methods: Matched plasma and bone marrow aspirate samples were recruited from patients undergoing minimal residual disease monitoring for acute myeloid leukaemia (n= 3). The plasma component of peripheral blood and bone marrow were collected by centrifuging whole blood and marrow aspirate at 3000 X *g* for 10 minutes. Samples were stored at -80 °C prior to use. EVs were separated from plasma and marrow using size exclusion chromatography (SEC) with the commercially available Izon columns (qEVsingle Gen2 70nm, Izon Science). Fractions 1–21 each containing 170 µl of elute were collected. Particle size and concentration were determined for each fraction using nanoparticle tracking analysis (NTA) with a NanoSight NS300 system (Malvern Technologies, Malvern, UK). Protein contamination of EV samples (1-21) was estimated by measuring absorbance at 280nm using a DS-11 spectrophotometer (DeNovix). Following lysis in urea lysis buffer and reprecipitation in 95% acetone, the presence of surface and cytosolic EV markers (CD63, CD9, CD81, Alix, HSP70), as well as plasma protein contaminants (APOA1, albumin), were assessed using Western Blot.

Results: NTA of samples enriched from plasma (n= 3) and marrow aspirate (n= 3) using SEC demonstrated the presence of particles in fraction 6-14. Spectrophotometer readings identified increased protein concentration in the later fractions of plasma and marrow EV samples, with protein contamination initially identified in fraction 10. Taken together, NTA and subsequent protein quantification identified fractions 6–9 as key fractions for subsequent analysis of small EVs from both plasma and bone marrow samples. This was confirmed with Western Blot analysis. EV fractions from marrow were pooled, lysed, and stained with EV surface and cytosolic markers as well as antibodies against abundant protein contaminants. Similarly, fractions enriched from plasma were pooled. Western Blot confirmed the presence of CD9, CD63, HSP70, Alix and the absence of albumin contamination from both pooled plasma and marrow samples.

Conclusion: We confirm the separation of EVs from human bone marrow aspirate using size exclusion chromatography, with comparable results to matched plasma samples. Next, we aim to use this protocol to characterise EVs separated from plasma and bone marrow of patients with myeloproliferative neoplasms using NTA, flow cytometry and mass spectrometry.

AN AUDIT TO ASSSESS THE APPROPRIATENESS OF COAGULATION BLOOD TESTING IN THE EMERGENCY DEPARTMENT OF MERCY UNIVERISTY HOSPITAL CORK

S McCarthy[1], F O'Flynn[2], J Tan[1], C Keohane[1]
[1]Department of Haematology, Mercy University Hospital, Cork, [2]Department of Geriatrics, Mercy University Hospital, Cork, Ireland

Introduction: Coagulation bloods tests, routinely test for Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT) and International Normalised Ratio (INR). Such tests, initially developed to monitor warfarin usage and evaluate for coagulopathies (1), are useful in other settings e.g., in liver disease/during thrombolysis. (2) However, outside of indicated settings, coagulation testing has less utility, with mildly deranged results not being associated with clinically significant changes in bleeding risk. (3,4)

Coagulation testing is often used indiscriminately/inappropriately and is highlighted as being particularly vulnerable to overuse given poor clinician understanding of its nature/utility. (3,5) Inappropriate testing has been associated with adverse patient outcomes (e.g., delaying treatment/surgery in false-positive testing) and increased healthcare costs. (6,7)

This audit aims to assess the appropriateness/nature of coagulation testing in the emergency department (E.D.) of Mercy University Hospital Cork (MUH), to guide interventions aimed at reducing overuse.

Method: All coagulation samples from the E.D. of MUH over a one-week period from 03/08/23-09/08/23 were included for analysis.

Data on patients' presentation to hospital, indication for coagulation testing and outcome were collected via retrospective review of medical notes. Appropriateness of coagulation testing was derived by comparing the indication for testing/presenting complaint with a list of indications developed in the MUH haematology department and based on guidelines devised by the British Committee for Standards in Haematology and Australasian College for Emergency Medicine. (8,9)

Data was analysed using *Jamovi version 2.3.21.* with descriptive statistics being produced. Differences in the proportions of appropriate/inappropriate as well as normal vs. abnormal testing between patient groups (e.g., those admitted vs. discharged) were compared using Pearson's Chi-Square Tests.

Results: 364 coagulation tests were included in the analysis. The sample was 50.8% female with a mean age of 55 years and with n=160 (44%) of patients being admitted.

N=46 (12.6%) of tests were ordered for an appropriate indication, with n=318 (87.4%) being ordered inappropriately. The most common appropriate indication was for "investigation of a patient with significant history of bleeding or bruising" (n=34 /9.4% of tests ordered). The most common inappropriate indications were for work-up of abdominal pain (n=67/18.5%) and chest pain (n=41/11.3%). There was a significantly lower proportion of inappropriate testing among admitted vs. discharged patients (83.8% vs 91.5%, p=0.027).

27.7% of coagulation tests ordered yielded ≥1 abnormal result. There was no significant difference in the proportion of abnormal tests between appropriate/inappropriate tests (21.7% vs. 28.9%, p=0.31). There was a significantly higher proportion of abnormal tests among those admitted vs. those discharged (41.3% vs. 18.6%, p<0.001).

Discussion/Conclusion: This audit assessed the appropriateness of coagulation testing from the E.D. of MUH, with 87.3% being deemed inappropriate. While no significant association was found between inappropriate testing and abnormality detection, patients ultimately admitted were both more likely to have had tests sent appropriately as well as yielding an abnormal result.
This high proportion of inappropriate testing tracks closely with baseline rates in similar audits in other healthcare jurisdictions. (1,9) Consequently, it is hoped that their successful attempts at reducing inappropriate testing rates can be emulated in our setting. (1,7,9,10)

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Managing the unmanageable: Haematology referrals and outpatient activity in a large tertiary referral centre.

N O'Connell[1], D Grzegorzek[1], A Busher[1], C Andrews[1,2], M Coyne[1,2], DG Connaghan[1], KF Fadalla[1,2], K Murphy[1,2], M Coyne[1,2], J Fitzgerald[1,2], M Power[1], L Smyth[1,2]
[1]Department of Haematology, St. Vincent's University Hospital, Dublin
[2]Department of Medicine, University College Dublin

Background: Demand for haematology outpatient services continue to increase exponentially. St. Vincent's University Hospital (SVUH) has seen growth in referrals and OPD activity of 177% over a 4-year period, and 307% over a 15-year period, with annual attendances of 5,957 patients in 2022. Increased demand compounded by the impact of the Covid-19 pandemic resulted in 36% (253/710) of new patient referrals waiting greater than 12 months for an appointment date, by July of 2021.

In 2021 a multi-annual national "Waiting List Action Plan" was launched, with the purpose of achieving the target time to 1st appointment of 10 week as outlined by SlainteCare. It facilitated the introduction of a temporary National Treatment Purchase Fund (NTPF) haematology clinic and was complemented by the provision of a 5th weekly clinic, led by a new consultant post, improved NCHD staffing and an enhanced consultant triage of new referrals.

Aims:

1. Assess the impact of the listed interventions on waiting times breaches, defined internally as new referrals waiting greater than 12 months for first appointment and nationally greater than 15 months.

2.Compare SVUH waiting times against national data.

3.Assess compliance with the SlainteCare 10-week target.

Methodology: Waiting list data was retrospectively obtained through the statistics office in SVUH and published national waiting list data on NTPF.ie. This data was exported to Excel for analysis.

Results: Increased clinic activity and additional triage of new referrals, reduced new referral waiting by 44% from 710 patients in July 2021 to 396 in July 2023. 381 patients were seen in the NTPF clinic, with 196 discharged after their first appointment. The median OPD wait time has reduced from 97 days in 2021 to 63 days in 2023. Most striking is the reduction from 35% (253/710) of patients breaching the 12 months target to 0% (0/253) (1).

This contrasts with the national experience, where there has been an 18% increase in patients awaiting review. 12-month breaches are down however from 30% (2387/7853) to 20% (1845/9197). 30% (2782/9197) are reviewed within the SlainteCare target. Data on SVUH haematology specific compliance with the SlainteCare OPD target as of July 2023 is not available, however 38% of all OPD referrals to SVUH are seen within target. (1)

Conclusions: Targeted interventions reduce waiting times and prevent breaches, even in the context of rapid growth in referrals. Increased capacity through sustained investment in NCHD and consultant staffing is crucial. Temporary NTPF clinics are an effective measure to improve new referral wait times but longer term management strategies are required to ensure sustainability of time to 1st appointment and ensure compliance with SlainteCare.

Recommendations: Further clinic capacity may be created through expansion of advanced nurse practitioner led clinics. While the 2023 Waiting List Action Plan calls for increased use of chronological scheduling to reduce waiting time breaches, the simultaneous development of standardised haematology national referral pathways and rapid access clinics may improve patient triage and ensure access to urgent care.

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Audit of Coagulation Sample Rejection in Beaumont Hospital Following January Changeover

N O'Connell[1,2], G Healy[1], D Fraughen[2], J Quinn[1], P Murphy[1], K Ewins[1], S Glavey[1]
[1]Department of Haematology, Beaumont Hosptial, Dublin, [2]Department of Medicine, Royal College of Surgeons in Ireland, Dublin,

Background: Following the January 2023 non consultant hospital doctor (NCHD) changeover laboratory scientists noticed a subjective increase in the coagulation sample rejection rate (SRR) from the emergency department (ED). The process of identifying and alerting the clinical teams to rejected samples, followed by retesting is labour intensive and costly. Out of hours it causes a disproportionate impact by occupying reduced laboratory staff. This may delay the turnaround time of other urgent investigations, a key labortaroy quality indicator.

Hypothesis: Given there is a dedicated phlebotomy service available during regular hours, we proposed that the increased SRR post changeover was likely due to increased pre-analytical error in samples taken by NCHDS unfamiliar with the sampling process compared with pre changeover.

Methods: All prothrombin time (PT) tests sent for a 14-day period before and after the NCHD changeover on 10th January 2022 (27/12/21 – 23/1/22) and the 9th of January 2023 (26/12/22 -22/1/23) were retrospectively identified using the Beaumont Hospital Laboratory Information Management System. This data was exported to Excel.
Statistical analysis was conducted to establish if there was a significant change in SRR comparing ED and wards, annually, pre and post changeover periods, or by subcategory for rejection. Continuous variables were analysed by non-parametric means. Categorical variables and proportions were analysed by Pearson's chi-squared test and Fisher's exact test. All analyses were performed using the gtsummary package v1.7.0 using R (version 4.2.0, R Foundational for Statistical Computing).

Results: 11,255 PT samples were sent from the ED and wards combined in the audit period, with a SRR of 3.3% (370/11255). 366 were rejected due to pre-analytical error. Under filling of collection tubes was the principal cause [67% (247/370)].

The number of PT requests and the rejection rate increased throughout the audit:

- Pre changeover 2022 the SRR was 1.6% (40/2430) with a 50% relative increase to 2.4% (69/2931) post changeover.
- Pre changeover 2023 the SRR was 3.9% (103/2627) with a 23% relative increase to 4.8% (158/3267) post changeover.
- There was a 300% relative increase in the SSR during the audit (1.6% to 4.8%) (p value < 0.001).

The post changeover increases in SSR affected both the ED and wards:

- ED SSR increased from 4.6% (35/768) pre changeover 2023 to 5.0% (44/884) post.
- Ward SRR increased from 3.7% (71/1910) pre changeover 2023 to 4.8% (114/2383) post.

Regarding out of hours (OOH) samples (19.00- 7.00):

- Pre changeover 2023 the OOH SRR was 4.5% (37/821)
- Post changeover 2023 the OOH SRR was 5.4% (45/835). 33% (15/45) were from the ED. OOH rejected samples accounted for 29% (45/154) of SRR post changeover 2023.

Increased OOH rejections while modest may have a disproportionate effect on laboratory workflow due to reduced staffing.

Conclusions: Coagulation requests and SRR are increasing annually. There is no significant difference between the ward and ED SRR. SRR increases following a changeover period and at night. Extended phlebotomy hours and staff training at induction on sampling technique and PT indications may reduce requests and improve the SRR. This may generate savings (estimated €7/test) and improved lab efficacy, particularly OOH(1). A limitation of this audit is the time taken by lab staff to process rejected samples is unmeasured.

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Audit of CT pulmonary Angiogram Turnaround Times in Beaumont Hospital

N O'Connell[1,3,4], D Grzegorzek[4], A Busher[4], C Brosnan[2], D Mulholland[2], K Ewins[1]
[1]Dept of Haematology, Beaumont Hospital, [2]Dept of Radiology, Beaumont Hospital, [3]Dept of Medicine, Royal College of surgeons in Ireland, [4]Dept of Haematology, St. Vincent's University Hospital

Background: Computed tomography pulmonary angiography (CTPA) is the most widely used imaging technique for suspected pulmonary embolism (PE). It has been suggested that overuse of CTPAs is prevalent, especially in emergency departments (ED) (1). We hypothesised that CTPAs were over requested in Beaumont Hospital and that the following targets were not being achieved:

1. The (UK) Royal College of Radiologist (RCR) acceptable CTPA positive rate of 15.4-37.4% (2).
2. The UK National Institute for Health and Care Excellence guideline (NG158): all patients with a Wells PE score ≤4 must have a positive D-dimer before proceeding to CTPA. (3)
3. The RCR recommendation that 90% of CTPAs for inpatients with suspected PE should be reported within one working day of receipt and acceptance of the scan request. (4)
4. The National Radiology Quality Improvement Programme (NRQIP) report turnaround time (time from imaging to report authorisation) of <24 hours for inpatient CT scans, and <12 hours for ED. (5).

Aims:

1. Assess compliance with the listed standards for November 2022.
2. Determine the average time from; request to scan, scan to report, request to report, to identify delays.

Methods: All CTPAs performed during the 1st-30th of November 2022 were retrospectively identified using the Picture Archive Communication System. Length of stay was calculated using the Patient Information Profile Explorer (PIPE) system. The Well's Score and D-dimers were retrieved from scan requests and PIPE. This data was exported to excel for analysis. 133 CTPAs were identified. 4 scans were excluded. Requests were divided into ED or inpatient based on information provided.

Results:

1. The overall positivity rate was 14.0% which is below the RCR's target (15.4-37.4%), suggesting excessive requests.
2. 33 requests had a Well's Score of ≤ 4. Of these 6 did not have a D-dimer in the request or on PIPE. All 6 were negative and avoidable following NG158. Compliance with NG158 was 82% (27/33).
3. Compliance with the inpatient RCR one working day target was 31% (19/61).There was 100% compliance with the NRQIP inpatient target and 83% (53/64) for ED requests.
4. The average time for all CTPAs between; request and scanning is 30 hours 19 minutes, and from scan to report is 3 hours 41 minutes.

Conclusions: Substantial delays occur while awaiting scanning. Increasing CT capacity and time in use may improve on pre-scan delays. Solutions include expanding regular scanning hours and staffing to the addition of a 3rd CT scanner.

Inappropriate requests can be minimised through strict adherence to clinical practice guidelines. Modification of the radiology ordering system to include mandatory Well's scores, and D-dimer if less than 4 would improve compliance. Introducing a PE pathway may improve positivity and reduce time taken for clinical decision to request imaging.

Allocation of a protected nurse to expedite radiology transfers during on call hours as part of a suspected PE pathway may offer immediate improvements. Currently ED/ward nurses must accompany patients to and from radiology out of hours which can lead to unnecessary delays due to inadequate staffing levels.

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MEAN RETICULOCYTE HAEMOGLOBIN: AN INEXPENSIVE TEST WITH A SUBSTANTIAL YIELD IN IRON-RESTRICTED ERYTHROPOIESIS

J William[1], A Alnajjar[1], A Burke[1]
[1]Haematology, Sligo University Hospital, Sligo

Background: A 2021 Lancet Haematology study, involving 204 countries, showed the global prevalence of anaemia is 24·3% (~1·92 billion cases), with data from Ireland showing 4.9% (~246,000 cases). The majority being females and secondary to Iron deficiency anaemia (IDA)[1]. The discovery of the hepcidin regulatory effect on iron absorption and plasma iron levels has redefined our understanding of Iron-Restricted Erythropoiesis (IRE) and as a result, criteria have been identified to distinguish three syndromes, namely absolute iron deficiency (ID), functional iron deficiency and/or iron sequestration [2,3].

The BSH guidelines endorse international age- and gender-specific anaemia thresholds: Hb <130 g/l for adult men and <120 g/l for adult non-pregnant women.

Furthermore, they define ID as:
- Serum Ferritin (Ferr) of <15 ng/ml, or If Ferr >15 with Transferrin Saturation (TSAT) <16%.
- Mean Reticulocyte Haemoglobin (Ret-He) <29 pg [4].

TSAT, which is a derived calculation using Serum Iron and Total Iron Binding Capacity, is influenced by factors present in the majority of hospitalised patients such as inflammation, malnutrition, infection, recent iron intake, malignancy, serum iron diurnal variation and progesterone [5,6]. Moreover, Iron Profile (IP) and Ferritin analysis combined costs €10.40, whereas Ret-He costs €5.20 [7]. Hence, we will assess if Ret-He could serve as a more sensitive alternative to TSAT in this study and establish a cut-off point for use in our laboratory.

Method: This is a cross-sectional, Single-Centred, one-week study performed at Sligo University Hospital. A Lab-system code was put in place to flag any patient with a Hb of less than 10 g/dl and to add-on a complete haematinic profile, Peripheral blood film, and reticulocyte count to the same-day sample. Two doctors reviewed patients' charts, and laboratory results and analysed the data collected using Microsoft Excel Software.

Inclusion Criteria:
1) Patients aged > 16 years old.
2) Patients with Complete data (Laboratory variables in question).
3) Patients with accessible medical charts, current and past medical history, and Drug History.

Exclusion Criteria:
1) Patients not fulfilling the inclusion criteria.
2) Patients from Outpatient clinics.

Results: The study comprised 44 participants, 24 males and 20 females, with an average age of 70.5±20 years. The mean Hb of all patients was 86g/L. N= 24 had non-iron deficient anaemia. The remaining n=20 were deemed ID after application of the BSH and other disease specific (CCF, CRF) defining criteria [8,9]. Where n=14 (70%) met ID criteria by Fer/TSat, 3 of these had Ret-He >27 and therefore the Ret-He was not additive in the diagnostic work up. In contrast, n=17 (85%) met ID criteria using Ret he, of which 6 would have been missed if Fer/TSat was used alone.

Additionally, after excluding individuals who received Iron replacement therapy (n=6) or were transfused (n=16) within the last 3 months, a Ret-He threshold of 27.2 pg displayed a negative predictive value of 93.7%, specificity of 88.2%, and sensitivity of 85.7% for identifying Iron Restriction Erythropoiesis (IRE).

Conclusion: Ret-He Cut-off of 27.2 pg demonstrated a high negative predictive value for IRE. Although both tests are inexpensive, Ret-He offers a better value and diagnostic yield.

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IRON DEFICIENCY ANEMIA: TAILORED DIAGNOSTIC CRITERIA GUARANTEE ADEQUATE INTRAVENOUS IRON REPLACEMENT THERAPY

J William[1], O Ahmed[2], M Eltahir[3], F Azani[4], A Burke[1]
[1]Haematology Department, Sligo University Hospital, Sligo, [2]Nephrology Department, Sligo University Hospital, Sligo, [3]Respiratory Department, Sligo University Hospital, Sligo, [4]Cardiology Department, Sligo University Hospital, Sligo

Introduction: Iron deficiency (ID) is a leading contributor to the global disease burden, causing clinical and functional impairments even in the absence of anaemia [1]. In Ireland, 246,000 individuals suffer from anaemia, primarily secondary to ID [2]. In adults, anaemia is defined as Hb <130 g/l in men or <120 g/l in non-pregnant women[3]. However, ID is suggestive with serum Ferritin (Ferr) of <15 ng/ml, or Ferr >15 and Transferrin saturation (TSAT) <16% in the general population[3]. Nonetheless, in Heart Failure (HF), ESC guidelines define ID as Ferr<100 or Ferr<299 and TSAT <20%, unlike in Chronic Renal Failure, where KDIGO criteria defines ID as Ferr <100 and TSAT<20%, Ferr<200 and TSAT<20% or Fer<500 and TSAT<30%, in Non-dialysis or Peritoneal Dialysis patients, Hemodialysis patients, or those on Erythropotien, respectively [4,5]. Additionally, estimating Iron Deficit (Dose required) via the Ganzoni Equation [Total iron deficit, mg = weight, kg x (target Hb, g/dL – actual Hb, g/dL) x 2.4 + iron stores, mg] is recommended [6,7]. A recent Irish study estimated that a single Iron Infusion visit has a budgetary impact of moe than € 46.5, in addition to drug cost[8]. Therefore, this audit aims to assess ID/ Iron Deficiency Anemia (IDA) diagnosis accuracy based on underlying comorbidity-specific guidelines and iron dosage ensue.

Method: This is a crossectional design audit involving patients in Sligo University Hospital who received Iron Infusion as a day case or during their inpatient stay. They had been diagnosed with ID/IDA between February and August 2023, as admitted patients or in OPDs (Clinics, Day Service Unit (DSU) or Dialysis Unit (DU)). Participants' medical charts and blood indices were reviewed to assess ID based on their underlying illness (HF, CKD, Renal Replacement Therapy (RRT) or Non-chronic illness [General]). Ganzoni equation was computed for all IDA patients to assess their required Iron replacement dose.

Results: 101 patients were included in this study, 52 Males and 49 Females, with a mean age of (69±17). The cohort included patients with HF (n=28), RRT (n=8), CKD (n=17), and non-chronic illnesses/General (n=48) patients. Inpatients comprised 42.6% (n=43) versus 47.4% (n=58) Outpatients (including Clinics, DSU and DU). Ferrinject® (1g = € 155) was the primary IV Iron product administered except for RRT patients who received Venofer® (200mg = € 103).

44.1% (19/43) of the Inpatients were mislabelled as IDA versus 5.6% (3/58) Outpatients. Only 12% (3/25) of the true IDA inpatients had their required iron dose calculated versus none in OPD (0/47). Sub-therapeutic dosing was observed in 36% (9/25) of the true IDA Inpatients versus 10.6% (5/47) Outpatients, with underdosin of >250mg observed in both inpatients and Outpatients, 20% (5/25) vs 8% (4/47), respectively. Notably, among the Inpatients, 48.8% (21/43) had >500mg overdose versus 8.6% (5/58) among Outpatients irrespective of their ID status.

Conclusion: Current data highlights considerable misdiagnosis and inadequate treatment among Inpatients, while outpatients were often over-treated. Tailoring treatment based on underlying comorbidity and applying the Ganzoni equation is paramount for effective treatment and reducing Day Service Units' workload. Monofer® might be preferable to Ferrinject® for specific patients due to its potential for higher infusion doses.

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Aptamer BT200 prolongs VWF half-life by blocking interaction with macrophage scavenger receptor LRP1

A Chion[1], S Aguila[1], J Fazavana[1], C Byrne[1], P Lopes[1], SE Ward[1], JM O'Sullivan[1], T McKinnon[2], S Zhu[3], J Gilbert[3], B Gilma[4], J O'Donnell[1]
[1]PBS. Irish Centre for Vascular Biology, RCSI, Dublin,
[2]Haematology, Imperial College London, London, UK
[3]Band Therapeutics, Kentucky, USA
[4]Clinical Pharmacology, Vienna, Austria

Background:

The pegylated aptamer BT200 binds to the A1 domain of VWF and significantly prolongs VWF half-life in vivo. Although the mechanism(s) involved have not been defined, the LRP1 scavenger receptor binds to the VWF A1 domain and contributes to physiological VWF clearance.

Aims:

To determine the molecular mechanisms through which the BT200 pegylated aptamer extends VWF half-life.

Methods:

Binding of full-length and selected VWF truncations to bone marrow-derived macrophages (BMDM) was assessed by flow cytometry in the presence or absence of BT200. Immunosorbent plate-binding assays were used to characterize binding to purified LRP1-ClusterII or Cluster IV receptors respectively. Finally, clearance of HEK293T-expressed VWF variants were investigated in *VWF*$^{-/-}$ mice.

Results:

BT200 dose-dependently inhibited binding of recombinant VWF (Vonvendi) & plasma-derived VWF (Fandhi) to BMDMs (maximal binding inhibition: 88.55 ± 4.73 % at 10 µM BT200). In addition, BT200 significantly inhibited binding of full-length rVWF to purified LRP1-Cluster-IV ($p = 0.0005$). Plate binding assays confirmed that the truncated VWF-A1A2A3 fragment and the isolated VWF-A1 domain both bound to LRP1 Cluster-II and Cluster-IV. In both cases, binding was again inhibited by BT200 in a dose-dependent manner, recapitulating the BMDM results. Finally, interaction of VWF-A1A2A3 fragment with HEK-293T transfected with full length LRP1 cDNA was ablated by BT200. In contrast, BT200 had no inhibitory effects on VWF-A1A2A3 binding to either MGL or SR-A1 macrophage clearance receptors. Since BT200 binds close to Lys 1405 in VWF-A1, site-directed mutagenesis of Lys 1405 study was performed. VWFA1-K1405A did not bind BMDMs, nor to coated LRP1-Cluster-IV. Furthermore, full-length rVWF-K1405A demonstrated a significantly increased half-life in *VWF*$^{-/-}$ mice compared to wild type VWF ($P=0.0049$).

Conclusions:

Our novel findings demonstrate that Lys1405 in VWFA1 is critical for interaction with the LRP1 scavenger receptor. BT200 binds to VWFA1 close to this key Lys1405 residue, thereby preventing interaction with LRP1 and consequently extending VWF half-life

The NAS/DFB Ambulance Service PE Survey (ASSURE Survey): assessing awareness of PE among pre-hospital care providers in Ireland

B Dillon[1], S Masterson[2], E O'Rourke[1], C Hughes[1], C Fox[1], O Gildea[1], I Loftus[1], M O'Reilly[3], C O'Donnell[2], N Bannon[4], F Ní Áinle [1,4,5], B Kevane[1,4,5]
[1]Haematology, Mater Misercordiae University Hospital, Dublin,
[2]Clinical Directorate, HSE National Ambulance Service, ,
[4]VTE Working Group, Ireland East Hospital Group, ,
[5]School of Medicine, University College Dublin, ,

Introduction: Acute pulmonary embolism (PE) represents a major source of cardiovascular morbidity and mortality globally. While prompt initiation of treatment reduces mortality risk, failure to recognise signs & symptoms of PE may result in delays in accessing therapy. This is particularly important in the community setting where PE still accounts for approximately 5% of out-of-hospital cardiac arrests.

Pre-hospital care providers play a major role in the initial assessment and triage of cardiovascular emergencies in the community as well as at the point of transferring care to hospital-based emergency medicine staff. In order to assess awareness around PE among pre-hospital providers, the Ireland East Hospital Group (IEHG) devised a survey in collaboration with the HSE National Ambulance Survey (NAS) and the Dublin Fire Brigade (DFB) service, with a plan to target subsequent educational initiatives at any potential knowledge gaps identified by the survey.

Methods: An online survey consisting of 10 questions relating to PE symptoms, signs, risk factors and treatment options was devised by the IEHG VTE working group in collaboration with NAS/DFB. The survey was distributed by the NAS Clinical Directorate to over 2,500 NAS and DFB practitioners via the NAS/DFB email cascade system. Practitioners were invited to access the survey via a QR code link, with reminders issued via the secure Saadian text messaging system on 2 occasions and by a memo issued to all practitioners in the NAS College database.

Results: 500 responses to the survey were received, representing a response rate of approximately 20%. Paramedics and advanced paramedics represented the majority of respondents (59.8% and 33.8% respectively) with Emergency Medicine Technicians accounting for 6.4%. From a geographical perspective, 10.4% of responses were obtained from DFB providers with the remaining responses spread evenly across all 8 NAS regional services nationally.

All respondents were familiar with the term 'pulmonary embolism'. While most were aware that PE frequently presents with chest pain and dyspnoea, 35% reported that they would not usually have considered PE as a possible differential diagnosis in patients presenting with collapse/syncope. Similarly, while most respondents recognised major surgery, pregnancy and personal/family history of thrombosis as being important VTE risk factors, 46% of respondents were not aware that cancer was a VTE risk factor and 30% did not consider COVID-19 to be associated with increased VTE risk. While 67.7% of respondents recalled having provided care to a patient with PE, 39% of respondents reported having never received education sessions regarding PE/VTE.

Conclusion: Pre-hospital care providers in Ireland are aware that acute PE represents a source of serious cardiovascular morbidity. However, this survey identified a number of knowledge gaps among providers relating to the manner in which PE may present in the community and the risk factors associated with increased thrombosis risk. In order to address these gaps, the IEHG in collaboration with NAS/DFB is currently developing an electronic PE awareness resource which will be distributed to all NAS/DFB care providers followed by a repeat survey to assess the effect of the intervention.

AGE REGULATES DESMOPRESSIN RESPONSES IN PATIENTS WITH LOW VON WILLEBRAND FACTOR AND TYPE 1 VON WILLEBRAND DISEASE IN THE LOVIC AND WIN STUDIES

F Atiq[1, 2], R Blok[2], CB van Kwawegen[2], **D Doherty[1]**, M Lavin[1, 3], JG van der Bom[4], NM O'Connell[3], J de Meris[5], K Ryan[3], SEM Schols[6], M Byrne[3], FCJI Heubel-Moenen[7], KPM van Galen[8], RJS Preston[1], CJ Fijnvandraat[9], RI Baker[10,11], K Meijer[12], P James[13], J Di Paola[14], HCJ Eikenboom[15]
[1]Irish Centre for Vascular Biology, School of Pharmacy and Biomolecular Sciences, Royal College of Surgeons in Ireland, Dublin, [2]Department of Haematology, Erasmus University Medical Center-Erasmus MC, Rotterdam, Netherlands, [3]National Coagulation Centre, St James's Hospital, Dublin, [4]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands, [5]Netherlands Hemophilia Society, Leiden, The Netherlands, [6]Department of Hematology, Radboud university medical center, Nijmegen and Hemophilia Treatment Center Nijmegen-Eindhoven-Maastricht, The Netherlands, [7]Department of Hematology, Maastricht University Medical Center, Maastricht and Hemophilia Treatment Center Nijmegen-Eindhoven-Maastricht, The Netherlands, [8]Van Creveldkliniek, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands, [9]Department of Pediatric Hematology, Emma Children's Hospital, Amsterdam University Medical Centres, University of Amsterdam, Amsterdam, The Netherlands, [10]Western Australia Centre for Thrombosis and Haemostasis, Perth Blood Institute, Murdoch University, Perth, WA, Australia, [11]Irish-Australian Blood Collaborative (IABC) Network, [12]Department of Hematology, University Medical Center Groningen, Groningen, The Netherlands, [13]Department of Medicine, Queen's University, Kingston, ON, Canada, [14]Department of Pediatrics, School of Medicine, Washington University in St. Louis, St. Louis, Missouri, USA, [15]Department of Internal Medicine, Division of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands.

Introduction: Desmopressin is the treatment of choice in many patients with Low VWF and type 1 VWD. However, not all patients respond well to desmopressin. Moreover, desmopressin is contra-indicated in patients > 60 years. Interestingly however, previous studies have demonstrated that increases in plasma VWF levels seen with ageing are attributable to enhanced VWF biosynthesis coupled with reduced VWF clearance. Therefore, we investigated the hypothesis that VWF biosynthesis and clearance, and hence DDAVP responses, may vary with ageing.

Methods: We investigated datasets from the Low VWF in Ireland Cohort (LoVIC) and Willebrand in the Netherlands (WiN) studies. All patients included in the LoVIC study had VWF levels in the 30-50 IU/dL range. Conversely, WiN patients had either a personal bleeding history or positive family history, combined with VWF levels ≤ 30 IU/dL. Desmopressin was administered intravenously at a dosage of 0.3 µg/kg (maximum dose capped at 28 µg/kg) or intranasally at a total dosage of 300 µg. Complete desmopressin response was defined according to the 2021 ASH/ISTH/NHF/WFH guideline.

Results: In total, 261 patients were included (178 WiN patients with type 1 VWD and 83 LoVIC patients with Low VWF). Based upon levels at inclusion in the WiN study versus original diagnosis, type 1 VWD patients were categorized into three groups - (i) 69 patients with persistent VWF levels < 30 IU/dL; (ii) 55 patients with partial correction in VWF levels into the 30-50 IU/dL range; and (iii) 54 patients with normalization of VWF levels > 50 IU/dL.

Importantly, a complete response to desmopressin was observed in only 58% of WiN patients with persistent VWF levels < 30 IU/dL, whereas 100% of WiN patients with partially corrected or normalized levels and 100% of LoVIC patients had a complete response to desmopressin ($p<0.001$).

Type 1 patients with persistent VWF levels < 30 IU/dL had significantly lower VWF:Ag at all time points after desmopressin compared to the other groups ($p<0.001$). Unexpectedly, VWF:Ag at 1, 4 and 24 hours after desmopressin was significantly higher in WiN normalized compared to LoVIC patients ($p<0.001$). Importantly however, the WiN normalized cohort was significantly older at the time of their desmopressin trial than the LoVIC group (41.9 ±13.8 years versus 32.9 ±10.7 years, $p=0.002$). Therefore, we hypothesized that the difference in VWF responses might be age-dependent. Indeed, older patients had both a significantly better initial desmopressin response at 1 hour after desmopressin ($p=0.018$), and a significantly prolonged half-life of VWF at 4 hours after desmopressin ($p=0.004$).

Finally, we performed a retrospective cohort study to investigate whether desmopressin response could be utilized to predict which type 1 VWD patients would normalize their plasma VWF levels with aging. We demonstrate that desmopressin response predicted the normalization of VWF levels with aging with a 100% negative predictive value ($p<0.001$).

Conclusion: Cumulatively, we demonstrate that desmopressin responses increase significantly in VWD patients and Low VWF patients as they get older. Given our findings, future studies assessing the clinical efficacy and safety of using attenuated desmopressin doses in older patients should be considered.

O-glycan and sialic acid residues differentially regulate von Willebrand factor trafficking, storage and secretion.

E Karampini[1], D Doherty[1,2], M Garre[3], S Elliott[1], B Cavanagh[4], J O'Sullivan[1], I Schoen[1], JS O'Donnell[1,2]
[1]Irish Centre for Vascular Biology, PBS, Royal College of Surgeons in Ireland, Dublin, Ireland
[2]National Coagulation Centre, St James's Hospital, Dublin, Ireland
[3]Super-Resolution Imaging Consortium, Royal College of Surgeons in Ireland, Dublin, Ireland
[4]Cellular and Molecular Imaging Core, Royal College of Surgeons in Ireland, Dublin, Ireland

Background: Von Willebrand factor (VWF) is a key hemostatic glycoprotein synthesized and secreted by endothelial cells. During biosynthesis, VWF undergoes extensive N- and O-linked glycosylation, before finally being stored in Weibel-Palade bodies (WPBs). WPB morphology influences VWF string formation upon activation. Although glycan alterations have been implicated in von Willebrand disease pathophysiology, the role of glycosylation in regulating VWF intracellular trafficking remains poorly understood.

Aims: In this study, we investigated the role of O-glycan moieties and terminal sialylation on intracellular VWF trafficking, WPB formation and VWF secretory pathways.

Methods: HUVECs were treated with the O-glycosylation inhibitor BG (Benzyl-α-GalNAc) or sialylation inhibitor FAX (P-3FAX-Neu5Ac). α2-3 sialylation was reduced by short hairpin RNA (shRNA) knockdown (KD) of ST3Gal4. WPB morphology and string formation was studied using confocal microscopy. VWF secretion was assessed by ELISA.

Results: Inhibition of VWF O-glycosylation by BG significantly increased basal VWF secretion ($p<0.01$). In contrast, inhibition of VWF sialylation by FAX significantly attenuated VWF release into the supernatant ($p<0.0001$). Similarly, KD of ST3Gal4 resulted in a significant decrease of VWF basal release ($p<0.01$). BG-induced inhibition of O-glycosylation in HUVECs markedly affected WPB formation, such that WPBs were significantly shorter and more circular in BG-treated cells compared to controls ($p<0.0001$). Additionally, BG-treatment resulted in the activation of A1 domain intracellularly and negatively affected the cells' ability to produce histamine-induced VWF strings under shear stress (1.5 ml/min) with both fluorescent-labelled and platelet-decorated VWF strings being significantly reduced in length ($p<0.0001$). In FAX and shST3Gal4 treated ECs, WPB morphology appeared normal without A1 activation, but a significant increase in the WPB number per cell was observed in FAX-treated ECs ($p<0.01$).

Conclusions: Our novel data suggest that VWF O-linked glycosylation and terminal sialylation critically regulate intracellular trafficking and internal storage of VWF in EC. Moreover, these glycan effects impact VWF biosynthesis through a variety of different mechanisms.

Examining Variability in the Diagnosis and Management of People with Bleeding Disorders of Unknown Cause

C Kelly[1,2], W Thomas[2], R Baker[4,5], M Lavin[1,2]
[1]National Coagulation Centre, St. James's Hospital, Dublin, [2]Irish Centre for Vascular Biology, School of Pharmacy and Biomedical Sciences, RCSI, Dublin, [3]Haematology Department, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom, [4]Western Australia Centre for Thrombosis and Haemostasis, Perth Blood Institute, Murdoch University, Perth, Australia, [5]Haemophilia Treatment Centre, Hollywood Hospital, Perth , Australia

Background: Bleeding disorder of unknown cause (BDUC) is characterised by a bleeding phenotype, with exclusion of non-haematological bleeding (e.g. scurvy), in the setting of normal haemostatic testing. [1–3] The recognition and registration of these patients has increased significantly in the last 10 years. [4] To date no standardised diagnostic criteria or treatment algorithms exist for people with BDUC. To correct this deficit the International Society on Thrombosis and Haemostasis (ISTH) and Von Willebrand factor subcommittee developed a focused project, aimed at understanding and addressing knowledge gaps, developing consensus pathways and ultimately improving care.

Objectives and Methods: The aim of this project was to determine the current international clinical practices in the investigation, registration and treatment of people with BDUC through an online structured survey of health care providers (HCP). The survey was available in the English and Spanish language and was distributed via the ISTH mailing list, associated societies and social media. The English survey remained open from 28th April 2022 to 1st July 2023, with the Spanish version available from 1st March 2023 to 1st July 2023.

Results: Two hundred and sixteen respondents from 39 countries were included in the final analysis. The clinical assessment of those with a possible bleeding disorder varied, with only 55% excluding hypermobility but high levels (80%) of bleeding assessment tools (BAT) usage. Nearly all respondents documented if there was a family history of bleeding (87.9%). In haemostatic testing only the prothrombin time (PT) and activated partial thromboplastin time (APTT) tests gained universal support. Interestingly 70.3% would perform ABO blood grouping in first line investigations whilst only 64.8% would perform a full blood count (FBC) and 68.5% a ferritin level.

With regards to surgical prophylaxis, tranexamic acid was favoured for minor procedures by 71.7% respondents, major procedures by 59.2% and pregnancy 58.3%. The management of postprocedural bleeding was heterogenous with responses favouring the use of desmopressin (DDAVP), platelets and in second line treatment recombinant factor VIIa (rFVIIa.) The management of heavy menstrual bleeding (HMB) in women despite combined oral contraceptive pill (COCP) use also proved to be challenging with HCPs picking multiple alternative first line strategies. The addition of tranexamic acid proved to be the most popular response (53%) with second line options favouring intrauterine device (IUD) (18.5%).
Delivery advice in patients with BDUC varied with 54.3% advising fetal precautions while 28.6% recommended no restrictions and 15.5% were uncertain. With regards to maternal precautions, spinal anaesthesia was permitted by only 16.3% of respondents and epidural in 13.2%. Majority would avoid use of spinal (55.2%) or epidural (61.2%) with uncertainty expressed by many respondents (20.1% and 21% respectively)

Conclusion: Significant variation exists in the recognition, registration and management of people with BDUC worldwide. There is a considerable difference in the laboratory investigations performed and the choice of haemostatic support prescribed for this cohort. This survey emphasises the need for consensus pathways to diagnose and treat BDUC in order to standardise and improve care for patients internationally.

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IMPLEMENTATION OF SINGLE FACTOR X REPLACEMENT TREATMENT IN ADULTS WITH INHERITED SEVERE FACTOR X DEFICIENCY

HV Maria Buruno[1,2*], **M Moriarty[1,3*]**, C Bergin[1], E Singleton[1], N Larkin[1], N O'Connell[1]
[1]National Coagulation Centre, St James's Hospital, Dublin 8,
[2]School of Medicine, University of Limerick, Castletroy, Limerick,
[3]School of Medicine, Trinity College Dublin, Dublin 2,

Introduction/Background: Inherited Factor X deficiency (FXD) is an extremely rare autosomal recessive coagulation disorder, with an increased prevalence in Ireland due to a founder mutation. Severe deficiency is associated with a high risk of spontaneous bleeding, highlighting the importance of effective prophylaxis. Inadequate Factor X (FX) treatment can lead to potentially life-threatening intramuscular haematomas, haemarthrosis and GI bleeding.[1] Prothromplex, a plasma-derived prothrombin complex, concentrate (PCC), is a widely used treatment for FXD but has been associated with thrombotic complications.[2] Coagadex is a plasma-derived, single factor X concentrate and may provide a safer, more specific and less burdensome replacement treatment for inherited FXD.[3] The aim of this study is to evaluate the treatment outcomes before and after an en-masse switch of FX replacement to Coagadex.

Materials and methods: A retrospective study was conducted of all patients >18 years registered in the National Coagulation Centre with severe FXD following an en-masse switch of prophylaxis from PCC to Coagadex in 2022. Treatment outcomes for 14 months pre- and post-switch were documented as part of routine care and included FX:C levels, bleed rates, FX consumption (evaluated by FX prescription, dispensing and administration), management of gynaecological bleeding and procedures. Bleeds were documented as traumatic or spontaneous and interval from last prophylactic treatment was recorded where available. A qualitative analysis was conducted based on patient reports of differences between the treatments.

Results: Five patients (3 male, 2 female, age range 21-34 years) were prescribed prophylaxis with FX replacement, initially with PCC and since 2022, with Coagadex. The median (range) of prescribed prophylaxis dose was 19 IU/kg (17-24) twice weekly for PCC and 25 IU/kg (24-30) once or twice weekly for Coagadex. Median (range) for annual consumption was 1988 IU/kg/yr (921 - 2457) for PCC and 1907 IU/kg/yr (1466 - 2984) for Coagadex. Median Annualised Bleeding Rates (ABR) were less than 2 for both products; 0.9 (range 0-2.6) on PCC and 1.7 (range 0-3.4) on Coagadex. Heavy menstrual bleeding was an ongoing issue for female patients, illustrating that gynaecological bleeding may not respond to FX prophylaxis alone. FX levels were taken opportunistically at clinic visits but interpretation was challenging due to incomplete administration records. Socioeconomic factors such as literacy and accommodation were noted to impede patient adherence. One major, five minor and two dental procedures were covered with PCC (n=3) and Coagadex (n=5) without excessive bleeding.Qualitative data showed that patient satisfaction improved with Coagadex, with reduced infusion volume making self-administration of prophylaxis “much easier”.

Conclusion: Comprehensive data collection in a small but complete adult patient cohort confirms that Coagadex prophylaxis provides equivalent bleed protection in comparison to PCC, with a reduced administration burden for patients. Heavy menstrual bleeding continues to pose a management challenge for women with severe FXD, even with prophylaxis. Adherence is essential for successful prophylaxis and is affected by socioeconomic factors. Further analysis is needed on long-term treatment outcomes to advocate for patients with this extremely rare disorder.

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RECURRENT VENOUS THROMBOEMBOLISMS, ANTICOAGULATION COMPLICATIONS, AND THE IMPORTANCE OF MDT REVIEW IN DECISION MAKING; A PROSPECTIVE STUDY.

T Nasibov[1], N Fyzul[1], P Kiely[2], M Watts[1], D O'Keeffe[1]
[1]Haematology, University Hospital Limerick , Limerick,
[2]Radiology, University Hospital Limerick, Limerick,

Background: Recurrence of venous thromboembolism (VTE) is associated with high mortality and morbidity but anticoagulation also confers high risks. Cancer, Antiphosholipid Syndrome, vascular disorders, Heparin induced Thrombocytopenia, and Pregnancy are a few known causes for recurrence. Although the acute treatment phase of VTE is 3 months, it is known that the residual effects of prior VTE remain in a significant number of patients eventually causing post thrombotic syndrome. These residual effects can mimic the appearance of acute thrombosis on Venous Doppler, and thus mimic a recurrent thrombotic event. This has the potential to result in a clinical recommendation for continued and possibly life long anticoagulation, with the inherent, potentially unnecessary bleeding risks associated. Elastography, compression and vein diameter are a few methods adopted by radiologists to distinguish between old and new clots on ultrasound[1]. However this requires previous scans for comparison and has limitations. We propose that a Multidisciplinary Meeting (MDM) is vital to confirm if recurrence is indeed true given the significant impact on patient management.

Aims: This study aims to assess the value of MDM review of recurrent VTE, which combines radiology, clinical history and d-dimer to evaluate whether a thrombus is truly recurrent. Prospective follow up of patients was then carried out to determine if the MDM decision was correct.

Methods: All patients reviewed in the Thrombosis MDM meeting between 2019 and 2021 who were defined as recurrent VTEs were included in this study. The MDM consists of comparing the prior and new scans by an expert Consultant Radiologist in discussion with the Consultant Haematologist and Physician. The clinical presentation, D-dimers, risk factors, treatment regimes, complications and MDM outcome were noted. These patients served as a cohort that were followed up by prospective analysis to 2023 to determine if these patients had further VTEs or anticoagulation related complications based on clinical and radiology review.

Results: 45 patients were identified with a recurrent PE (8, 17.8%) or DVT (37, 82.2%). After MDM review, 22 (48.9%) were determined to have evidence of previous VTEs without features of a new VTE. 8 of these 22 patients (36.4%) had an elevated d-dimer with 9 (40.9%) being negative. 19 (42.2%) were deemed to be new and 4 (8.89%) were indeterminate but treated as new. Active treatment was ceased in 10 (22.2%) and 4 (8.89%) had already completed 3 months of anticoagulation prior to MDM. The 3-month anticoagulation course commenced on diagnosis was completed in those who were significantly symptomatic with persisting risk factors (8, 17.8%). 19 (42.2%) patients who were deemed no new VTE had their anticoagulation stopped by three months while 3 (6.66%) were reverted to their prophylactic life-long anticoagulation. Life-long anticoagulation was started in those with a new event where at least one thrombus was deemed to be unprovoked 20 (44.4%).

On follow up 20 (44.4%) patients had repeat scans to evaluate further events with only 1 (2.22%) being positive for a breakthrough event. This patient had underlying cancer and was on anticoagulation at this time.

Summary/Conclusion: MDM review of patients presenting with recurrent VTE is vital. Clinical assessment with radiology evidence enabled 48.9% of patients to have their diagnosis of a new VTE changed thus allowing cessation of anticoagulation in 42.2% and reversion to prophylaxis in 6.66%. One of these patients on long-term anticoagulation had a subsequent VTE with progression of their lung malignancy.

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THE BURDEN OF VENOUS THROMBOEMBOLISM AND THE CHALLENGES IN DELIVERING ADEQUATE CARE IN THE SETTING OF POVERTY, HOMELESSNESS, AND SOCIAL EXCLUSION: A SINGLE CENTRE CROSS-SECTIONAL STUDY

E O'Rourke[1], S Toolan[1], B Dillon[1], C Hughes[1], I Loftus[1], O Gildea[1], C Fox[1], D Scott[1], L Solomon[1], F Ní Áinle [1-5], S Maung[1,3], M Fay[1,3], A Fortune[1,3], B Kevane[1-5]

[1]Haematology, Mater Misericordiae University Hospital, Dublin, [2]Irish Network for VTE Research (INViTE), Dublin, [3]School of Medicine, University College Dublin, [4], Rotunda Hospital, Dublin, [5]UCD Conway Sphere Research Group, University College Dublin

Introduction: Social exclusion is a multi-dimensional state characterised by the inability to participate in the normal social, economic and cultural activities of society. It arises as a result of an interplay between adverse biopsychosocial factors including poverty, deprivation and ill-health. Social exclusion is frequently experienced by homeless people, people with substance misuse disorders and other marginalised populations including prisoners, sex workers and people with severe mental illness (1-4). Socially excluded persons (SEP) frequently encounter challenges in accessing healthcare and exhibit earlier onset of disease and higher mortality rates (1-4).

Venous thromboembolism (VTE) is a leading cause of morbidity and mortality globally. Low socio-economic status is associated with an increased VTE risk. Among SEPs, VTE risk is particularly increased among those who engage in injecting drug mis-use (IVDU; injecting of heroin or other drugs into groin veins) (5-7). In Ireland, social exclusion & homelessness are associated with high rates of IVDU.

The Mater Misericordiae University Hospital serves a diverse urban population in inner-city Dublin. In this study we aimed to determine the proportion of new VTE referrals to the thrombosis clinic which related to SEP and to identify the challenges faced by this population.

Materials and Methods: A cross-sectional study was undertaken where records pertaining to new acute VTE referrals to a specialist thrombosis clinic during the 12-month period from June 2021-May 2022 were assessed. The characteristics of individuals who met criteria for social exclusion (current or prior IVDU; methadone use; hepatitis C; homelessness; incarceration; or severe/enduring mental illness) were compared to the general population of VTE patients.

Results: There were 170 new VTE referrals of which 35 (21%) related to SEPs. Within the SEP group, 22 (62.9%) reported active/prior IVDU and 19 (54.3%) were homeless. 13 (37.1%) had a concurrent major mental illness and 16 (45.7%) had hepatitis C and/or HIV.

In comparison to the general VTE population, SEP were significantly younger [median age 46 (IQR 42-55) vs 62 (IQR 47-72) years; p<0.001] and a higher proportion had a history of prior VTE (57.1% vs 23.7%; p=<0.001). The majority of SEP with prior VTE had a history of active/prior IVDU (16/20; 80%). The rate of non-attendance for clinic review was higher in the SEP group (57.1% vs 20%; p<0.0001) and current treatment status was unknown in 25.7% of the SEP group in contrast to 8.1% in the general population (p=0.02). The rate of re-attendance at the emergency department was significantly higher in the SEP population (42.9% vs 12.6%; p=<0.001).

Conclusion: SEPs make up a substantial proportion of patients with acute VTE presenting to our institution. These vulnerable patients present with complex care needs and co-morbidities including high rates of recurrent VTE, psychiatric illness and homelessness. Delivering adequate VTE treatment is challenging, as evidenced by the high rates of non-attendance, loss to follow-up, re-attendance for unscheduled emergency care and recurrent VTE among this population. Novel approaches to the delivery of care are urgently required in order to mitigate the potential risk of mortality and chronic morbidity associated with VTE in this population.

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A novel role for itaconate in trained immunity and myeloid cell-mediated hypercoagulability

AM Rehill[1,2,3], S McCluskey[1,2,3], G Leon[1,2,3], TAJ Ryan[4], AE Ledwith[4], H Charles-Messance[4], EA Day[4], C McMahon[3], JS O'Donnell[1,2], AM Curtis[2], LAJ O'Neill[4], FJ Sheedy[4], RJS Preston[1,2,3]
[1]Irish Centre for Vascular Biology, RCSI University of Medicine and Health Sciences, Dublin,
[2]School of Pharmacy and Biomolecular Sciences, RCSI University of Medicine and Health Sciences, Dublin,
[3]National Children's Research Centre, Our Lady's Children's Hospital Crumlin, Dublin,
[4]School of Biochemistry and Immunology, Trinity College Dublin, Dublin,

Background: The mechanisms underlying the increased risk of venous thromboembolism in patients with chronic inflammatory disease or haematological malignancies remain poorly understood. We previously demonstrated that disease-associated 'trained immunity' in myeloid cells, a phenomenon describing long-term innate immune cell memory as a result of prior exposure to an inflammatory stimulus, leads to enhanced myeloid cell hypercoagulability, offering a possible mechanism by which increased thrombotic risk in inflammatory diseases may occur. Metabolic reprogramming is a key hallmark of trained immunity and is required to sustain long-term transcriptomic and epigenomic changes necessary for training. Itaconate is a product of the TCA cycle intermediate *cis*-aconitate that has been characterised to exhibit a broad array of immunomodulatory activities. Consequently, we hypothesised that itaconate may contribute to myeloid cell trained immunity and hypercoagulability.

Aim: To investigate the role of endogenous itaconate on trained immunity and hypercoagulability in myeloid cells both *in vitro* and *in vivo* using mice deficient in the enzyme necessary for itaconate production (*ACOD1*$^{-/-}$)

Methods: Murine bone marrow-derived macrophages from wild type and *ACOD1*$^{-/-}$ mice were trained with β-glucan, washed, and left for 7 days before lipopolysaccharide (LPS) re-stimulation. *In vivo* immune cell training was achieved by i.p. β-glucan administration. Cell gene expression and function were analysed by RT-qPCR, ELISA, flow cytometry and cell-based calibrated automated thrombinography.

Results: Surprisingly, bone marrow-derived macrophages derived from *ACOD1*$^{-/-}$ mice could not be "trained" with β-glucan and exhibited significantly reduced proinflammatory gene expression (*TNFA* and *IL6*) compared to wild-type mice upon LPS restimulation. Moreover, no difference in IL-6 and TNFα production was observed between β-glucan-trained and LPS-treated alone groups in *ACOD1*$^{-/-}$ macrophages. In parallel, *ACOD1*$^{-/-}$ cells were largely deficient in supporting plasma thrombin generation compared to macrophages isolated from wild-type mice. β-glucan-trained macrophage-dependent thrombin generation on *ACOD1*$^{-/-}$ macrophages was associated with significantly reduced peak thrombin and endogenous thrombin potential (ETP) for all treatment conditions, and significantly prolonged lagtime in b-glucan-trained *ACOD1*$^{-/-}$ macrophages when compared to wild-type cells. To assess whether loss of itaconate production also impaired trained immunity and myeloid cell procoagulant function *in vivo*, WT and *ACOD1*$^{-/-}$ mice were trained with either i.p injection of β-glucan or saline 3 weeks before sacrifice. Plasma from β-glucan-trained normal mice exhibited greater thrombin generation compared to plasma from PBS-administered mice, but *ACOD1*$^{-/-}$ mouse plasma exhibited significantly impaired thrombin generation, even in mice previously trained with β-glucan. Systemic inflammatory stimuli can initiate bone marrow (BM) trained immunity via adaptations in hematopoietic stem and progenitor cells that promote a long-term myeloid bias. A β-glucan-induced increase in BM myelopoiesis was observed in normal mice, but not in *ACOD1*$^{-/-}$mice. Remarkably, both mature haematopoietic progenitor cells and bone marrow-derived macrophages from β-glucan-trained mice possessed enhanced procoagulant activity compared to PBS-treated mice, but this effect was lost in cells from the *ACOD1*$^{-/-}$ mice.

Conclusions: This study demonstrates a novel role for endogenous itaconate in controlling myeloid procoagulant activity and regulating trained immunity. Moreover, these data suggest that endogenous itaconate represents a tractable therapeutic target for attenuating thromboembolic risk in inflammatory diseases associated with maladaptive trained immunity.

MULTIPLE MYELOMA AND THROMBOSIS: A REVIEW OF CURRENT RISK ASSESSMENT AND THROMBOPROPHYLAXIS PRACTICE

KS Saif[1], DS Swan[2], JQ Quinn[3], SG Glavey[4], KW Ewins[5], PM Murphy[6], BC Cummings[7]
[1]Haematology, Beaumont hospital, Dublin, Ireland

INTRODUCTION: Venous thromboembolism (VTE) is a major complication of multiple myeloma which can lead to significant morbidity and mortality. The risk of VTE is highest during the first 6 months after diagnosis, and is affected by factors including patient age, co-morbidities, disease related issues such as renal impairment and treatment related factors, e.g. use of immunomodulatory drugs (IMiDs). (Stefano, 2022)

Prophylactic anticoagulation in newly diagnosed multiple myeloma (NDMM) is not standardized. The risk stratification models available are not uniformly recommended or utilised and suggestions regarding choice of thromboprophylaxis vary across publications. (Stefano, 2022) Use of direct oral anticoagulants (DOACs) is increasing in MM and may provide a more favourable option than low-molecular weight heparin (LMWH) injections.

METHODS: We conducted a retrospective chart review of VTE risk-assessment in NDMM patients presenting to Beaumont hospital from 1/4/2022-20/11/2022. Data collected included age, gender, ethnicity, BMI, MM subtype, ISS stage, VTE risk assessment documentation, choice of anticoagulant/antiplatelet, MM systemic anti-cancer therapy (SACT) and cytogenetics. VTE risk was retrospectively performed using the validated IMPEDE score, which considers IMID use, BMI ≥ 25 kg/m2, recent pelvic, hip, or femur fracture, use of an erythropoiesis-stimulating agent, doxorubicin chemotherapy, dexamethasone use, Asian/pacific islander race, prior history VTE history, central venous catheter, and choice of anti-thrombotic agent. Patients with scores of ≤3, 4–7, and ≥8 are considered to have low, intermediate or high risk of VTE within the first 6 months of treatment initiation. (Sanfilippo, 2019)

RESULTS: 30 patients were identified. 16 (53.3%) were males, 14 (46.6%) females, and all were Irish. Median age was 60.5 (range 41-80). Of the 24 patients who received (SACT), 7 had light chain disease, 14 had IgG and 3 had IgA myeloma. Staging was possible in 14 cases of which, 6 were Stage I, 4 were Stage II and 4 were Stage III. 4 patients had high-risk cytogenetics. The majority of patients (n=14) received an IMiD-containing induction regimen, with CyBorD (cyclophosphamide/bortezomib/dexamethasone) and RVD (lenalidomide/bortezomib/dexamethasone) identified as the most commonly chosen regimens (8 patients each). Out of 24 patients 15 (62.5%) had no documentation of VTE risk assessment, 9 (37.5%) had an informal risk assessment, 7 of these were started on prophylactic anticoagulation and 2 were started on aspirin. 7 patients had a low-risk IMPEDE score, 11 an intermediate-risk score and 6 were high-risk. Of the high-risk patients, 2 received no anti-thrombotic agent, 1 received aspirin, 1 LMWH and 2 apixaban. 1 patient with an intermediate-risk score developed a PE.

CONCLUSION: Out of 24 NDMM patients, 70% (17) had an intermediate to high risk of developing VTE as per the calculated IMPEDE score and 1 patient developed an acute VTE. Choice of thromboprophylaxis varied, with high-risk patients receiving aspirin or no thromboprophylaxis in some cases. Use of apixaban appears to be increasing in this setting. Following on from this work, we have implemented a formal VTE risk assessment for all NDMM patients within the newly formed Myeloma MDT on the National Cancer Information System.

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A RETROSPECTIVE REVIEW ON THE USAGE OF ANDEXANET ALFA IN UNIVERSITY HOSPITAL LIMERICK

C TAN[1], D O'KEEFFE[1], N O'BRIEN[2]
[1]Haematology , University Hospital Limerick, Limerick, Ireland
[2]Blood transfusion laboratory, University Hospital Limerick, Limerick , Ireland

Introduction: Anticoagulants are widely used for the management of arterial and venous thromboembolism (VTE). Since the introduction of direct factor Xa inhibitors, warfarin has largely been replaced[1]. However, it's only recently in April 2023 that andexanet alfa, the reversing agent to direct factor Xa inhibitors, was funded in Ireland. In June 2023, the Irish Haematology Society Coagulation Special Interest Group published a national guideline on the appropriate indication and usage of this product [2].

University Hospital Limerick (UHL) has the privilege to have access to andexanet alfa shortly after its introduction to Ireland since in May 2023. In UHL, andexanet alfa is stored in the blood bank and is therefore rapidly available to patients upon approval by the consultant haematologist. As this product is still relatively new in Ireland, we decided to conduct a retrospective review on the usage of andexanet alfa in UHL. Our review aims to increase our experience of using this product by understanding our patients' demographics, indications, nature and severity of bleed and clinical outcome.

Materials and methods: To achieve our aim, we conducted a retrospective review from May 2023 and this is still ongoing to date. We are using multiple sources for data collection including patients' medical charts, laboratory information system (iLAB) for blood results, time of request and blood products administered. The BloodTrack® system was used to track the collection and administration time of andexanet alfa, and NIMIS radiology for scan indications and result. From these sources, we are able to obtain data including patients' demographics, indication for anticoagulation, type of direct factor Xa inhibitor patients were on, bleeding site and severity, dose of andexanet alfa needed and time of request. In addition, we are also able to establish the presence of renal and/or hepatic impairment at the time of bleed as well as patients' clinical outcome at 7 days post-bleed.

Preliminary results: Data collection is currently ongoing and we will have additional patients and data. To date, there has been 8 patients (7 males) who received andexanet alfa to reverse their anticoagulation in UHL since May 2023 with an average age of 82 (ranging 68-91). At the time of bleed, 75% of the patients were on anticoagulants for atrial fibrillation and the rest for VTE. 75% were on apixaban and 25% on rivaroxaban. 7 had intracranial bleed of which 50% were traumatic due to falls. One other patient sustained a massive unstable gastrointestinal bleed with Hb of 3. The average duration from request of andexanet alfa to administration was 49 minutes. At 7 days post bleeding, 75% of patients were alive. Further clinical outcome is being determined in due course.

Conclusion: Our preliminary results suggest that andexanet alfa has been appropriately and rapidly given in the event of life-threatening bleed to patients who received apixaban or rivaroxaban. Most of the haemorrhages were intracranial and half due to falls. Our review indicates that andexanet alfa is an important new treatment for reversal of life-threatening bleeds in this patient group.

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EVALUATING THE USE OF TRANSFIX TO STABILISE ANTIGEN EXPRESSION IN BONE MARROW LYMPHOCYTES UNDERGOING FLOW CYTOMETRY

J Bradley[1], L McArt[1], R Morilla[2], A Niblock[1,3]
[1]Department of Haematology, Antrim Area Hospital, Northern Ireland
[2]Royal Marsden NHS foundation, HMDS
[3]School of Medicine, Ulster University, Northern Ireland

Lymphomas are a complex, heterogeneous group of diseases which arise due to the clonal proliferation of lymphoid cells at various stages of differentiation.[1] The internationally accepted World Health Organisation (WHO) classification system for haematolymphoid tumours recognises over 90 lymphoma subtypes. Integrated diagnostic laboratories with morphology, immunophenotyping, genetics and molecular allow the lymphomas to be classified. The dependence of each technique varies depending on the type of lymphoma. Biopsy s can be lymph nodes, peripheral blood PB or bone marrow BM depending on the site of disease. With liquid biopsy's the multiparameter immunophenotyping technique of flow cytometry (FC) provides information about cell populations within a short timeframe, allowing a rapid preliminary diagnosis to be made.

It does have its limitations especially loss of cell viability and surface marker degradation. Lymphocyte marker expression is stable for up to 48 hours, after which time antigenicity starts to deteriorate, affecting light scatter properties.[2] As the other diagnostic modalities take longer like the trephine biopsy, any additional work up is usually performed by immunohistochemistry IHC. If the FC sample could be stabilised for several weeks then the haematopathologist has the option of requesting further flow cytometry markers over slower IHC.

TransFix contains formaldehyde and forms cross-links between amino acids preventing cellular degradation caused by enzymatic digestion and apoptosis and is a CE-IVD approved stabilising agent for PB and CSF.[3,4] In PB samples, TransFix stabilises lymphocyte subset marker expression and allows consistent FC results to be achieved for up to 14 days after sample acquisition. The ability of TransFix to extend lymphocyte antigen stability in bone marrow aspirate BMA samples has had limited evaluation.

The aim of this study is to establish whether TransFix can preserve and stabilise BMA lymphocyte antigen expression, allowing accurate and consistent FC results to be achieved over an extended period without compromising sample quality.

This study was a joint study between the Antrim Area Hospital and the Royal Marsden HMDS. Patients with suspected lymphoma were selected to have a Euroflow Lymphocyte Screening Tube or equivalent tested. PB and BM testing occurred with validated EDTA and then TransFix within 24hours. The TransFix samples underwent repeated testing for degradation up to D15. PB samples, the most notable observation was the significant (P <0.05) increase of the B cell population in TransFix® when compared to EDTA. All EDTA PB and BM were diagnostic at initial testing. The TransFix treated BM samples stabilised the majority of antigen expression up to D15 with predicted degradation. The main issue with TransFix in the BM was with the kappa and lambda expression. The populations did not separate effectively to allow clonality to be demonstrated. The ability to demonstrate clonality in B cells is of crucial importance and therefore our study cannot recommend the use of Transfix treated BM in isolation. This study had limitations including sample size, and although 2 different TransFix concentrations were explored the optimal concentration was not found and may continue to prove difficult due to the degree in variability of BM cellularity with age and disease.

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IMPLEMENTATION OF A RAPID WHOLE-BLOOD PLATELET GLYCOPROTEIN ASSAY BY FLOW CYTOMETRY FOR NON-ACCIDENTAL INJURY INVESTIGATION

K Clarke[1], V Vijayakumar[2], S Mitchell[1], G Beattie[1], R Gooding[1], C Corrigan[1], C Macartney[3]
[1]Haematology Department, Belfast City Hospital, Northern Ireland, [2]Haematology Department, Swansea Bay University Health Board, NHS Wales, [3]Royal Belfast Hospital for Sick Children, Belfast, Northern Ireland

Non-accidental injury (NAI) is a serious and challenging issue that requires careful investigation to ensure the safety and well-being of children. Haematological investigation is required when physical maltreatment is suspected in a child presenting with bruising or bleeding, to identify/exclude the presence of an inherited or acquired bleeding disorder that may have influenced the propensity to bruising/bleeding[1]. The 2022 BSH Good Practice Paper[1] has suggested that a two-stage approach for laboratory investigation with first-line tests involving full blood count, blood film, and coagulation screen to include PT, APTT and fibrinogen. Second-line testing should include Von Willebrand factor antigen and activity, factor assays (II, V, VII, 1-stage and chromogenic VIII, XI, X, XI and XIII), platelet aggregometry, platelet nucleotide studies and flow cytometry.

Flow cytometry (FC) is a laser-based technology that can characterise and profile cells within a heterogenous liquid sample dependent on the addition of target-specific fluorochrome-labelled antibodies. The heritable platelet disorders Bernard Soulier Syndrome (BSS) and Glanzmann's Thrombasthenia (GT) are severe platelet function disorders, that can be detected by FC based on reduced expression of glycoprotein Ib-α (CD42b) and IIb/IIIa (CD41/CD61) expression, respectively. Historically, this assay has been performed within the Belfast City Hospital and required a minimum sample volume of 8000 µL to obtain platelet-rich plasma (PRP). This excluded many of the paediatric patients from testing due to such large starting sample volume. There was also difficulty in interpreting the true loss of CD61 expression due to weak fluorochrome intensity.

We proposed the validation of a modified platelet glycoprotein assay by FC which aimed to reduce sample volume requirements by using whole blood (WB), add diagnostic robustness using brighter fluorochromes as well as improving on sample processing efficiency using a more streamlined protocol.

A total of 14 samples, (10 controls, platelet counts 26 – 386 x 10^9/L and 4 confirmed BSS patients, platelet counts 20 – 547 x 10^9/L) were used to compare our current PRP method to the modified WB method which requires only 5 µL of EDTA peripheral blood. The WB method demonstrated sensitivity = 1, specificity = 1, positive predictive value = 1, negative predictive value = 1 highlighting the ability of this assay to accurately detect all known cases of BSS whilst calling no false positives, in patients with thrombocytopenia down to a platelet count of 20 x 10^9/L.

To improve the fluorescence intensity of CD61, the fluorochrome was changed from PerCP to FITC. This produced brighter and more consistent results of positive CD61 expression that provided more confidence regarding true CD61 negativity. CD61 PerCP failed to accurately detect 46% of true positive expression making detection of antigen expression loss in our true positive case difficult, whilst CD61 FITC was brighter and more consistent detecting 100% of true positive cases.

We were also able to demonstrate improved testing efficiency with a decrease in processing time by 35%

Assessment of platelet glycoproteins GPIb-α and GPIIb/IIIa (CD42b, CD41a and CD61) expression by FC using WB represents an alternative method for assessing platelet function with higher specificity, minimal blood volume as well as low sensitivity to interfering substances such as drugs, anti-platelet agents or diet. We propose that the WB method for platelet glycoproteins by FC could be used as a front-line, rather than second-line test for patients undergoing NAI investigation to exclude Bernard Soulier Syndrome/Glanzmann's Thrombasthenia.

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"Defining the pro-survival signalling of the bone marrow microenvironment of multiple myeloma."

GP Sullivan[1], LF Flanagan[1], SV Glavey[2], T Ní Chonghaile[1]
[1]Department of Physiology and Medical Physics, Royal College of Surgeons in Ireland, Dublin,
[2]Department of Pathology, Smurfit Building, Beaumont Hospital, Royal College of Surgeons in Ireland, Dublin,

Despite major advances in the treatment of multiple myeloma (MM), it remains an incurable disease. Survival rates are improving but are still only marginally above 50% over five years. In MM, responses to treatment are not durable, resistance develops and the patient relapses. How such resistance emerges is poorly understood. We hypothesise that an influential aspect of treatment may be the secretory response of the tumour and associated stroma towards the therapeutic agent, altering the microenvironment and response to treatment.

Here, we focus on the cell-death induced by two therapeutic agents: the proteasome inhibitor bortezomib (Velcade®), routinely used in upfront MM treatment. Additionally, we explore the BCL-2 antagonist ABT-199 (venetoclax/Venclexta®), which has gained much attention in MM and is being actively investigated in numerous ongoing clinical trials. Utilising MM tumour cell lines and patient samples we observed protection from the killing effects of bortezomib following co-culture with stromal bone-marrow fibroblast cell lines or patient-derived stroma. To our surprise, in the same systems, we found significantly enhanced venetoclax-induced cell death.

Using a variety of complementary laboratory-based techniques this dichotomous response was interrogated further. Peptide-based BH3-profiling chemosenstivity assays were used to assess mitochondrial priming and changes in anti-apoptotic dependence upon co-culture with stroma. Unbiased cytokine arrays were used to screen secretory factors that may be altering the sensitivity to drugs, with evidence of increased pro-inflammatory/pro-survival signalling factors upon drug treatment. Specifically, enhanced interleukin-6 (IL-6), interleukin-10 (IL-10) cytokine release and CCR2 chemokine receptor engagement in co-cultures was found, upon drug treatment. These features are being explored further using mass-spectrometry secretome analyses in parallel with therapeutic neutralisation strategies conducted in patient-derived samples. Prospective results may identify improved therapeutic combinations for myeloma patients aimed at improving survival rates for this cancer.

NATIONAL "SNAP-SHOT" OF MULTIPLE MYELOMA TREATMENT PATTERNS IN IRELAND

OM Abdelzaher*[1,2,3], IM Drozdz*[1,2,3], J William[4], A Al Baghdadi[5], K Prykhodko[4], A Dyszkiewicz[4], J Krawczyk[4], C McEllistrum[5], D Swan[1], A Hayat[4], J Sargent[1], J Quinn[1], P Murphy[1], SV Glavey[1,2,3]
[1]Department of Haematology, Beaumont Hospital, Dublin, [2]Department of Pathology, RCSI University of Medicine and Health Sciences Beaumont Hospital, Dublin, [3]Multiple Myeloma Research Group, Royal College of Surgeons in Ireland, Smurfit Building, Beaumont, Dublin, [4]Department of Haematology, Galway University Hospital, [5]Department of Haematology, Limerick University Hospital

Introduction: Multiple Myeloma (MM) is characterized by proliferation of plasma cells in the bone marrow. Approximately 400 patients are diagnosed with MM in Ireland annually, accounting for 10% of blood cancer patients[1]. Novel therapies have driven unprecedented survival rates in this incurable cancer with overall survival (OS) of more than 12 years and 8 years in patients aged <70 or >70 respectively[2]. There are now 20 individual therapies approved for treatment of MM in Europe including proteasome inhibitors, immunomodulators, monoclonal antibodies, T-cell directed therapies, bisphosphonates and steroids. The current European guidelines for diagnosis, treatment and follow up of MM[3] recommend, where feasible a three-drug regimen for treatment of newly-diagnosed MM (NDMM) and various triplet, doublet or single agents in the heterogenous relapsed/refractory (RRMM) population. Irish patterns of MM treatment depend on NCCP approved regimens, clinical trial and compassionate access availability. Given the welcome increase in OS it is increasingly important to define triple and penta-refractory cohorts in order to inform clinical trial feasibility and reimbursement. To date no national data on treatment patterns of MM in Ireland, in the era of novel agents exists. This study aimed to audit the use of anti-MM therapies nationally in Ireland.

Methods: This national audit was conducted using a cross-sectional design over a specified 3 month period (Jul – Sept 2023) at Beaumont Hospital, Galway University Hospital, and Limerick University Hospital. Audit approval was sought at each site. Current and previous treatment data was collected for all MM patients attending haematology day ward services at the three institutes over the specified time period. Each subject had their data collected at a single time point using a "snap-shot" methodology.

Results: 227 patients had full data available for inclusion in the study at time of abstract writing. Average age was 69 (range 40-91). 46.4% of patients were < 70 years and 53.7% of patients had undergone autologous stem cell transplant (ASCT). 10% of patients had been diagnosed with MM within the previous six month period and the average time since diagnosis was 5 years. 44% of patients were receiving first line therapy which included patients who were receiving lenalidomide maintainence following ASCT. 21.5%, 12.6, 11.2 and 5.5% of patients were receiving 2nd, 3rd, 4th and 5th line treatment respectively. 10% of patients were on 5th or greater line of treatment, reflecting the increasing complexity of MM treatment in the day ward setting. 6.2% of patients were receiving treatment on a clinical trial. The most commonly used regimens in the first and second line were RVD (66%) and DVD (29%), respectively.

Importantly, 68/227 (30%) of patients were triple class refractory (TCR), defined as disease progression during or after treatment with an immunomodulatory drug and proteasome inhitibor and monoclonal antibody. 22% of TCR patients were penta-exposed (6.6% of total cohort).

Conclusion: This data provides the most comprehensive picture to date of MM treatment patterns using novel agents in Ireland. Encouragingly 6% of patients were enrolled on clinical trials, which is on target with the National Cancer Strategy objectives. With increasing OS for MM patients the population of TCR and penta-refractory patients is rapidly expanding and there remains an unmet need for access to T-cell directed therapies such as antibody-drug conjugates, bispecific T-cell therapies and CAR-T therapies for these patients.

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AN AUDIT OF DARATUMUMAB, WEEKLY BORTEZOMIB AND DEXAMETHASONE (DVD) IN RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM)

RA ALFarsi[1], RH Bashirbhoy[1], JA Dillon[2], PH Murphy[2], DA Swan[2], PA Thornton[2], JE Sargent[2], SI Glavey[2], JO Quinn[2]

[1]medical school, Royal College of Surgeons in Ireland, Dublin, [2]Department of Hematology , Beaumont hospital, Dublin,

In recent years the treatment landscape for multiple myeloma (MM) has seen significant advancements with the development of new drug regimens, resulting in improved overall survival rates. However, despite these developments, the disease remains incurable(1-3). On foot of the CASTOR randomised phase III clinical trial, the daratumumab, bortezomib and dexamethasone (DVD) regimen has been approved for patients with relapsed refractory multiple myeloma (RRMM) (4,5). The primary objective of this audit was to evaluate the effectiveness and tolerability of daratumumab, bortezomib, and dexamethasone (DVD) in real-world patients with relapsed refractory multiple myeloma (RRMM), along with number of prior treatment lines, and different types of treatments received.

This audit was conducted in Beaumont hospital and data was collected for multiple myeloma patients who underwent DVD treatment between 2020 and 2023. Both medical records and laboratory results were used to obtain relevant information. Importantly, DVD was administered according to national cancer control programmed (NCCP) weekly protocol: Daratumumab (1800 mg) was administered on a weekly basis during cycles 1- 3, followed by once every three weeks from cycles 4-8, and then monthly starting from cycle 9 until disease progression. Initially, daratumumab was given intravenously, but after June 2020, it was switched to subcutaneous administration. Bortezomib (1.3mg/m2) was given subcutaneously on a weekly basis (CASTOR trail was given twice weekly) during cycles 1-3 (on day 1, 8, and 15), while dexamethasone was orally administered at a weekly dose of 40mg during cycles 1-3 (on day 1, 8, and 15). (6)

Sixteen patients with a median age of 71.5 years were included in the audit. A primary objective was to evaluate the response rates based on the International Myeloma Working Group (IMWG) criteria, including very good partial response (VGPR), partial response (PR), and stable disease (SD) (7). One patient achieved a VGPR, six patients achieved PR, and two patients had stable. Adverse events were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) v5, with most events being grade 2 or lower. Only one case of infusion reaction (grade 2) and two cases of peripheral neuropathy (grade 1) were reported.(8)

In conclusion, this audit was conducted in small heterogenous patient group with limited follow up. Despite the limitations of a small sample size and limited follow-up, the audit showed encouraging efficacy for DVD treatment with weekly bortezomib therapy. The results demonstrate favourable response rates and tolerability. However, to validate these results and explore the potential of DVD with weekly bortezomib further, larger-scale studies are necessary.

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JAK2 ALLELE FREQUENCY IN PATIENTS WITH MYELOPROLIFERATIVE NEOPLASMS

J Jasiakiewicz[1, 2], R Brown[1], V Greer[1], K McDowell[1, 2], K Clarke[1], F Buckley[3], C Crean[1], A Hindley[1], J McGimpsey[1], D Finnegan[1], C Arnold[1], N Cunningham[1], RJG Cuthbert[1], MA Catherwood[1], MF McMullin[1, 2]
[1]Haematology Department, Belfast Health and Social Care Trust, Belfast, Northern Ireland, UK
[2]Centre for Medical Education, Queen's University Belfast, Belfast, Northern Ireland, UK
[3]Haematology Department, NHS Highland, Inverness, Scotland, UK

Introduction: Myeloproliferative neoplasms (MPNs) are a group of chronic disorders of the bone marrow characterised by the overproduction of clonal myeloid stem cells (1). MPNs are divided into three subtypes, polycythaemia vera (PV), essential thrombocythaemia (ET) and primary myelofibrosis (PMF). These subtypes are differentiated from each other based on bone marrow morphology, blood counts and molecular genetics (1, 2, 3). The most common mutation found in MPNs, present in up to 95% of PV cases and 50% of ET and PMF cases is a mutation in exon 14 of the *JAK2* gene denoted as V617F (4, 5). Recent studies have suggested that measuring the *JAK2* V617F variable allele frequency (VAF) could be of clinical significance (6). Specifically, the use of *JAK2* V617F VAF in differentiating the three subtypes of MPNs has been discussed with studies demonstrating that the VAF in PV and PMF is higher than in ET patients. (7, 8, 9)
Our aim was to investigate the role of the *JAK2* V617F mutation allele burden in newly diagnosed MPN patients.

Methods: All patients attending the study centres who were diagnosed with PV, ET and PMF during the period 1st January 2019 to 31st January 2021 were selected for study. Demographic characteristics and clinical information were collected for all patients. DNA was extracted from peripheral blood samples and *JAK2* V617F VAF was determined by qPCR.

Results: There were 89 patients with ET, 63 patients with PV and 7 patients with PMF identified during the study period. Demographic data showed a mean age for MPN diagnosis of 72 years and that this value was similar for all subgroups. A significant increase in platelet counts was observed in the ET 720 × 109/L (68-1513) group when compared to the PMF 333 × 109/L (range 83-528), ($P<0.001$) and PV 502 × 109/L (range 129-1112), ($P<0.001$) group. The mean haematocrit values were significantly raised in the PV 54.6% (range 46-67) group compared to ET 42.6% (range 29-50), ($P<0.001$), however, no significant change was observed in PV versus the PMF 20.8% (range 20.8-20.8) group. Similarly, mean haemoglobin concentrations were significantly increased in PV 180 g/l (range 139-228), versus ET 139.9 g/l (range 93-169), ($P<0.001$) and PMF 99.5 g/l (range 68-131), ($P<0.001$). Mean *JAK2* V617F VAF was significantly higher in PV 50% (range 1.48-89.6) vs ET 19.5% (range 0.9-65.96), ($P<0.001$). A significant increase in *JAK2* V617F VAF was also observed in ET vs PMF 41.2% (range 17.9-71.1), ($P<0.001$). However, no statistically significant difference in *JAK2* V617F VAF was observed between the PMF and PV groups.

Conclusion: The study analysed demographic characteristics, clinical information and *JAK2* V617F VAF in a cohort of 159 MPNs patients. The mean *JAK2* V617F VAF was highest in the PV group and lowest in the ET group, in line with previously published studies. *JAK2* V617F allele frequency could potentially aid in differentiating between either PV or PMF and ET but not between PV and PMF. Based on the results, *JAK2* V617F VAF alone would not be a reliable indicator of specific MPN subtype.

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NEXT GENERATION SEQUENCING AS AN ALTERNATIVE TO KARYOTYPING TO DETECT COPY NUMBER VARIATIONS IN MYELOID MALIGNANCIES

R Brown[1], C Crean[1], K McAuley[1], R Forsythe[2], D Finnegan[2], C Arnold[2], N Cunningham[2], MF McMullin[2, 3], A Logan[1], MA Catherwood[1]

[1]Regional Molecular Diagnostic Service, Belfast Health and Social Care Trust, Belfast, Northern Ireland, UK

[2]Haematology Department, Belfast Health and Social Care Trust, Belfast, Northern Ireland, UK

[3]Centre for Medical Education, Queens University Belfast, Belfast, Northern Ireland, UK

Introduction: Myeloid malignancies are a group of heterogeneous clonal diseases caused by multiple genetic alterations including deletions, insertions and duplications of sections of DNA known as copy number variations (CNVs) (1). As such, the identification of CNVs has played an integral part in the diagnosis and prognosis of myeloid malignancies highlighted by the inclusion of cytogenetic data within the international prognostic scoring systems (IPSS) for myeloid malignancies (2). Karyotyping has been the gold standard for the identification of CNVs in myeloid malignancies for decades (3). However, with the incorporation of next generation sequencing (NGS) into routine diagnostic use, the potential for this to complement existing karyotyping analysis should be considered. Our aim was to investigate the comparability of cytogenetic data provided by karyotyping and NGS.

Methods: Karyotyping analysis was performed on G-banded chromosomes isolated from metaphase arrested cells. Data were presented as per the International System for Human Cytogenetic Nomenclature 2020 (4). Total genomic DNA was sequenced using a Myeloid NGS assay covering common sequence, structural and copy number variations in genes involved in myeloid neoplasms. Alignment, de-duplication and variant calling was performed using the MyeloidTS_WF bioinformatics pipeline v1.1.

Results: A cohort of 206 patients were tested in parallel for CNVs by both karyotyping and NGS. NGS identified 93 genomic variants with CNVs in 49 (23.8%) of the 206 patients. The most commonly occurring events were deletions of 7p (18.2%) and 5q (7.5%) and a gain of chromosome 8 (8.6%). Karyotyping identified 179 genomic events with CNVs in 75 (36.4%) of the 206 patients. The most commonly occurring events were a gain in chromosomes 8 (7.8%), loss of chromosome Y (5.6%) and deletions in 5q (5.0%) and 7q (3.4%). These CNVs are consistent with known cytogenetic events in myeloid malignancies (5, 6). Taken together, karyotyping and NGS described 272 genomic events. Of these, 128 (47.1%) were detected by both techniques, while 30 (11.0%) and 76 (27.9%) were detected only by NGS or karyotyping respectively. 38 (14.0%) CNVs detected by karyotyping were outside of the regions reported by the NGS panel. Of the 106 non-matching events 16 (15.1%) could be described as compatible, with evidence of the same chromosomal rearrangement despite not providing a direct match.

Conclusions: This study compared the detection of CNVs by karyotyping and NGS. The data presented shows inconsistencies in CNV detection between the two techniques. The limit of detection for copy number variants by the myeloid NGS panel used was 40% neoplastic DNA content. This is likely to be contributing to the discrepancies observed between the two techniques. Additionally, the myeloid NGS panel used in this analysis only reported on targeted regions covered by the assay. As such, the introduction of NGS panels with wider coverage and improved limits of detection for CNVs may improve complementarity with karyotyping. Results from this study suggest that while this specific NGS panel may provide a useful complementary tool to karyotyping it should not be used as an alternative approach.

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TEN YEARS OF PAEDIATRIC PROTOCOL USE IN ADULT ACUTE LYMPHOBLASTIC LEUKAEMIA; A SINGLE CENTRE EXPERIENCE

A Busher[1], L Bacon[2], N O'Connell[1], L Smyth[1,3], M Coyne[1,3], DG Connaghan[1], K Fadalla[1,3], K Murphy[1,3], J Fitzgerald[1,3], M Power[1], C Andrews [1,3]
[1]Department of Haematology, St Vincent's University Hospital, Dublin
[2]Department of Haematology, St James' Hospital, Dublin
[3]Department of Medicine, University College Dublin

Introduction: Although paediatric acute lymphoblastic leukaemia (ALL) has cure rates of >90%, adult ALL remains a difficult disease to treat with cure rates approximately half those seen in children (1). Paediatric outcomes have improved with the use of risk stratified, multi-agent chemotherapy and central nervous system prophylaxis. DeAngelo et al concluded that paediatric like treatment strategies for adults is feasible with improved outcomes when compared to adult based regimens (2).

Aim: The aim of this study is to determine the outcomes of patients with ALL treated with paediatric based chemotherapy protocols during their ten years of use at our tertiary level university hospital.

Methods: All patients aged 18 and over with a diagnosis of ALL between 2013-2023 were identified by the St Vincents University haematology database. Inclusion criteria included a diagnosis of ALL/LBL by the WHO 2022 classification of haematolymphoid tumours and those treated with UKALL protocols. Baseline characteristics were collected. Overall survival (OS) was calculated using the Kaplan-Meier method.

Results: Forty three patients were diagnosed with ALL between 2013 and 2023. Twenty six were treated with a UKALL protocol. The median age at diagnosis was 45 (IQR=27). 34 % (n=9) of patients were female. KMT2a was the commonest cytogenetic rearrangement, seen in 15.3% (n=4) of patients, with BCR-ABL seen in 11.5% (n=3). Two patients had therapy associated ALL and were previously treated for myeloma and breast cancer. Eighteen patients were treated with UKALL14, 5 (19%) treated with UKALL 60+ and two were treated with UKALL 2011. The three patients who had BCR-ABL mutations were treated with TKI inhibitors. All patients (n=26) had CSF samples taken at diagnosis. No patients had CSF involvement. Three patients had extramedullary involvement at the time of diagnosis with 2 patients having mediastinal disease, both diagnosed with LBL.

There was no 30- or 60-day induction mortality. Seventeen patients (65.3%) attained a complete remission (CR) post induction. Of those who achieved a CR, 52% (9/17) underwent allogeneic transplant (AlloSCT) with a median age of 37 (IQR=27). The majority (88%) received myeloablative conditioning and 77% (7/9) using a matched unrelated donor (MUD). There was no transplant related mortality and only one patient died due to relapse post-transplant. Seven patients relapsed with median duration from remission to relapse was 219 days (IQR 231 days). Median duration of follow up was 2.3 years (IQR 3.7 years). OS at 3 years was 59.12%.

Conclusion: Our findings demonstrate favourable outcome among patients treated with paediatric based treatment protocols for ALL as CR was achieved post induction in two-thirds of patients, this is in keeping with previous observational cohort studies (3). Although numbers were small, it also confirms the role of AlloSCT for consolidation for high risk ALL. With the introduction of ALLTogether protocol in the paediatric setting, and the incorporation of monoclonal antibodies such as blinatumomab and inotuzumab in front line, scope remains to further improve long term outcomes for adults with ALL.

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THE SHIFTING TREATMENT PARADIGM OF TREATMENT OF CHRONIC LYMPHOCYTIC LEUKAEMIA: RESULTS OF A SINGLE-CENTRE RETROSPECTIVE ANALYSIS

M Charan[1], N Harten[1], P Thornton[1], D Swan[1]
[1]Haematology, Royal College of Surgeons - Ireland, Dublin, Ireland

Introduction/Background: Chronic Lymphocytic Leukaemia (CLL) is primarily a disease of older adults. The disease is often indolent, with systemic anticancer treatment (SACT) only indicated when patients meet the International Workshop (IWCLL) criteria. Treatment is individualized and considers factors such as frailty, mutation-status, and quality of life (1). The 2018 British Society of Haematology guidelines (BSH) primarily recommended chemo-immunotherapy as front-line therapy (2), however more recent recommendations favour targeted therapies, particularly since the COVID-19 pandemic (3). We performed a retrospective analysis of trends in treatment since 2015 in Royal College of Surgeons, Ireland - Connolly Hospital Blanchardstown (CHB), Dublin.

Materials and methods: A chart review was conducted of 17 adults aged > 60 who received CLL treatment since 2015. Treatment response was classified as complete response (CR) (normalized full blood count (FBC) with lymphocytes < 5,000/uL), partial response (PR) (FBC not normalized), or no response.

Results: Front-line therapies included: ibrutinib (n=5), chlorambucil/obinutuzumab (n=3), obinutuzumab/venetoclax (n=2), fludarabine/cyclophosphamide/rituximab (FCR) (n=3), venetoclax (n=2), acalabrutinib (n=1), and bendamustine/rituximab (n=1). Seven patients had second-line therapy during the study window: ibrutinib (n=4), acalabrutinib (n=2), and venetoclax (n=1). Reasons for beginning second-line treatment were mainly limited to relapse, treatment failure, or adverse effects.

Considering patients in 3 timeframes, from 2005-2015, 100% of patients were treated with chemotherapy, from 2016-2019, 12.5% received chemotherapy, 37.5 chemoimmunotherapy and 50% immunotherapy alone, and from 2020 onwards, 100% of patients received immunotherapy alone.

Of those treated with chemotherapy, two of the three patients on FCR commenced secondary treatment with ibrutinib (one relapse and one treatment failure), whereas the third achieved a CR and remains in remission. The patient on bendamustine/rituximab achieved a CR before relapsing and commencing ibrutinib. Two patients treated with chlorambucil/obinutuzumab remain in CR, and one relapsed following achievement of a PR, after which they commenced ibrutinib.

There were four patients on venetoclax based therapies. Of those on obinutuzumab/venetoclax combination therapy, one was intolerant and switched to acalabrutinib, while the other is in ongoing treatment. Both patients on venetoclax alone achieved a CR with no secondary treatment.

Lastly, there were six patients on kinase inhibitors. Of those on ibrutinib as their primary treatment, two stopped due to treatment failure and adverse effects (GI toxicity), switching to venetoclax and acalabrutinib, respectively. Two remain on ibrutinib having achieved a PR and a CR respectively, and 1 attained a CR but discontinued due to bladder cancer. The patient on acalabrutinib achieved a CR and did not need secondary therapy. None of the 7 patients receiving subsequent SACT were treated with chemotherapy.

Conclusions: Overall, in keeping with current recommendations there has been a clear shift in the treatment paradigm of CLL from standard chemotherapy towards targeted agents. The Bruton tyrosine kinase inhibitor Ibrutinib, was the most common second-line treatment. Chemotherapy was not given to any patient second-line in this review and had not been used alone as a primary therapy since 2019. This is likely due to the improved tolerance of targeted agents and the preference of oral therapies during the COVID-19 pandemic (4).

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A CLINICAL AUDIT OF IVIG USE IN THE HAEMATOLOGY DAY UNIT

JB Coffey[1], GM Crotty[1]
[1]Department of Haematology, Midland Regional Hospital Tullamore, Tullamore, Ireland

Introduction: Malignant haematological conditions can cause impaired production of functional immunoglobulin, resulting in secondary immunodeficiency disorders. This can predispose patients to recurrent and/or severe infections. To reduce this risk, intravenous immunoglobulin replacement [IVIG] is indicated in select cases. Midland Regional Hospital Tullamore [MRHT] has a Haematology Day Unit which can facilitate regular IVIG infusions for patients with haematological malignancies who require it for prevention of infections.

Methods: We audited an 8-week period between 7th March to 2nd May 2022. Patients with haematological malignancies attending for IVIG administration were selected. A chart review was conducted and retrospective data was collected including demographic data (such as age, gender and haematological diagnosis) and treatment data (including treatment frequency, dose information and immunoglobulin levels). Patient's clinic letters were also reviewed in order to assess whether treatment benefit had been assessed. The current practice in terms of initiating and monitoring IVIG therapy was compared with current NCCP best practice guidelines[1].

Results: A total of 16 haematology patients received IVIG in the day ward in this period. Patient ages ranged from 49 to 89 years old, with an average age of 70. The most frequent haematological diagnoses were myeloma (56%) and CLL (25%), with Hodgkin's lymphoma [HL], MGUS and hairy cell leukaemia [HCL] making up 6.3% each. All of the patients audited received IVIG monthly. Monthly doses ranged from 10g to 40g, with a mean dose of 28.8g (0.36g/kg). Doses received were highest in patients with myeloma (mean of 30.83g / 0.38g/kg) and lowest in patients with MGUS (mean of 20g / 0.25g/kg). Duration of therapy ranged between 6 months to 14.4 years, with an median duration of 3.75 years. 31% of patients had been receiving IVIG for over 3 years, and the average dose in these patients was 28.5% lower than in those who were within 3 years of starting treatment. (22.6g vs 31.6g). Immunoglobulin levels were checked in all patients prior to commencing treatment. 25% of patients audited had IgG levels >4g/L prior to commencing treatment. Trough IgG levels were checked in all patients undergoing treatment, with 68.75% achieving trough levels of >4g/L. Reduced frequency of infections was mentioned in 81% of patient's clinic review letters.

Conclusion: This study demonstrated several relevant findings. There was a wide variation in IVIG doses used, and doses were seen to vary depending on indication for therapy. A significant proportion of patients had been receiving IVIG for several years, and doses used tended to be lower in those receiving IVIG for longer. This suggests that treatment is being adjusted as time goes on to provide the lowest effective dose. Of note, 25% of patients audited did not comply with current NCCP guidelines for commencement of IVIG prophylaxis, as initial IgG levels were >4g/L. While clinical judgement clearly has a role in deciding ongoing management, future efforts could be made to improve compliance with best practice guidelines, in order to save costs and reduce potential overtreatment

1) 'NCCP Guidance Document 0017– Patient selection for the use of immunoglobulin replacement therapy in cancer patients with secondary immunodeficiency'

DEVELOPMENT OF A NOVEL IMMUNOCOMPETENT XENOGRAFT MODEL FOR MULTIPLE MYELOMA IN THE CHICK EMBRYO

IM Drozdz[1,2,3], C Yoong[1], RM McAvera[2], CE Richards[4], H Jahns[5], SV Glavey[2,3], AM Hopkins[1]
[1]Department of Surgery, RCSI University of Medicine and Health Sciences, Beaumont Hospital, Dublin, [2]Department of Pathology, RCSI University of Medicine and Health Sciences, Beaumont Hospital, Dublin, [3]Multiple Myeloma Research Group, RCSI University of Medicine and Health Sciences, Beaumont Hospital, Dublin, [4]Department of Molecular Medicine, RCSI University of Medicine and Health Sciences, Beaumont Hospital, Dublin, [5]University College Dublin Veterinary Hospital, University College Dublin

Introduction/Background: Multiple Myeloma (MM) is an incurable malignancy, featuring uncontrolled proliferation of plasma B cells in the bone marrow. Constituting ~10% of all haematological malignancies, ~400 individuals annually are diagnosed with MM in Ireland. Despite the existence of some *in vivo* models of MM, new and innovative models are needed to faithfully replicate disease complexity, evolution, and the microenvironmental interplay inherent to MM. This project aims to develop a cutting-edge immunocompetent chick embryo xenograft model of MM, a pioneering initiative within the Irish research landscape. We have already established this model for solid tumours, including breast[1] and lung[2], in our lab. It offers an economically-efficient alternative to murine models plus excellent compliance with the 3R principles of minimizing animal experimentation. Furthermore, in the era of immunotherapies for MM, the necessity of a high-fidelity immunocompetent xenograft model for MM characterization and drug assessment is paramount. Establishment and implementation of Ireland's first chick embryo MM model thus holds translational promise for exploring disease mechanisms and identifying novel ways to drug them.

Methods: Fertilized hen eggs were incubated at 37^{o}C on Embryonic Development Day (EDD) 0. On EDD3, 4mL albumin was aseptically withdrawn, and a small dorsal window was exposed and re-covered with a semi-permeable membrane. On EDD7 or 9, the semi-permeable membrane was removed, and human MM cell lines (JJN3, KMS18, RPMI8226, U266) separately implanted onto the chorioallantoic membrane (CAM) using alternate matrices (absorbable haemostatic film, collagen type I, Matrigel). The window was re-covered and the eggs re-incubated at 37^{o}C. Following 7 days of tumour development, tumour xenografts plus their surrounding CAM were photographed prior to extraction and fixation for immunohistochemistry. The rationale for our cell line selections was based on proliferation rate and cytogenetics. JJN3 and KMS18 both contain high-risk translocations, t(14;16) and t(4;14), respectively, and are highly-proliferative cell lines. Meanwhile, RPMI8226 and U266 have standard risk translocations, t(16;22) and t(11;14) and proliferate slowly. MM drug treatment studies involving Bortezomib, Lenalidomide, and Dexamethasone are ongoing in this model and in parallel *in vitro* experiments.

Results: To date, we have successfully established MM xenograft tumours using two different conditions. Matrigel has been the most supportive matrix, with the inoculation of 1x10^{6} JJN3 or U266 cells producing highly-vascularized, grossly-visible MM tumours (n=5 embryos) measuring approximately 0.5x0.4x0.2cm in successful replicates. Haemostatic film worked well with RPMI8226 and U266 cells at the same cell count but produced an inferior vascular network (n=4 embryos). Haematoxylin and eosin staining of thin sections revealed viable plasma cells within and around both matrices, further confirmed by CD138 positivity. Responsiveness of each model to the selected panel of MM drugs is currently being determined.

Conclusions: Progress thus far suggests the successful generation of a viable immunocompetent MM xenograft model in the chick embryo. The next phase will involve its validation with clinically-relevant MM therapeutics being tested *in vivo*, alongside the expansion of cell lines and extension into patient-derived xenografts.

Acknowledgements: This study was funded by Breakthrough Cancer Research and the HRB (grant HRCI-HRB-2022-020 to AMH and SVG).

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CREATING AN INFORMATIVE MULTIPLE MYELOMA PATIENT INFORMATION BOOKLET: DESIGNING AN EFFECTIVE PATIENT-PUBLIC INTERACTION (PPI) PANEL

IM Drozdz[1,3,5], NA McAuley[1,5], M Kelly[2], G Walpole[2], AM Hopkins[1], SV Glavey[3,4,5]
[1]Department of Surgery, RCSI University of Medicine and Health Sciences Beaumont Hospital, Dublin, [2]Multiple Myeloma Ireland, [3]Department of Pathology, RCSI University of Medicine and Health Sciences Beaumont Hospital, Dublin, [4]Department of Haematology, Beaumont RCSI Cancer Centre, Dublin
[5]Multiple Myeloma Research Group, Royal College of Surgeons in Ireland, Smurfit Building, Beaumont, Dublin

Introduction: Multiple Myeloma (MM) is a complex haematologic malignancy that is primarily characterized by the abnormal proliferation of plasma cells within the bone marrow. On average, around 400 people are diagnosed with MM in Ireland each year. With a global incidence rate on the rise, it is crucial to equip patients with comprehensive knowledge to not only navigate their diagnosis, and treatment options but also to gain an understanding of what research is being done in Ireland and what their contribution can mean for advancing research. Patient and Public Involvement (PPI) in research enables research to be conducted with and by patients, involving them as stakeholders in all aspects of research from conception, design and participation to dissemination.[1]

In the era of modern healthcare being intimately intertwined with research, patient education plays a pivotal role in cultivating a patient-research partnership. Researchers engaging with patient samples for their studies must ethically and transparently communicate the purpose, potential benefits, and implications for their research, fostering a mutual understanding that contributes to informed consent.

To address this issue for MM patients in Ireland we worked in collaboration with Multiple Myeloma Ireland, the Health Research Board (HRB) and Breakthrough Cancer Research to develop patient information resources and a patient forum for PPI in MM. Following consultation with the patient forum, a booklet was developed that aims to distil relevant information for patients and the public in relation to research activity in MM.

Materials/Methods: To form the PPI panel, we integrated insights from researchers, nurses, clinicians, Multiple Myeloma Ireland, the HRB, and Breakthrough Cancer Research. Patient forum representatives were approached for involvement in the project by their physicians or Multiple Myeloma Ireland representatives. The patient forum met online with researchers and clinicians and ongoing laboratory research and clinical trials were discussed. A booklet outline was proposed by the PPI forum and the booklet was then developed by a PhD and MSc student.

The panel incorporated the views of both female and male patients, along with caregivers. Panel members were invited to review the booklet as it was developed and contribute to content and perspectives. Patient advocacy was central to the booklet development.

Results/Conclusion: PPI enables meaningful development of research goals and objectives in order to address unmet needs of MM patients. Our project provides a roadmap for grass-roots PPI development for an incurable blood cancer on a national basis in Ireland. Our PPI panel provided high quality patient focused input to enable patients and caregivers to access relevant information about research for MM patients from the time of diagnosis. We anticipate that this form of engagement will increase patient satisfaction with research knowledge and equip patients with the tools they require to advocate for high quality preclinical studies and clinical trials.

Acknowledgements: This study was funded by Breakthrough Cancer Research and the HRB (grant HRCI-HRB-2022-020 to AMH and SVG).

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INVESTIGATING THE EFFECT OF OSTEOBLASTS ON NATURAL KILLER CELL CYTOTOXICITY AGAINST ACUTE MYELOID LEUKAEMIA IN VITRO

L Durkan, E Szegezdi
[1]School of Biological and Chemical Sciences, University of Galway, Galway, Ireland

Introduction: Natural killer (NK) cell-based therapies have entered clinical testing as a novel cancer immunotherapy thanks to their inherent anti-tumour cytotoxicity. Acute myeloid leukaemia (AML) is one cancer NK cells are being developed to treat. When adoptive NK cells are administered to patients, their therapeutic efficacy may be reduced as the NK cells encounter and navigate the complex bone marrow environment. One feature of this environment that may inhibit the ability of NK cells to target leukemic cells is the presence of osteoblasts. Osteoblasts are derived from mesenchymal stromal cells. They are a major and active cellular component of the bone marrow and regulate steps of haematopoiesis. The aim of this work was to investigate the potential effect of osteoblasts on NK cell functionality.

Methods: Osteoblast cultures were obtained by *in vitro* differentiating bone marrow mesenchymal stromal cells (BMSC) isolated from AML patients by culturing the cells in the presence of dexamethasone, ascorbic acid-2-phosphate and β-glycerophosphate. Osteogenic differentiation was confirmed with alizarin red staining. NK cells were derived from peripheral blood of healthy donors and expanded on lymphoblastoid cell layers in the presence of interleukin-2. NK cell functionality was assessed in cytotoxicity assays by combining NK cells with fluorescently tagged AML cells (MOLM-13) and measuring the viability of the AML target cells with flow cytometry.

Results: AML patient-derived BMSCs could differentiate into osteoblasts after culture in osteogenic differentiation medium for 16 days. Direct co-culture of NK cells with the osteoblasts impaired NK cell cytotoxicity, reducing their ability to kill target AML cells. NK cell viability from osteoblast co-cultures was also reduced.

Conclusions: With this study, we provide data on OB-NK cell interactions. This has revealed that OB presence may be a potential barrier to optimal NK cell efficiency in the bone marrow. This could have an impact on the efficacy of adoptive NK cell therapy for AML treatment.

PBL HAS SIMILAR OUTCOMES TO DLBCL IN SINGLE CENTRE STUDY

P Eustace[1], L Smith[2,3], M Coyne[2,3], DG Connaghan[2], K Fadalla[2,3], K Murphy[2,3], J Fitzgerald[2,3], M Power[2], C Andrews[2,3]

[1]Department of Medicine, University of Limerick, Limerick, [2]Department of Haematology, St. Vincent's University Hospital, Dublin, [3]Department of Medicine, University College Dublin, Dublin

Introduction: Primary bone lymphoma (PBL) is a rare subtype of lymphoma that exclusively affects skeletal tissue and accounts for around 1% of all lymphomas. The majority of PBLs represent non-Hodgkin lymphoma (NHL) and diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS) is by far the most common histological type. Due its rarity and dearth of prospective clinical trials, guidelines on the diagnosis and management are lacking (1).

Aim: We present a case series of 13 patients with PBL and discuss clinical and histological characteristics and outcomes. Outcomes including progression free survival (PFS) and overall survival (OS) will be compared to patients with DLBCL from our centre.

Methods: Patients aged 18 years or older diagnosed between January 2016 until December 2022 with PBL and DLBCL, according to the WHO 2022 classification of haematolymphoid tumours, were identified using the St Vincents University lymphoma database. Baseline clinical and histological characteristics were collected. Subtype of DLBCL was performed using Hans criteria. PFS and OS rates was calculated using the Kaplan-Meier method.

Results: There were 13 patients with a diagnosis of PBL identified. The median age was 62.7 (38-83) and there was a female:male ratio of 3:10. All patients had a WHO classification of DLBCL NOS (not otherwise specified) and all had a germinal centre subtype. Five patients (38.5%) had B symptoms with bone marrow involvement in 3 patients (23%) and one patient having CNS involvement. The majority of patients had an ECOG of 1 (0-3) and an NCCN-IPI of 4 (range 3-7). Ten patients (76%) received R-CHOP, one patient received R-CODOX-M/R-IVAC and one patient received R-mini CHOP due to age and comorbidities. Eight patients (80%) achieved a complete remission (CR) and this was confirmed by PET-CT. Of the 8 patients who received a CR, 5 patients (62%) received consolidative radiotherapy. Two patients (20%) were considered primary refractory. One received palliative management and the other received two further lines of treatment (R-ICE and R-ESHAP) but remained refractory. Three patients achieving a CR post primary therapy relapsed. Only one patient received salvage chemotherapy and proceeded to autologous stem cell transplant (ASCT) and remains alive in CR. OS at 2 years was 76.5%. We then compared PFS and OS of PBL to patients with DLBCL (n=83). When baseline characteristics of the two groups were compared there was no significant differences. PFS was similar between the groups (p=0.83). OS at 2 years for DLBCL was 69.2%. Although there was an increased OS of patients with PBL, there was no significant difference (p=0.58) between the two groups.

Conclusion: Although our numbers were small, this case series reveals that PBL treated with standard chemotherapy followed by RT have excellent outcomes and have similar OS to DLBCL. Prior to the introduction in the past few years of immunotherapies such as BITES and CAR T cell therapy for relapsed/refractory DLBCL, there were few options for these patients and this is reflected in our case series.

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p53 ALTERATIONS & POD24 IMPACT ON TREATMENT OUT-COME IN PATIENT WITH MANTLE CELL LYMPHOMA (MCL). MULTI-CENTRE RETROSPECTIVE STUDY

R Faryal[3], B Hennessy[1], S Kumar[1], L Sutton [2], D Swan[1], M Griffin[2], O Osarhieme[2], C Schilling[2], M Nur[2], E Lee[2], R Shatwan[4], A Quinn[4], M Catherwood[5], A Hayat[3], E Elhassadi[1]
[1]Haematology Department , University Hospital Waterford, Waterford, [2]Pathology Department, University Hospital Waterford, Waterford, [3]Haematology Department , University Hospital Galway , Galway, [4]Pathology Department, University Hospital Galway , Galway, [5]Molecular Department, , Belfast University Hospital, Belfast

Background: This study delves into the influence of p53 alterations and Progression of Disease within 24 months (POD24) on MCL treatment outcomes. Particularly, the research scrutinizes the viability of p53 mutations as early predictive indicators for disease progression within a 24-month timeframe (POD24) utilizing our MCL patient cohort.

Methods: p53 expression percentage and the determination of mutational status were executed through stringent application of immune-histochemical techniques (with a cut-off >30% for positivity) and Sanger sequencing.POD24 was defined as relapse or progression of MCL within 24 months of initiation of systemic therapy. Survival analysis was carried out using Prism10 software and applying Log-rank (Mantel-Cox) test for statistical significance.

Results: Out of 121 MCL patients, majority of cases were advanced disease and had male predominance (78%). The median age was 67 years. Most patients presented with Classical MCL (78%) histological sub-type, 19 patients (19%) with blastoid variant including 3 patients progressing from an indolent disease. In the evaluable cohort, 48% patients achieved complete response, 23% patients achieved a partial response, 10% had progressive disease. .

Fourteen diagnostic biopsy samples and 3 relapsed samples showed p53 overexpression (IHC) with underlying deleterious mutation confirmed by Sanger sequencing (SS). While the remaining samples (86/ 86%) showed low p53 expression coupled with wild-type TP53 in the evaluable samples (75%) by SS.

POD24 were evaluated in 46 patients with disease relapse, progression and lymphoma-related death. Twenty-two patients had POD within 24 months (POD<24), while the remainder experienced disease relapse or progression after 24 months (POD>24).

Survival Data: As of the final data compilation on July 31, 2023, 38% patients remained alive, while 62% patients had died including 39% lymphoma-related deaths in the evaluable cohort. The overall survival (OS) and progression-free survival (PFS) rates for the entire cohort were at 71 and 49 months, respectively. The prognostic significance of age (<65 years) and MIPI score, was substantiated within this cohort, P-values of <0.0001and 0.0192.

In the subgroup subjected to treatment, the median OS and PFS durations for the p53 wild-type subset were 94 months and 54 months, respectively. In contrast, the presence of p53 disruption engendered a dismal prognosis and adverse treatment outcomes with less favourable median OS and PFS of 16 months; ($P < 0.0026$) and 8.5 months ($P < 0.0001$) respectively.

The validation of Progression of Disease within 24 months (POD<24) as an indicator of poor prognosis was underscored by the relapse/progression cohort. Within this subset (POD<24), the median OS and PFS intervals were observed to be 17.5 months and 11.5 months, respectively, yielding a statistically significant P-value of <0.0001 for both parameters (95% CI 1.999- 9.913 and 0.08471-0.45) for OS and PFS, respectively. A majority (71%) of instances manifesting p53 disruption at the time of diagnosis, along with two samples obtained from relapsed disease biopsies, demonstrated a POD<24 profile.

Conclusion: The utilization of p53 alteration screening exhibits the potential role as a surrogate biomarker for POD24, both during early diagnostic assessment and within the context of relapsed disease.

EXPRESSION OF EXHAUSTION MARKERS ON THE SURFACE OF T-CELLS AND CAR-T CELLS IN THE RECIPIENTS OF CD19 CAR-T CELL THERAPY

H Foy-Stones[1], CL Bacon[2], C Armstrong[2], A Kilgallon[3], DG Doherty[3], AM Mc Elligott[3], T Hervig[4], N Casey[1], N Orfali[2], E Vandenberghe[2], R Henderson[2], E Higgins[2], N Gardiner[1]
[1]Cryobiology Laboratory Stem Cell Facility, St. James's Hospital, Dublin, [2]National Adult Stem Cell Transplant and Adult CAR-T cell Programme, Department of Haematology, St. James's Hospital, Dublin, [3]Trinity Translational Medicine Institute, Trinity College, Dublin, [4]Irish Blood Transfusion Service, Dublin

Introduction: T-cell exhaustion is a state of functional impairment that occurs due to prolonged exposure to antigenic stimulation. In chronic infections and cancer, these exhausted T-cells can lose their ability to respond to antigens. The dynamics of T-cell exhaustion involves the expression of a number of receptors on T cells and their inhibitory ligands on other cells. We present our preliminary findings of exhaustion markers on circulating T-cells and CD19 CAR-T cells post CAR-T-cell infusion.

Materials and Methods: Using flow cytometry, we assessed the expression levels of exhaustion markers on the surface of total T cells and CD19 CAR-T cells in recipients' peripheral blood mononuclear cells (PBMCs) post-CAR-T cell therapy. Characterisation of T-cell-immunoglobulin-and-mucin-domain-containing-3 (TIM-3), Programmed-cell-death-1 (PD-1), B-and-T-lymphocyte-attenuator (BTLA), Cytotoxic-T-Lymphocyte-Associated-Protein-4 (CTLA-4) and Lymphocyte-Activation-Gene-3 (LAG-3) was performed on ten patients at 1, 3 and 6 months post-CAR-T cell infusion.

Results: TIM-3 exhibited the highest levels of elevation post-CAR-T infusion, followed by PD-1, BTLA, CTLA-4 and LAG-3.

At 1, 3 and 6 months post-CAR-T cell therapy, TIM-3 was expressed by >20% of total T cells and >60% of CD19 CAR-T cells. Furthermore, in our complete remission (CR) group, we observed a higher percentage of TIM-3 on total T-cells at 1, 3 and 6 months post-infusion compared to the persistent disease (PD) and partial response (PR) groups. On CD19 CAR T-cells, we observed a higher percentage of TIM-3 in the CR group at 1 month post-infusion, and then in the PD and PR groups at 3 and 6 months post-infusion.

PD-1 expression was also observed at high levels on the surface of T cells at 1, 3 and 6 months (range: 13.16-22.35%). Similarly, we observed high levels of PD-1 on CD19 CAR-T cells (range: 44.17-59.62%). At 1 month post-infusion, our CR group exhibited higher levels of PD-1 on T cells, whereas the expression of PD-1 on CAR-T cells was similar between all groups at 1 month. At 3 and 6 months post-infusion, our PD and PR groups expressed higher levels of PD-1 on both T-cells and CD19 CAR T-cells.

The expression of BTLA on T-cells and CD19 CAR-T cells was higher in the PD and PR groups at 3 and 6 months post-infusion. CTLA-4 was demonstrated at higher levels on CD19-CAR-T cells in the PD group at the 1, 3 and 6-month time points, whereas the highest levels of CTLA-4 on T-cells were evident in the CR group at 3 months post-infusion. We observed, that LAG-3 expression levels were the lowest of all exhaustion markers that we monitored during our study. Across all time points, the mean LAG-$3^+CD3^+CD19CAR^+$% was <10% and the mean LAG-3^+CD3^+% was <1.0%.

Conclusions: In conclusion, we investigated if T-cell exhaustion is among the contributing factors that impact the effectiveness of CAR-T cell therapy. We observed high levels of exhaustion markers on the surface of T-cells and CAR-T cells post-infusion. Despite the apparent negative aspects of T-cell exhaustion, our preliminary research has suggested that it might be associated with a positive overall outcome. Further research on additional patients at further time points is required to determine if these exhaustion markers are a negative or positive indicator of overall outcome post-CAR-T cell therapy.

ASSOCIATION OF CD56$^+$ T CELLS WITH THE ABSENCE OF GRAFT VERSUS HOST DISEASE IN PATIENTS UNDERGOING REDUCED-INTENSITY CONDITIONING ALLOGENEIC STEM CELL TRANSPLANT

H Foy-Stones[1], C Armstrong[2], N Orfali[2], DG Doherty[3], AM McElligott[3], T Hervig[4], CL Bacon[2], E Conneally[2], C Flynn[2], P Hayden[2], PV Browne[2], E Vandenberghe[2], R Henderson[2], M Ní Chonghaile[2], M McElheron[3], N Gardiner[1]

[1]Cryobiology Laboratory Stem Cell Facility, St. James's Hospital, Dublin, Ireland
[2]National Adult Stem Cell Transplant and Adult CAR-T cell Programme, Department of Haematology, St. James's Hospital, Dublin, Ireland
[3]Trinity Translational Medicine Institute, Trinity College, Dublin, Ireland
[4]Irish Blood Transfusion Service, Dublin, Ireland

Introduction/Background: Despite the efficacy of reduced-intensity conditioning allogeneic stem cell transplantation (RIC allo-SCT) in treating blood cancer, a significant number of patients develop graft versus host disease (GvHD). GvHD occurs when donor T-cells recognise the recipient as foreign and mount an immune response that subsequently causes the destruction of host tissues. Chronic GvHD in particular results in substantial morbidity and a reduction in the quality of life. We report preliminary results on post-transplant immune monitoring of innate lymphocytes, including CD56$^+$ T-cells, gamma delta (γδ) T-cells and NK cells, in patients post-RIC allo-SCT for myeloid malignancy at St James's Hospital.

Materials and methods: In this longitudinal study, we biobanked peripheral blood mononuclear cells (PBMCs) from twenty patients undergoing RIC allo-SCT for AML (n=13), MDS (n=3), MPN (n=3) and CMML (n=1) at serial time points: pre-transplant and days 28, 60 and 100 post-allo-SCT transplant. We performed flow cytometry analysis on PBMCs using multicolour antibody panels for CD4$^+$ T-cells CD8$^+$ T-cells, NK cells, iNKT cells, CD56$^+$ T-cells and subsets of γδ T-cells. Statistical analysis was conducted using R Studio (V4.2.3).

Results: GvHD manifested in 70% of cases (n=14). Within this group, 13 patients experienced acute GvHD (aGvHD) categorised as grade I (n=4), grade II (n=8) and grade III (n=1). Chronic GvHD (cGvHD) developed in 4 patients, and three of these patients had both aGvHD and cGvHD. The average time to onset of aGvHD was 61±34 days, whereas cGvHD was 299±141 days.

At day 28 post-transplant, the mean absolute number of CD56$^+$CD3$^+$PBMC/µL was 3.96 ± 4.18. We observed significantly lower numbers of CD56$^+$ T cells in patients who subsequently developed cGvHD compared to those who did not (mean 1.38 ±1.19 vs. 2.65 ±2.66, p=0.039).

At day 60 post-transplant, we did not observe any statistical difference between the presence or absence of GvHD and CD56$^+$ T-cells (p>0.05).

At day 100 post-transplant, the mean absolute number of CD56$^+$CD3$^+$PBMC/µL was 2.67 ±2.41. Again, a lower mean was observed in patients who subsequently developed cGvHD compared to those who did not (mean 0.87 ± 0.57 vs. 3.12 ± 2.49, p=0.039).

At days 28, 60 and 100 post-transplant, we found no associations between CD56+ T-cells and steroid treatment, recipient age, sex or donor age (p>0.05). In addition, we found no association between GvHD and NK cells or invariant NKT cells (p>0.05). No association was identified between CD56$^+$ T-cells and the incidence of relapse (p>0.05).

Conclusions: Through immune panel investigations at serial time points, we found a significant correlation between low CD56$^+$ T-cell count and subsequent GvHD development. Slower CD56$^+$ T-cell recovery in the early post-transplant period associates with a higher incidence of subsequent cGvHD. Additional patient testing and functionality studies are warranted to investigate the predictive value and the mechanism by which CD56$^+$ T-cells may play a protective role against GvHD post-RIC allo-SCT without compromising graft versus leukaemia effects.

SERIAL MONITORING OF CIRCULATING CD19 CAR-T CELLS IN PATIENTS POST CAR-T CELL THERAPY

H Foy-Stones[1], CL Bacon[2], C Armstrong[2], A Kilgallon[3], DG Doherty[3], AM Mc Elligott[3], T Hervig[4], N Casey[1], N Orfali[2], E Vandenberghe[2], R Henderson[2], E Higgins[2], N Gardiner[1]
[1]Cryobiology Laboratory Stem Cell Facility, St. James's Hospital, Dublin, Ireland
[2]National Adult Stem Cell Transplant and Adult CAR-T cell Programme, St. James's Hospital, Dublin, Ireland
[3]Trinity Translational Medicine Institute, Trinity College, Dublin, Ireland
[4]Irish Blood Transfusion Service, (IBTS), Dublin, Ireland

Introduction/Background: Chimeric antigen receptor T cell (CAR-T) therapy has demonstrated success in the treatment of relapsed/refractory high-grade B-cell malignancies. Currently, the most utilised target for CAR-T is the B-cell surface antigen CD19. However, with reported response rates of up to 50%, we are left with the question of what differentiates responders from non-responders, as various factors play a role in the success of CAR-T. Here we report preliminary results on serial monitoring of circulating CD19 CAR-T cells in patient's peripheral blood mononuclear cells (PBMCs) post-CAR-T cell therapy, to assess if CAR-T cell persistence is a useful indicator for patient outcome.

Materials and Methods: We examined ten patients who underwent CD19 CAR-T cell therapy for the treatment of relapsed/refractory diffuse large B cell lymphoma (DLBCL). Serial flow cytometry analysis was performed on biobanked PBMCs at 1, 3 and 6 months post CAR-T cell therapy infusion. The detection of circulating CD19 CAR-T cells was performed using the Miltenyi CD19 CAR detection reagent on the FACSCanto II (BD). Analysis was conducted using FlowJo and GraphPad Prism software.

Results: We longitudinally investigated CAR-T recipients that were treated with Kymriah® (n=8) and Yescarta® (n=2) at St James Hospital. The cohort included individuals varying in age (median 59 years; range 27-73) and sex (XY: n=7, XX: n=3). At 6 months post CAR-T cell infusion, six patients achieved complete remission (CR), one patient demonstrated a partial response (PR) and three patients had persistent disease (PD).

At 1, 3 and 6 months post CAR-T cell therapy the mean CD19 CAR percentages were 3.04 (0.59-13.35%), 2.73 (0.71-11.29%) and 1.03 (0.35-3.09%) respectively, with mean absolute numbers of $CD3^{+}CD19CAR^{+}$PBMC/µL of 4.13 (0.34-23.4), 1.62 (0.33-4.26) and 0.58 (0.21-1.09). Here we demonstrated a decrease in the CD19 CAR percentage and absolute numbers over time in patients post CAR-T cell therapy.

At 1 month post-CAR-T cell therapy, the mean CD19 CAR percentage was highest in the CR group (4.91%, range 0.85-13.35%) compared to the PD group (0.65%; range 0.59-0.75%). The mean absolute numbers of $CD3^{+}CD19CAR^{+}$PBMC/µL were also higher in patients with CR (6.50 PBMC/µL, range; 0.63-23.41) compared to PD (0.99 PBMC/µL, range; 0.34-1.59). Furthermore, the mean CD19 CAR percentage and PBMC/µL were highest in the CR group at 3 months post-infusion.

At 6 months post CAR-T cell therapy the mean CD19 CAR PBMC/µL was also higher in the CR group (0.71 PBMC/µL, range; 0.49-1.09) compared to the PD group (0.25 PBMC/µL range; 0.21-0.31). However, a higher mean CD19 CAR percentage was observed in the PD group (1.74, range; 0.39-3.08) compared to the CR group (0.82, range; 0.35-1.98).

Conclusions: In conclusion, we demonstrated that CAR-T cell persistence decreases over time. A higher percentage of CD19 CAR-T cells was observed at 1 and 3 months post-infusion in the CR group compared to the PD group, and the reverse was observed at 6 months post-infusion. We predict that longitudinal monitoring of CD19 CAR-T cells at further time points will shed light on whether the persistence of CD19 CAR is one of the contributing factors that can differentiate between responders and non-responders.

A *GATA1* low expressing *JAK2* V617F positive model identifies epigenetic mechanisms regulating *GATA1* target genes and megakaryocytic differentiation.

G Greenfield[1], MF McMullin[2], K Mills[1]
[1]Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, Belfast, UK
[2]Centre for Medical Education, Queen's University Belfast, Belfast, UK

Introduction: *GATA1* is a master transcription factor in both erythroid and megakaryocytic differentiation. Megakaryopoiesis is dysregulated in myeloproliferative neoplasms (MPN) with a bias towards megakaryocyte differentiation evident at the haematopoietic stem cell level in myelofibrosis and essential thrombocythaemia. In addition, aberrant megakaryopoiesis in MF results in abnormal megakaryocytes which play a critical role in mediating fibrosis and inflammation. These abnormal megakaryocytes are observed to lack GATA1 protein expression in comparison to normal controls. We had previously observed a downregulation of megakaryocytic priming in *JAK2* V617F positive UKE1 cells following single cell dilutional colony formation and resulting from significant *GATA1* downregulation. This cell model provided an opportunity to investigate the epigenetic control of *GATA1* expression and the *GATA1* target genes without needing to artificially perturb the cells.

Materials and Methods: UKE1 cell transcriptional phenotypes were analysed using RNA sequencing. Differential gene expression profiling using DESeq2. ATAC sequencing undertaken using Active Motif ATAC-Sequencing Kit in triplicate. FASTQ files were aligned were trimmed and aligned to Hg38 genome. Peak calling using Genrich and differential peak analysis performed using Diffbind. ChIP-seq peaks for GATA1, NCOR1, HDAC3 and TBL1XR1 obtained from ENCODE database for K562 cells. *GATA1* expressing cells from single cell dataset GSE144568 analysed in Seurat in R.

Results: *GATA1* expression is significantly downregulated in UKE1 cells with loss of megakaryocyte priming in comparison to the original parental UKE1 cells (Log2FC -4.82, Adj. p value 1.60E-61). This loss of megakaryocytic priming was associated with a significant change in the chromatin landscape with 8,838 ATAC peaks differentially less accessible. Genes associated with these peaks were enriched for roles in megakaryocytic biology. GATA1 transcription factor binding motifs were significantly over-enriched in the most significantly altered regions. Loss of chromatin accessibility at two *GATA1* enhancer regions was identified. Using ENCODE datasets for GATA1 ChIP-sequencing in related *GATA1* expressing, erythro-leukaemia K562 cells, we were able to match the loss of chromatin accessibility with GATA1 ChIP-seq peaks in enhancer regions related to multiple genes upregulated during megakaryopoiesis including *GP1BA, ITGA2B, RUNX1, TUBB1* and *KLF2*. This demonstrates chromatin remodelling associated with loss of GATA1 expression at GATA1 target genes. GATA1 was observed to directly modulate expression of *TBL1X*, a member of the NCOR/SMRT epigenetic complex. When binding peaks from K562 ChIP-sequencing datasets were compared to the ATAC data from UKE1 cells, there was significant over-enrichment for co-localisation of GATA1 with the NCOR/SMRT components NCOR1, HDAC3 and TBL1XR1 at the most significantly downregulated sites of chromatin accessibility. This co-localisation was frequently observed at genomic regions associated with megakaryocytic gene expression and was also observed at both GATA1 enhancer regions. Analysis of publicly available single cell sequencing data in myelofibrosis patients demonstrates an upregulation of NCOR/SMRT components at the critical stage of megakaryocytic priming in CD34+ cells.

Conclusions: These results suggest a novel feedback mechanism linking GATA1 with the NCOR/SMRT complex in the co-regulation of expression of both GATA1 and GATA1 target genes which will be further investigated and may represent a new therapeutic target to manipulate megakaryopoiesis in *JAK2* V617F positive MPN.

GENOMIC CHARACTERISTICS AND OUTCOMES OF CHRONIC MYELOMONOCYTIC LEUKEMIA IN SINGLE CENTRE STUDY CONFIRM HETEROGENOUS DISEASE WITH POOR OUTCOMES IN TRANSFORMED DISEASE.

D Grzegorzek[1], L Smyth[1,2], M Coyne[1,2], DG Connaghan[1], K Fadalla[1,2], J Fitzgerald[1,2], K Murphy[1,2], JM Power[1], C Andrews[1,2]
[1]Department of Haematology, St. Vincent's University Hospital, Dublin,
[2]Department of Medicine, University College Dublin, Dublin,

Introduction: Chronic myelomonocytic leukemia (CMML) is a clonal hematopoietic stem cell disorder with overlapping features of myelodysplastic syndromes and myeloproliferative neoplasms, and has a risk of transformation to AML which is ~15% over 3-5 years (1). The management is challenging due to significant clinical heterogeneity. Treatment strategies range from watchful waiting to Hematopoietic Stem Cell Transplant (HSCT), which remains the only curative therapy

Aims: The aim of this study is to determine the clinical characteristics including genomics of patients with CMML treated at our hospital. We aim to assess outcomes of patients especially those that have transformed to AML.

Methods: All patients aged 18 and over with a diagnosis of CMML between 2015-2023 were identified by the St Vincents University haematology database. Inclusion criteria included a diagnosis of CMML by the WHO 2022 classification of haematology and tumours. Baseline characteristics were collected. Overall survival (OS) rates were calculated using the Kaplan-Meier method.

Results: There were 33 patients diagnosed with CMML in the time period. Two patients were excluded as records were not available. Bone marrow histology was available for 90% (28/31) patients.

Cytogenetics were available for 97% (30/31). 90% (27/30) were normal karyotype, abnormalities detected in 10% (3/30) patients, and included: 45X (-y), 47XX (+8) and 48XY (+8, +21). Next Generation Sequencing (NGS) was available for 74.2% (23/31). Average number of mutations was 2.7 (0-7). Of the mutations that are considered high risk, 43% (10/23) had ASXL1, 17.4% (4/23) had NRAS, 17.4% (4/23) RUNX1, and 8.7% (2/23) SETBP1 mutation. Other mutations documented included SRSF2, TET2, KRAS, IDH1 and FLT3. Patients were classified into CMML 0, 1 or 2 categories as per WHO 2016 criteria: 29% (9/31), 52% (16/31) and 19% (6/31) respectively. Patients were risk stratified by the CPSS-Mol scoring system and 39% (9/23) were Low Risk, 4.34% (1/23) Intermediate-1, 34.7% (8/23) Intermediate-2, and 21.7% (5/23) were high-Risk groups.

58% (18/31) patients underwent clinical surveillance, 32.25% (10/31) were treated with Azacytidine, 3% (3/31) received induction chemotherapy. (OS) rate was 47.2% at 4 years in entire group.

Nine patients (27%) transformed to AML, with NGS available for 5 of those. The average number of mutations on NGS increased from 2.65 prior to transformation to 4 post transformation. Two patients received induction chemotherapy and 6 patients received azacytidine. Two patients were transplanted – one remains in a complete remission and other relapsed 6 months post transplant.

OS rate was 48% at 4 years for entire study group (n=31) however OS for patients who transformed to AML (n=9) was 17% at four years. In terms of CPSSmol, OS was 100% with low risk disease at 4 years, 57% for intermediate disease and no high risk patients were alive at 4 years.

Conclusions: Our study revealed outcomes in our institution correlated with the CPSSmol and confirms the heterogeneity of the disease. Genomic profiles were also consistent with previous studies (1) and despite small numbers, progression to AML was accompanied by increased mutational burden. Outcomes post transformation to AML remains poor and represent an unmet clinical need.

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AUDIT OF INPATIENT SYSTEMIC ANTI-CANCER THERAPY ADMINISTRATION

I Hughes[1], R Karlsson[1], C Browne[1], CL Bacon[1]
[1]Haematology, St James's Hospital, Dublin,

Introduction: Systemic anti-cancer therapy is a collective term comprising chemotherapy, immunotherapy and targeted therapies.[1] There is a risk of infusion reactions, some of which may be life-threatening, with these therapies. These are most common during the first administration (i.e. Cycle 1 Day 1) and the risk lessens with each subsequent administration.[2] Ideally, resources should be optimised to ensure the best outcome in the event of such an occurrence.

The National Cancer Control Programme has recommended that all chemotherapy should be commenced during normal working hours when support services and expert advice are available.[3] The SJH SACT Management Policy advises that SACT should be administered within core working hours and that inpatient prescriptions for 'same day administration' must be prescribed, verified by the Clinical Pharmacist and confirmed for manufacture by 11am on the day of treatment.[4]

The objective of this audit was to evaluate the compliance of our department with these policies. We further analysed the potential factors leading to out-of-hours administration of treatment to highlight where improvements could be made.

Methods: A retrospective study was conducted to review the records of inpatients who received C1D1 SACT on the Haematology/Oncology ward in SJH during June and July of 2023. We included patients who had been electronically prescribed SACT on the National Cancer Information System. We used the SJH electronic patient record to document demographics, diagnoses and infusion reactions. We used NCIS to document the specific treatment including prescribing time, offheld time, pharmacist verified time and the administration times. This data was tabulated and analysed.

Results: 36 patients were included in the study; 14 (39%) Haematology patients and 22 (61%) Medical Oncology patients. The median number of infusions in each regimen was 2 (range 1 - 4 infusions). The median duration of infusions was 3 hours (range 20 mins - 48.5 hours). The average time of commencing the first infusion was 14:08 (range 09:33 - 17:31). There were 2 (5.6%) infusion reactions requiring a medical review, both within working hours.

The compliance rate to the NCCP recommendation to commence chemotherapy within working hours was 80% (June 93.3%; July 71.4%).

The compliance rate to the SJH SACT policy to administer (complete) treatment within core hours was 27.8% (June 46.7%; July 14.3%).

The compliance rate to the SJH SACT policy to prescribe, verify and confirm treatment for manufacture before 11am was 66.7% (June 53.3%; July 76.2%).

- 94.4% Verified by Physician before 11am.
- 91.7% Verified by Pharmacist before 11am.
- 69.4% Confirmed for manufacture before 11am.

Conclusions: Established recommendations and policies exist for administering SACT within working hours to ensure adequate staff and resources are available to manage potential infusion reactions. This audit found that although most SACT is commenced within working hours, the majority of these are completed out of hours when less expertise is available to manage potential infusion reactions. Potential targets for improvement would be to provide education to prescribing physicians on the importance of confirming the prescription for manufacture before 11am and requesting nursing staff to commence C1D1 regimens with multiple infusions as a priority.

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USING STRUCTURE-BASED MODELLING AND PRECLINICAL MURINE XENOGRAFT AVATARS TO IDENTIFY EFFECTIVE DRUG COMBINATIONS IN HIGH-RISK ACUTE LEUKAEMIA

L Jones[1], O Rukhlenko[1], C Carmody[1,2], K Wynne[1], B Kholodenko[1], J Bond[1,2,3]
[1]Systems Biology Ireland, University College Dublin, Dublin,
[2], SFI Centre for Research Training in Genomics Data Science, ,
[3], Children's Health Ireland at Crumlin, Dublin,

Introduction:

Alterations causing hyperactivation of kinases are common in acute myeloid leukaemia (AML) regardless of patient age and are typically associated with poor outcome. Activating mutations in NRAS and KRAS genes respectively occur in approximately 15% and 5% of newly diagnosed AML cases, causing aberrant activation of downstream RAF/MEK/ERK kinases. There are currently no satisfactory treatment approaches targeting RAS-mutant AML, and as such new therapeutic options are needed. Using a structure-based modelling approach, we recently showed that combining two different classes of RAF inhibitors synergistically reduces downstream signalling and cell viability in RAS- and RAF-mutant solid tumour models. This approach leverages different conformational states of the DFG motif and the αC-helix (αC-IN/DFG-IN / αC-OUT/DFG-IN / αC-IN/DFG-OUT) in the two protomers of a RAF dimer (asymmetry), and affinity of these conformations for different inhibitor classes (Type 1/1.5/2). Here we have applied our modelling approach to RAS-mutant AML, identifying effective RAF inhibitor combinations which may provide novel therapeutic avenues for this high-risk patient group.

Methods:

We generated basal phospho-proteomics data for five RAS-mutant cell lines (3 x NRAS-mut, 2 x KRAS-mut). These data, alongside single agent dose responses, were input into our existing rule-based model of RAS/RAF/MEK/ERK signalling. Fixed-ratio drug combinations were performed against all cell lines and synergy determined using the HSA Synergy model. To generate AML patient-derived xenografts (PDXs), patient samples were inoculated into NSG-SGM3 mice via the lateral tail vein. Engraftment was assessed by chimerism of human vs. mouse $CD45^+$ cells in peripheral blood.

Results:

Rule-based modelling predicted two iterations of RAF inhibitor combinations as synergistic against RAS-mutant AML: i) Type 1 (αC-IN/DFG-IN) / Type 2 (αC-IN/DFG-OUT) and ii) Type 1.5 (αC-OUT/DFG-IN) / Type 2. In line with predictions, both combination types were synergistic against RAS-mutant AML cell lines. Combined lifirafenib (Type 2) and encorafenib (Type 1.5) was synergistic against both NRAS- and KRAS-mutant lines (HSA score range = 11-19.9). For combined lifirafenib and SB-590885 (Type 1), synergy was observed against NRAS-mutant lines (HSA score range = 10.8-19.7), while mild additivity was achieved against KRAS-mutant lines. We have now generated 2 NRAS-mutant paediatric AML PDXs, which will be used to validate these results *in vivo* in a clinically relevant model.

Conclusions:

We have utilised a systems biology approach to identify novel, non-obvious kinase inhibitor combinations which are effective against RAS-mutant AML. These combinations will now be assessed in patient-derived xenograft models of paediatric RAS-mutant AML, and potentially provide a promising therapeutic avenue for treating RAS-mutant AML.

Impact of progression of disease with 24 months (POD24) on follicular lymphoma treatment outcome. A single centre retrospective study

A Jones[1], B Hennessy[1], S Samuel[1], M Khan[2], L Fei[2], S Kumar[1], A Bannaga[1], M Griffin[2], M Nur[2], E Elhassadi[1]
[1]Haematology Department, University Hospital Waterford, Waterford , Ireland
[2]Pathology Department, University Hospital Waterford, Waterford , Ireland

Introduction: Follicular lymphoma stands out as a prevalent, yet manageable, low-grade lymphoproliferative disorder. With the introduction of rituximab, an estimated 80% of treated patients now enjoy a survival rate exceeding 10 years. However, within this context, there exists a subset of patients - roughly 10-20% - who experience disease progression within an unexpectedly short span of 2 years post-treatment, a phenomenon referred to as POD24. Notably, this subset tends to exhibit a more aggressive disease course. This retrospective analysis of follicular lymphoma cases diagnosed at our centre, aims to assess the influence of POD24 on overall treatment outcomes.

Methods: Using our pathology database, patients with a biopsy-proven follicular lymphoma diagnosis were identified and included in this study (1999-2022). Patient's consent was obtained. Patients demographic characterises, Follicular Lymphoma International Prognosis Index (FLIPI) score, treatment applied, disease relapse / disease progression and survival data were evaluated. Survival data using Prism10 software and applying Log-rank (Mantel-Cox) test for statistical significance were analysed. The study cut-off time 31/01/2023.

Results: The study cohort comprised 153 patients with follicular lymphoma diagnosed over the study period. The median age at diagnosis was calculated at 60.5 years, with 78 male patients (51.3%) and 74 female patients (49%). Stratification of FLIPI scores at the time of diagnosis yielded proportions of 36% for low risk, 32% for intermediate risk, and 31% for high risk.

Within the subset subjected to therapeutic interventions (127 patients or 83%), chemo-immunotherapy was the predominant treatment approach (102 patients or 83%). A subset of patients (4) received chemotherapy in isolation, whereas single-agent Rituximab was administered to 5 patients (4%), and 16 patients (13%) were treated solely with radiotherapy. Notably, 90 patients (71%) received Rituximab maintenance. The reminder patients were either unfit for any therapy or on a 'watch and wait' approach.

As of the final data compilation on Jan 31, 2023, 129 patients (84%) remained alive, while 24 patients (16%) had died. The evaluation of Overall Survival (OS) and Progression-Free Survival (PFS) for the entire cohort yielded results where median values remained unreached**.** The OS of patients with high risk FLIPI was 171 months, while the intermediate and low-risk subsets exhibited indefinite OS durations**.**

In the subset characterized by relapse post-initial therapy (33 patients or 26%), including 6 patients (5%) treated with radiotherapy alone, and 8 patients demonstrated transformation into high-grade disease. Notably, within the relapsed subgroup, 10 patients (30%) encountered disease relapse or progression within the critical 24-month period (POD<24). Their OS and PFS were 84 and 19 months, respectively, showing less favourable outcomes compared to the POD>24 group, which exhibited respective figures of 241 and 141 months.

Conclusion: In light of the findings, this study provides evidence of the adverse impact of POD<24 on treatment outcomes in follicular lymphoma. Currently, early biological predictive markers for POD24 are lacking, and a follow-up project aims to address this. In essence, this study underscores the pressing need to reshape the treatment landscape through proactive intervention strategies to address the distinctive treatment challenges faced by high-risk patients.

DDX41 mutations in haematopoietic malignancy

KL Liston[1], GB Buckley [1], VM Mykytiv[1]
[1]Department of Haematology, Cork University Hospital , Cork, Ireland

Introduction/Background: There have been major advances in the classification of myeloid neoplasms in recent years with a shift in focus toward the identification of causative and/or actionable genetic abnormalities. This is reflected in both the 2022 revised World Health Organisation (WHO) classification and the 2022 International Consensus Classification (ICC) (1,2).

Somatic mutations identified on next generation sequencing (NGS) panels are now known to be highly impactful on diagnosis, risk stratification and disease response monitoring in myeloid malignancy. The increased use of NGS has led to a rise in the number of germline genetic abnormalities identified as part of the work up for myeloid malignancy. Germline DDX41 mutations are known to have a predominately adult-onset phenotype and can predispose to both myeloid and lymphoid malignancy. Detection of a somatic variant that is suspicious of being germline in nature requires confirmatory testing and fibroblast-derived DNA from skin biopsy samples is currently the recommended confirmatory test (3).

Materials and methods: This case series aims to describe the clinical features associated with DDX41 mutations in myeloid malignancy. We discuss 4 cases of myeloid malignancy in which a DDX41 mutation was identified through NGS assessment at diagnosis. In all cases a somatic variant was initially detected with a variant allele frequency (VAF) of greater than 40%. Skin biopsies were sent for sequencing of cultured fibroblast DNA to determine if the mutations were germline in origin.

Results: The median age of DDX41 mutation identification in this series was 70 years old. The haematological neoplasms associated with this mutation included chronic myeloid leukaemia, acute myeloid leukaemia (AML) with T-large granulocyte leukaemia (T-LGL), AML with myelodysplasia (MDS) related cytogenetic abnormality and MDS/AML. Two cases were managed with successful allogeneic stem cell transplant, one with a matched unrelated donor transplant and one with a matched sibling donor transplant. At the time of writing this abstract, 1 of the 4 cases has been confirmed through fibroblast-derived DNA to be germline in nature. The 3 remaining cases have had skin biopsy samples sent and are awaiting confirmatory results.

Conclusion: Germline mutations such as DDX41 can be initially detected through NGS analysis and may occur more frequently than previously documented. They have important clinical implications in terms of haematopoietic malignancy risk in family members of affected patients. It is also important to identify germline mutations in potential related allogeneic stem cell donors as reintroduction of a DDX41 mutation at the time of transplant can lead to an increased risk of donor derived leukaemia.

As the use of NGS continues to rise in myeloid malignancy, it is likely that there will be a further increase in the detection of germline mutations. It is therefore essential that haemato-oncology clinicians have an understanding of the potential clinical implications of germline mutations on patients and their families.

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DESIGNING AND TESTING NOVEL PEPTIDE INHIBITORS TO ANTAGONIZE JUNCTIONAL ADHESION MOLECULE-A (JAM-A) DIMERIZATION IN MULTIPLE MYELOMA

NA McAuley[1,2], IM Drozdz[1,2], R McAvera[2], M Brennan[3], M Devocelle[5], SV Glavey[2,5], AM Hopkins[1]
[1]Department of Surgery, RCSI University of Medicine and Health Sciences, Dublin, [2]Multiple Myeloma Research Group, RCSI University of Medicine and Health Sciences, Dublin, [3]Department of Pharmacy and Biomolecular Sciences, RCSI University of Medicine and Health Sciences, Dublin, [4]Department of Chemistry, RCSI University of Medicine and Health Sciences, Dublin, [5]Departments of Haematology and Pathology, Beaumont RCSI Cancer Centre, Dublin,

Background/Aims: Junctional Adhesion Molecule A (JAM-A), encoded by the *F11R* gene, is a tight junction protein whose expression is dysregulated in various cancers. Interestingly dimerization of JAM-A in *cis* (same cell) and *trans* (different cell) conformations has distinct functional effects and has been linked to oncogenic traits such as migration versus physiological traits such as cell-cell adhesion (2,4). It has recently been reported that increased JAM-A protein expression in multiple myeloma (MM) patients associates with reduced overall survival. MM is a malignancy characterized by the clonal expansion of aberrant plasma cells in the bone marrow and has a desperately low 5- year survival rate of less than 50%. Since MM remains an incurable disease, it is important therefore to investigate the possibility that antagonizing JAM-A may be of use clinically for this cohort of patients. The aim of this study was to investigate the druggability of JAM-A in MM.

Materials/Methods: Using the CoMMpass and GEO accession portals, we first investigated correlations between *F11R* expression and MM patient survival during progression from pre-malignant disease: monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM (SMM) to newly diagnosed / refractory disease. Using Molecular Operating Environment (MOE) software, we next built a peptide library to antagonize JAM-A *cis*-dimerization based on foundational work in the laboratory. Top-ranking peptide candidates were then synthesized and tested via ligand-binding assays and *in vitro* cytotoxicity assays, namely CellTitreGlo and LiveDeadAll staining. Finally, in conjunction with a public-patient involvement (PPI) panel, a lay information booklet was designed to spread awareness about MM research and to empower the patient voice.

Results: Interrogation of the CoMMpass and GEO accession portals revealed that overall survival and progression-free survival were significantly reduced in MM patients with high JAM-A gene expression. This supports our hypothesis that functional antagonism of JAM-A could be a novel therapeutic approach to treat MM. Several anti-JAM-A peptides were designed to exhibit improved binding stability to 9 protruding residues in the JAM-A *cis*-dimerization site (R59, E61, K63, L72, Y75, M110, E114, Y119, E121) by introducing peptide modifications such as acetylated amino terminals and D-amino acids. The most effective JAM-A ligands have been selected for *in vitro* cytotoxicity testing in MM cell lines including JJN3 (high JAM-A expression) and KMS18 (low JAM-A expression) in both suspension and 3D matrix (RASTRUM ™ Inventia Life Science) configurations.

Conclusions: Our work demonstrates that JAM-A is aberrantly expressed in aggressive forms of MM, defined by reduced overall survival shown in Kaplain Meier curves. A library of anti-JAM-A peptides to antagonize oncogenic pathways has been created and is currently being tested *in vitro*, with a view to future scale-up into *in vivo* models. By completion, this project will have generated new data on JAM-A signaling in MM disease progression and explored the possibility of using JAM-A antagonists as a future treatment approach for MM patients. Additionally, a booklet surrounding MM research will be launched nationally in September 2023. This booklet is hoped to increase awareness of the disease and to encourage a sense of community among patients.

Acknowledgements

This study was funded by Breakthrough Cancer Research and the Health Research Board via grant HRCI-HRB-2022-020 (to AMH and SVG).

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SKY92 MOLECULAR PROFILING IN COMBINATION WITH MRD RISK PROFILING TO IDENTIFY HIGH-RISK MULTIPLE MYELOMA PATIENTS IN IRELAND (SKIP-MM)

R McAvera[1], I Drozdz[1], H Black[1], J Quinn[2], P Murphy[2], P Thornton[2], R Cummins[3], T Cichocka[4], E Szegezdi[4], M Perera[5], G Crotty[5], R Clifford[6], N Keane[7], J Krawcyzk[7], V Mykytiv[8], E Elhassadi[9], M Coyne[10], O Abdulmalek[1], M O'Dwyer[11], S Glavey[1,2,3]

[1]Multiple Myeloma Research Group, Department of Pathology, Royal College of Surgeons in Ireland, Beaumont, Dublin, [2]Department of Haematology, Beaumont RCSI Cancer Centre, Dublin, [3]Molecular Pathology Laboratory, Royal College of Surgeons in Ireland, Dublin, [4]Blood Cancer Network Ireland, University of Galway, Galway, [5]Department of Haematology, Midland Regional Hospital Tullamore, Tullamore, [6]Haematology, University Hospital Limerick, Limerick, [7]Haematology Department, Galway University Hospital, Galway, [8]Department of Haematology, Cork University Hospital, Cork, [9]Haematology Department, University Hospital Waterford, Waterford, [10]Department of Clinical Haematology , St Vincent's University Hospital, Dublin, [11]School of Medicine, University of Galway, Galway

Introduction: Multiple Myeloma (MM) is a genomically complex malignancy of plasma cells. Novel therapies have produced unprecedented survival rates, which underscores the necessity to move toward a personalised treatment strategy. Currently the Revised International Staging System (R-ISS) is used to stratify patients into risk groups, however, this has not informed international guidelines towards risk-adapted treatment approaches. In Ireland, data is lacking on genomic drivers that may be population specific for MM patients. Additionally, minimal residual disease (MRD) negativity is a strong predictor of survival. This study evaluates genomic risk in newly diagnosed MM (NDMM) patients in Ireland using a highly prognostic, validated, gene expression profile (SKY92) alongside MRD testing by NGS.

Methods: BM samples from transplant-eligible NDMM patients (n=96) were collected at diagnosis and 100 days post autologous stem cell transplant (ASCT). Samples were enriched for mononuclear cells and CD138+ plasma cells, and DNA/RNA extracted. The MMProfiler™ microarray (SkylineDx) was performed in-house to detect the SKY92 gene signature (high-risk, survival <2 years at diagnosis) and several cytogenetic abnormalities. Where possible, microarray results were compared with routine clinical FISH results.

Diagnostic samples were assessed for clonal IGH rearrangements using LymphoTrack™ NGS assays (Invivoscribe®) on an Illumina MiSeq platform. In follow-up samples, MRD was monitored using a single LymphoTrack assay according to the clonotype identified at diagnosis.

Results:

The MMProfiler™ test attained results in >80% of patients, which in our cohort was higher than that achieved using FISH. The SKY92 high-risk signature was detected in 33.3% of patients. These patients were more likely to present with high-risk cytogenetics t(4;14) and gain(1q) ($p<0.05$), and the majority were classed as ISS-stage II (42%) or III (42%), whilst standard-risk were mostly ISS-stage I (54%) as expected. Cytogenetics detected by FISH and MMProfiler™ were concordant for 77.3% of cases (17/22). In discordant cases, the MMProfiler™ detected additional high-risk abnormalities that were not detected by FISH due to the higher sensitivity of MMProfiler™.

MRD testing: IGH-FR1 and IGH-Leader assays detected clonal rearrangements in 80% of patients at diagnosis. Remaining patients will be sequenced using additional LymphoTrack IGH assays (IGH-FR2/3) until a clonal sequence is determined. Patients are being followed prospectively and to date we have determined MRD status in 8 patients post ASCT. Detection of MRD is at a sensitivity of 10^{-5} (5/8 MRD+). Preliminary data shows that MRD positivity is associated with early relapse, but is independent of risk-status at diagnosis.

Conclusions: A significant proportion of MM patients in Ireland present with SKY92-high-risk disease. We are confident the correct subgroup are detected since they show high-risk cytogenetic and clinical features. Moreover, MMProfiler™ results are obtained within 4 days, a much faster turnaround than current FISH analysis (6+ weeks). We show high clonal characterisation of diagnostic BM samples using NGS, which can be used for sensitive MRD detection. As our study continues, we will evaluate the clinical significance of SKY92 in combination with MRD testing as a superior prognostic repertoire of testing for MM patients that can be provided locally and efficiently. These methods will improve risk stratification, and in future aid with risk-adapted therapy approaches.

Post-transplant Lymphoproliferative Disorder following Solid Organ Transplant: An Audit from the National Centre for Renal Transplantation

L McDonald [1], W Nablisi[1,2], M Wootton[1,2], P Murphy[1], J Seargent[1], P Thornton[1], D Swan[1], S Glavey[1], M Keogan[3], D Little[4], P Conlon[5], J Quinn[1]

[1]Department of Haematology, Beaumont Hospital, Dublin, [2]Department of Medicine, Royal College of Surgeons , Dublin, [3]Department of Immunology, Beaumont Hospital, Dublin, [4]Department of Urology and Kidney Transplantation, Beaumont Hospital, Dublin, [5]Department of Nephrology, Beaumont Hospital , Dublin,

Background: Post-transplant lymphoproliferative disorder (PTLD) is a rare disease that is characterised by abnormal lymphoid proliferation following either solid organ or haematopoietic stem cell transplantation(1). The pathogenesis is related to prolonged immunosuppression, dysregulated T Cell function and many cases are associated with Epstein Barr Virus (EBV)(2). The clinical presentation and natural history are heterogenous, with responses to immunosuppression reduction (RIS) alone in some patients and poor outcomes in patients with aggressive pathology(3).

Methods: This retrospective audit studied 42 patients diagnosed with PTLD following solid organ transplant (37 renal, 4 pancreas-kidney, 1 lung) between 2000 and 2023 in Beaumont Hospital.

We reviewed pre-diagnosis patient characteristics including indication for transplant, length of immunosuppression, EBV status, as well as analysing clinical presentation, treatment regimens and outcomes. Diagnostics and treatment regimens were compared to the recent BSH guideline “Front line management of PTLD in adult solid organ transplant recipients”, published in 2021(4).

Results: The median age at diagnosis of PTLD was 54 years (range 19-73). The median duration of immunosuppression was 13 years (1-30), and the median number of immunosuppressive agents was 3 (2-4); these included prednisolone (89%), azathioprine (57%), tacrolimus (54%), cyclosporine (46%) and mycophenolate (37%).

Monomorphic B-cell neoplasms were the most common histological subtype, with 19 (45%) DLBCL, three patients (7%) had plasma cell neoplasms, and two (5%) had Burkitt lymphoma. Fourteen patients (33%) were classified as having other B-cell neoplasms. Rarer histological subtypes included T-cell neoplasms (3, 7%) and classical Hodgkin lymphoma (1, 2%). EBV status was assessed in only 24 patients (57%), and of those only 5 (21%) were EBV positive.

Treatment regimens varied among patients and included RIS, immunotherapy, chemotherapy, radiation and palliative care. The median number of lines of treatment was 3 (range 2-4), with the most common treatment being chemo-immunotherapy (used in 65%). Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) was the most common regimen used in these patients. RIS was implemented in all cases, but was inadequate as each patient required a subsequent line of therapy. Four patients (9%) received no treatment due to frailty. Radiological remission was only documented in 16 patients (38%).

Nineteen patients were alive at the time of analysis (45%), and the median OS was 4.9 years. Patients classified as other B-cell neoplasms had the poorest median OS (11 months), followed by Burkitt Lymphoma (11.5 months). Patients with plasma cell neoplasms and T cell neoplasms had a median OS of 3.2 years and 4 years respectively . Median OS for patients with DLBCL and HL were much longer (9.3 years and 14 years respectively).

Conclusions: This audit demonstrates the heterogeneity of PTLD with regards to its presentation, histopathological subtype and response to treatment. Overall survival for patients with aggressive subtypes is poor, which therefore necessitates a consensus on optimal treatment regimens.

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CLINICAL AUDIT: ADHERENCE OF GALWAY UNIVERSITY HOSPITAL HAEMATOLOGY DEPARTMENT TO THE BRITISH SOCIETY OF HAEMATOLOGY GOOD PRACTICE PAPER GUIDELINES 2022 FOR THE WORKUP OF NEWLY DIAGNOSED/ RELAPSED ACUTE MYELOID LEUKAEMIA

C Meyer, A Hayat, N Keane, J Krawczyk, A Kwiatkowska, J Tan, S Ni Loingsigh, Y Nunez
[1]Haematology Department, Galway University Hospital, Galway,

Introduction: The classification of acute myeloid leukaemia (AML) is evolving, and recent guidelines reflect that. The British Society of Haematology (BSH) recently updated their guidance regarding recommended workup for cases of AML, with an increased emphasis on the genetic basis for defining disease. Regional variations in laboratory practices may result in significant heterogeneity in access to investigations as well as laboratory turnaround times. This audit evaluates the adherence to the latest standards of AML care in the GUH Haematology Department.

Methods: Newly diagnosed or relapsed cases of AML from September 2022 to February 2023 were identified using pharmacy records for relevant treatment protocols. Patients eligible for the Hovon 150 trial were excluded. Data was analysed using Microsoft Excel.

Results: 10 patients were included (n = 10), 5 male and 5 female. 7 patients had newly diagnosed AML and 3 suffered from relapsed disease.

Blood film morphology was performed in all cases (100%).

90% of cases had a bone marrow procedure at time of diagnosis, with the single remaining patient having had a marrow 4 months prior to relapse as part of minimum residual disease (MRD) monitoring. Aspirate quality was deemed adequate in 80% of cases with blast enumeration performed in 80% and immunohistochemistry in 90% of cases.

All cases (100%) had a standard 8 colour flow cytometry panel performed on a first pull bone marrow sample. In 80% of cases, flow cytometry analysed blast cells for CD33. Flow samples were not analysed for MRD markers, an area that fails to meet the standard of care. Flow cytometric analysis of CSF was performed in a single patient. The turnaround time for all samples were less than 3 working days, meeting the standard of care.

Karyotyping was performed in 90% of cases with 80% also analysed by FISH. Myeloid gene scan was performed in 70% of cases and MRD analysis in 80%. *PML-RARA* analysis was performed in the 2 cases where acute promyelocytic leukaemia was suspected morphologically. *FLT3* analysis was performed in 50% of cases, subdivided into *ITD* mutation (66,7%) and *TKD* mutation (33%). *KMT2A* analysis was performed in 60% of cases. 90% of cytogenetic samples and 80% of MRD samples reached the referral laboratories within the advised timeframe. Cytogenetics and KMT2A analysis were the only genetic results back reliably within the advised turnaround time (80% of cases respectively).

In relapsed cases, only one patient had all tests deemed essential by the standard of care (karyotyping, myeloid gene scan and *FLT3* analysis) performed.

No sample storage for biobanking occurred, an area that lacks to meet the standard of care.

Areas where the standard of care was not met might be improved in 45% of cases, whereas improving the remainder would be more challenging and reflects challenges on a system level.

Conclusion: Overall, the workup of newly diagnosed and relapsed AML cases in GUH did meet the standard of care as set out in the BSH Good Practice Paper. Genetic analysis had the lowest adherence, which likely reflects system challenges outside the control of the GUH Haematology team. This audit demonstrates what benefit might be obtained from a centralised analysis of patient data, allowing for a unified final report. Limitations include incomplete access to patient data.

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IS AGE TRULY JUST A NUMBER WHEN IT COMES TO ALLOGENEIC STEM CELL TRANSPLANTATION? - OUR NATIONAL EXPERIENCE IN PATIENTS AGED OVER 70 YEARS

M Murray[1], C Armstrong[2], CA Galligan[2], M Ni Chonghaile[2], A Lavan[3], K Coghlan[4], G Sheil[5], E Guinan[5], C Flynn[2], E Conneally[2], N Orfali[2]

[1]Medical Department, St James's Hospital, Dublin, [2]HOPe Directorate, St James's Hospital, Dublin, [3]Medicine for the Elderly Directorate, St James's Hospital, Dublin, [4]Physiotherapy Department, St James's Hospital, Dublin, [5]Physiotherapy Department, Trinity St James's Cancer Institute, Dublin, Ireland

Introduction: Myeloid malignancies predominantly affect the elderly.[1,2] Yet survival outcomes for older patients are poor, particularly in those aged over 70 years.[3] This is partially due to more resistant disease biology in older patients, where malignancy often develops from underlying age-related clonal haematopoiesis or emerges after prior chemo-/radio-/immune-therapy.[3] Moreover, treatment decisions are often more difficult in the elderly, where patient frailty and co-morbidity often pose substantial barriers to curative strategies - particularly allogeneic stem cell transplantation (AlloSCT).[4]

With novel therapies, older patients may attain disease remissions with less toxicity. In parallel, increased international experience with reduced-intensity conditioning platforms have reduced the risks associated with alloSCT. In this era, advanced chronologic age no longer represents an absolute contra-indication to transplantation. Instead, multi-disciplinary input into selecting and optimizing candidacy is preferred and an understanding of the unique physical and psychosocial challenges facing the elderly cohort is required.

Methods: We retrospectively report on our national experience to date of alloSCT in patients aged over 70 years, examining patient and disease characteristics along with post-transplant complications and outcomes. Data was collected from our electronic patient record with local research and innovation board approval.

Results: Our cohort comprises of 6 patients (4M/2F), with the first transplanted in April 2021. The median follow-up time to date is 466 days (range 187-850d).

Patients included:

- A 70-year-old male with MDS and excess blasts (KMT2A-partial tandem duplication)
- A 71-year-old female with NPM1-AML and persistent molecular disease after 2 lines of therapy (Concurrent KRAS mutation)
- A 73-year-old male with complex karyotype therapy-related AML (ASXL1, TET2 and CBL mutations)
- A 73-year-old male with MDS and excess blasts (ASXL1, RUNX1, SRSF2 and CSF3R mutations)
- A 73-year-old female with proliferative CMML (ASXL1, RUNX1, STAG2 & EZH2 mutations)
- A 74-year-old male with AML (ASXL1, DNMT3A, IDH2, FLT3-ITD mutations)

All patients were classified CIBMTR Disease Risk Index (DRI) high, conferring a 2-year overall survival of 33% [5]. Five of six had pre-existing comorbidities, most commonly cardiovascular. All were reviewed by a Geriatrician prior to admission for review of function, frailty and polypharmacy.

Patients were conditioned with a reduced-intensity fludarabine, busulfan and Anti-thymocyte globulin, before receiving peripheral blood stem cell grafts (1 sibling/5 unrelated).

All patients engrafted. Three developed acute graft versus host disease (GVHD) requiring steroid therapy; this was poorly tolerated in one patient, who developed psychiatric symptoms and a subsequent osteoporotic fracture. One patient developed chronic GVHD. All patients had at least one re-admission after transplant with infection. Blood pressure problems have been pervasive and one patient has survived an aortic dissection. One patient relapsed at 6 months. To date all patients are alive.

Conclusion: AlloSCT is feasible in patients over 70 years and may enhance survival. However, this population requires multi-disciplinary support and increases demands on staff time. Our patients have been carefully selected which likely biases positive outcomes. Our current transplant infrastructure is under-equipped to deal with high volumes of older patient referrals but increased resourcing could expand access to this potentially curative treatment.

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ASSESSING VARIATION IN THE NUMERATION OF PLASMA CELLS IN MYELOMA BETWEEN HAEMATOLOGISTS.

A Niblock[1,2], D Waddell[1], P Copeland[1], G Brown[1]
[1]Haematology department, Antrim Area Hospital, N. Ireland,
[2]School of Medicine, Ulster University, N. Ireland

Background: Plasma cell dyscrasias (PCD) are a heterogeneous group of diseases characterised by the expansion of monoclonal bone marrow (BM) plasma cells (PC). [1] The most common is monoclonal gammopathy of undetermined significance (MGUS) which is a premalignant PCD that consistently precedes plasma cell myeloma (PCM) with a 1% risk of progression per year.[2,3]

The small numbers of MGUS that do progress, proliferate their malignant PC. Once the clonal PC are >10% of the BM cells this is termed PCM. If there is no evidence of ROTI, then it's referred to as smouldering myeloma (SM) or asymptomatic myeloma. If there is evidence of ROTI or the PC are >60% of nucleated BM cells, then this is PCM requiring treatment. [4]

Therefore the classification of PCD into MGUS, SM and PCM rely on an accurate clonal plasma cell count. When a bone marrow biopsy is removed from a patient the liquid aspirate is made into slides for morphological evaluation including numeration of plasma cells, samples are also sent for flow cytometry and cytogenetics. The trephine biopsy is paraffin embedded and cut into slides with immunochemistry applied. There is a known variation between the plasma cell count in the aspirate, flow cytometry and trephine with the latter yielding a higher plasma cell count.

Haematologists regularly report bone marrow biopsies and therefore given the importance of accurately numerating plasma cells it was decided for quality control purposes assessing for variation.

Method: Over a 3 year period 179 bone marrow biopsies where performed on patients with PCD reported by 5 haematologists. 36 MGUS, 43 SM and 100 with PCM.

All trephine CD138 positive plasma cells were counted again by one haematologist who was blind to the original report. As a control this haematologist was also blindly reviewing their own trephines.

Data analysis was difficult as the original reports occasionally gave ranges rather than exact counts or reported heavy clustering of plasma cells in patchy bone marrows. 6 bone marrows were excluded for this reason.

Results: In the MGUS cohort there was minimal variation <2% between all the reporting haematologists.

Interestingly in the SM/PCM variation increased. The control group seen an average variation of 4% and when comparing across haematologists this increased to 7% with a range of 10%.

We found reassuringly that all 173 reported diagnoses did not change.

It makes sense proliferation of clonal PC is labelled as a malignant process like PCM, the original 10% with the addition of 60% are somewhat arbitrary cut offs. Based on our study reports at the 10% cut off do not vary as much as the 60% cut off. This 60% level for treatment could be less (eg>50%) based on human variation. Computer counting of plasma cells if validated could be a more consistent, reproducible method especially as guidelines are based on numeric cut offs.

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ADVANCING BIOBANKING AND SAMPLE UTILIZATION IN BLOOD CANCER RESEARCH: A REPORT FROM THE BLOOD CANCER NETWORK IRELAND (BCNI) BIOBANK, CORK.

C Nolan[1], E Szegezdi[2], D O'Shea[3], E Molloy[3], V Mykytiv[3], M R Cahill[3]
[1]Cancer Research @UCC, University College Cork, Cork, Ireland
[2]Apoptosis Research Centre, University of Galway, Galway, Ireland
[3]Haematology Department, Cork University Hospital, Cork, Ireland

The Blood Cancer Network of Ireland (BCNI) biobank, part of the collaborative network founded in 2016, stores and provides researchers with high-quality patient samples. Patient samples from all hospitals in the BCNI network (UHG, CUH, UHL, St. James's, Beaumont, Mater, Waterford Hospitals) are processed and stored at some sites and centrally in UNiversity of Galway, under Blood Cancer Biobank Ireland.

The curated biobank has emerged as a critical resource, housing a large repository of blood cancer samples. There is a total of 717 participant records registered on the BCNI Biobank database, with 1668 registered fractions. Among the 717 recruited patients, CUH contributes 264, University Hospital Limerick-171, Beaumont Hospital-115, UHG-84, St James'-52, Mater Hospital-18, University Hospital Waterford-9, Midlands Regional Hospital-4. Out of the total of 1668 collected fractions, only 46 have been used. This accounts for just 2.75% of the total samples. This finding underscores the need to address challenges related to promoting sample use and fostering collaborative research. Despite BCNI's wealth of available samples, there appears to be underutilization of the biobank resources.

One of the major strides in BCNI's efforts involves the expansion to biobanking to lymphoma and in UCC specifically to circulating cell-free DNA (cfDNA) sampling. This promising dimension offers new insights into non-invasive monitoring of lymphoma patients. Liquid biopsy may be complimentary to tissue biopsy as it can reflect a more accurate mutational and molecular landscape and provide tissue access when biopsy sites need difficult access- brain and retroperitoneum.

As we embark on expanding the biobanking to lymphoma (which has been an aim of the initial BCNI consortium), it is vital to recognize the untapped potential of our existing biobank. To ensure effective utilization of samples and compliance with the FAIR (Findable, Accessible, Interoperable, and Reusable) principles, the BCNI biobank is striving to adopt strategies that appropriately showcase its stored sample collection and data assets. We highlight the need for a nationwide promotional campaign to enhance awareness and encourage investigators to capitalize on the wealth of resources available. A concerted effort to promote and foster sample utilization through collaborative research endeavours would advance research and knowledge for blood cancer patients.

REAL WORLD DATA IN MANTLE CELL LYMPHOMA FROM ST JAMES' HOSPITAL BASED ON THE EMCL REGISTRY; A PROTOTYPE FOR NATIONAL IRISH HAEMATOLOGY REGISTRIES

J Nolan[1], A Hanlon[1], L Higgins[1], M Ní Chonghaile[1], G Faulkner[1], M Martin[1], C Flynn[1], E Conneally[1], N Orfali[1], P Browne[1], P Hayden[1], C Waldron[1], R Henderson[1], CL Bacon[1], G Lee[1], R Flavin[2], F Quinn[3], E Vandenberghe[1]
[1]Department of Haematology, St James' Hospital, Dublin, [2]Department of Histopathology, St James' Hospital, Dublin, [3]Cancer Molecular Diagnostics Laboratory, St James' Hospital, Dublin 8, Ireland

Introduction: Mantle cell lymphoma(MCL) comprises 6% of lymphomas affecting predominantly older men, follows a variable clinical course and a frequently poor prognosis. Clinical heterogeneity is attributed to secondary genetic mutations associated with identifiable bio-markers (MIPI, pathological sub-type, SOX-11expression, IgVH mutation status and TP53 disruption) which define clinical course and treatment choice such as chemo-immunotherapy, targeted therapy(BTKi), CAR-T and BiTE therapy. Real-world data is increasingly used to study large, unselected patient cohorts which contrast with the sub-selection of clinical trial cohorts; the European MCL registry(initiated 2015) is currently used in SJH. This first RWD analysis defines clinically relevant bio-markers, cohorts benefitting from specific management pathways, benchmarks patient outcomes with international groups and forms a resource for future research combined with our consented bio-bank.

Materials and methods: MCL patients attending SJH from 01/01/2015 onwards were included; diagnostic, treatment and clinical course data-points were EMCL registry-based with the first patient diagnosed in 1992. The cohort included Intensive Treatment(IT) defined by intensive chemo-immunotherapy(Int-CIT) and cellular therapies(auto/allo-HCT or CAR-T) or RHCVAD-RMA, Non-Intensive Treatment(NIT) and Observation cohorts. Evaluable outcomes included OS and Event-Free Survival(EFS);prognostic markers analysed included MIPI, histological subtype, SOX11,TP53-disruption.

Results: Fifty-nine patients included: 42(71%) male with median age 63(*range 37-91*)years. Median OS was not reached(NR) and EFS 4.7 years with median follow-up 7.2*(range 0.15-30)*years.

IT cohort included 29 patients: 26(90%)male, median age 60(*range 37-76*)years. Diagnostic features included high-MIPI(15 of 29 evaluable)20%, blastoid/pleomorphic histology in 7(24%) and TP53-disruption in 4(22%). Twenty-two(76%) received R-AraC-based CIT; 19 proceeded to cellular therapies(15-auto-HCT, 3-allo-HCT, 1 CAR-T). Seven(24%) received RHCVAD-RMA; 2 subsequently received allo-HCT. Eight(28%) patients needed second line treatment: BTKi in 6(75%), AraC-based regimens in 5(63%) and 1 received Venetoclax. OS and EFS were NR and 5 years respectively; TP53-mutation and pleomorphic/blastoid variants adversely affected OS and EFS with a median follow-up of 9.3(range 1.7-19)years. Five(71%)of 7 RHCVAD-RMA treated patients remain in CR1 after median 14.7(*range9.7-19*)years.

Twenty-five patients were treated with NIT: 15(60%)M, median age 69 years(*range41-91*) with high MIPI in 9(47% of 19 evaluable), blastoid/pleomorphic variants in 6(24%) and TP53-mutation in 2(14%). Twelve(48%) were treated with CIT(R-Bendamustine/R-BAC/R-CHOP), 36% with BTKi(n=9) on clinical trials, 8% with Rituximab(n=2) and 1 each with surgery/radiotherapy/chlorambucil. OS and EFS were NR and 2.9 years (median follow-up 4.1 years(*range0.2-30.8years*)).

Five asymptomatic patients (2 with SOX11-negative leukaemic non-nodal and 3 with gastrointestinal MCL) were followed with observation. With median follow-up 2.9years(*range0.2-8.9*), 100% of patients are alive and one progressed after 1.5 years.

Discussion: This RWD exemplifies MCL heterogeneity with improved outcomes in IT and NIT cohorts since the introduction of consolidation cellular-therapy in 2010[1] and BTKi availability. The excellent outcomes of the RHCVAD-RMA cohort with a median EFS of 14.7 years was an unexpected finding. A subset of patients (TP53-mutated, aggressive histology) continue to have poor OS and may benefit from more intensive treatment with BiTE, BTKi or CAR-T early in the treatment pathway. Indolent patients identified by initial observation and frequent SOX11-negativity may have long survivals without treatment including SOX11-negative leukaemic MCL. Further expansion, analyses and bio-marker identification is planned on this RWD series and we would welcome collaboration with other Irish haematology units.

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IDENTIFYING MALIGNANT CELLS IN ACUTE MYELOID LEUKAEMIA USING GENOMIC ALTERATIONS INFERRED FROM SINGLE-CELL RNA SEQUENCING DATA

M Ó Dálaigh [1,2,3], A Conforte[3], S Coughlan[1,2], E Szegezdi[1,3]
[1]Centre for Research Training in Genomics Data Science, Ollscoil na Gaillimhe - University of Galway, Galway, [2]School of Mathematical and Statistical Sciences, Ollscoil na Gaillimhe - University of Galway, Galway, [3]Apoptosis Research Centre, Ollscoil na Gaillimhe - University of Galway, Galway,

Background: Acute myeloid leukaemia (AML) is an aggressive malignancy, resulting in the accumulation of poorly differentiated blasts in the bone marrow (BM). Relapse is common and has been attributed to the incomplete eradication of leukaemic stem cells (LSCs). LSCs are similar to normal haematopoietic stem cells, thus identifying LSCs is a challenging task. Single cell transcriptomics (scRNA-seq) have allowed for the characterisation of genomic alterations in AML(1) and exploiting this knowledge may aid in identifying malignant cells. We hypothesised that AML cells may differ from normal haematopoietic cells in the complement of expressed single nucleotide variants (SNVs) and copy number variations (CNVs) which could be used to demarcate the malignant cells.

Methods: We performed scRNA-seq on 28 longitudinal samples (diagnosis, n=10; remission, n=7; relapse, n=11) from BM aspirates of 10 patients. Variants were called with BCFtools and previously characterised AML mutations were identified using a previously published reference(2). CNV profiles were generated with the R package CopyKAT(3) which uses expression levels of adjacent genes to infer genomic copy number and predicts the cells' ploidy state (diploid/aneuploid).

Results: We identified AML-relevant SNVs in 9 samples from 5 patients but less than 1% of cells contained variants of interest and the genomic sites of these SNVs were covered by reads in less than 10% of cells. CNV profiles provided richer data and identified approximately 50% of the cells to be aneuploid, with the expected trend of a higher proportion of aneuploid cells present at diagnosis and relapse compared to remission.

Conclusion: The sparse coverage of the single-cell transcriptome data precludes the use of individual SNVs for categorising cells as normal or malignant. CNV profiles on the other hand, may have the power to identify malignant cells even in cells with no reads mapping to locations of known AML driver mutations.

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MULTI-DISCIPLINARY MANAGEMENT TO INCREASE UNDERSTANDING AND OPTIMIZE OUTCOMES IN VEXAS

R O'Doherty[1], R Mc Dermott[2], K Fadalla[5], R Conway[3], S O'Gorman[4], N Conlon[2], N Orfali[1]
[1]Haematology, St James's Hospital, Dublin, [2]Immunology, St James's Hospital, Dublin, [3]Rheumatology, St James's Hospital, Dublin, [4]Dermatology, St James's Hospital, Dublin, [5]Haematology, St Vincent's University Hospital, Dublin,

Introduction: VEXAS syndrome (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) is a rare novel auto-inflammatory disease caused by somatic mutations in the *UBA1* gene in hematopoietic progenitor cells.[1] E1 enzyme refers to the ubiquitin-activating enzyme encoded by *UBA1*, acquired mutations in this X-linked gene result in decreased ubiquitylation and activated innate immune pathways.[2] A diagnosis of VEXAS should be considered in adult males with treatment-refractory inflammatory symptoms with associated haematologic abnormalities.[1] Patients are predisposed to MDS and plasma cell dyscrasias, where additional somatic clonal aberrations are seen. The auto-inflammation and progressive bone marrow failure leads to substantial morbidity and mortality.[1]

Methods: We examine the clinical phenotype and clonal signatures of 3 VEXAS patients managed at our centre with multi-disciplinary input from haematology, immunology, rheumatology and dermatology at a dedicated VARIS (Vasculitis And Rare Inflammatory Syndromes) clinic.

Results: Patient 1 is a 79-year-old man, who presented with fevers, an ill-defined head and neck inflammatory process, recurrent thrombosis and macrocytic anaemia. His bone marrow revealed subtle vacuolation of myeloid precursors but no morphologic malignancy. A *UBA1* p.Met41Val mutation (VAF 56%) was identified with no additional mutations. He was initiated simultaneously on prednisolone and Ruxolitinib. His inflammatory symptoms and anaemia resolved, he continues on Ruxolitinib and prednisolone 7.5mg daily.

Patient 2 is a 60-year-old man, who presented with Sweet's syndrome, relapsing polychondritis and migratory thrombophlebitis. At diagnosis he had transfusion-dependant macrocytic anaemia and thrombocytopaenia. Bone marrow demonstrated multilineage dysplasia with vacuolation and confirmed a *UBA1* p.Met41Leu mutation (VAF 77%) with concurrent *ZRSR2* mutation (VAF 15%). Again the inflammatory symptoms stabilised with prednisolone and Ruxolitinib, however, the anaemia persisted despite erythropoietin replacement. We are preparing to initiate Azacitidine and plan to move to a sibling allogeneic transplant in the absence of response.

Patient 3 is an 82-year-old co-morbid man who presented with fevers, giant cell arteritis and Sweet's syndrome along with anaemia and thrombocytopaenia. His bone marrow showed dysplasia with a *UBA1* p.Met41Val mutation (VAF 79%) and *DMNT3A* mutation (VAF 40%). This patient was commenced on single-agent Ruxolitinib but shortly after diagnosis he died from an unrelated illness.

Conclusion: To our knowledge, this is the largest series of VEXAS cases examined at a single Irish centre to date. These cases highlight the heterogeneity of clinical manifestations and support a previously-reported association between specific UBA1 variants and severity of inflammatory symptoms.[4] In our series *UBA1* p.Met41Val mutations resulted in aggressive systemic inflammation affecting tissue beyond skin and cartilage.

Described therapeutic strategies for VEXAS include high-dose glucocorticoids and steroid-sparing agents.[5] In our experience, Ruxolitinib has proven to be particularly effective in managing systemic inflammatory symptoms and ameliorating anaemia of inflammation.

The presence of additional clonal haematopoietic mutations along with transfusion-dependent anaemia is associated with increased mortality in VEXAS.[3] In patients with concomitant MDS, hypomethylating agents may have utility. In non-frail patients, allogenic bone marrow transplantation can be considered as curative therapy. VEXAS patients benefit from multi-disciplinary input and early assessment of transplant candidacy. We are happy to accept nationwide referrals of confirmed VEXAS cases to our VARIS clinic.

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Germline Predisposition to Acute Myeloid Leukaemia: Implications for Allogeneic Stem Cell Transplantation

R O'Doherty[1], LA Sutton[2], K Cadoo[3], PV Browne[1], C Flynn[1], E Conneally[1], N Orfali[1]
[1]Haematology, St. James's Hospital, Dublin, [2]Cancer Molecular Diagnostics, St. James's Hospital, Dublin, [3]Clinical Cancer Genetics, St. James's Hospital, Dublin, Ireland

Introduction: The advent of next-generation sequencing has revealed that hereditary AML is more common than previously understood. It is estimated that up to 15% of cases may carry a predisposing germline variant, often in the absence of early disease onset, phenotypic abnormalities, longstanding cytopaenias or familial clustering.[1] This bears particular significance on allotransplant decisions, with considerations for both patients and potential donors. Beyond donor selection and transplant timing, germline mutations may increase patient susceptibility to graft versus host disease (GVHD) and to late treatment toxicity.[2] Evidence-based guidelines in this evolving arena are lacking and much may be learned from anecdotal experience.

Methods: We retrospectively reviewed outcomes in Irish patients transplanted for AML with a strong suspicion of germline contribution in physician memory. Germline origin was supported by variant detection in cultured skin fibroblasts, variant detection in ≥2 family members or persistence of the variant in remission marrow samples at allele frequencies of ≥40%.

Results: We identified 4 patients (3M/1F) from 2 families with germline *RUNX1* variants diagnosed at a median age of 51 years (Range 23-64y). The most frequently observed concurrent aberrations were trisomy 8 (n=2) and somatic *RUNX1* mutations (n=2). One patient had a matched sibling who tested negative for *RUNX1* mutations prior to donation. The remainder received unrelated grafts. Notably, two patients fit for myeloablative conditioning remain alive and disease-free at 11 and 15 years, while two conditioned using reduced-intensity platforms relapsed at 7 months and 5 years post-transplant.

Three male patients with germline *DDX41* mutations underwent reduced-intensity transplantation all aged 62-64 years. With a shorter median follow-up of 286 days, all are alive in remission. Two were transplanted using a post-transplant cyclophosphamide platform, due to a reported higher risk of severe GVHD in this cohort.[2] Of these, one developed GVHD of the skin/gut/liver after a *DDX41*-negative sibling transplant but is well on continued immunosuppression at 10 months. The other has suffered a primary graft failure after a mismatched unrelated graft and is currently undergoing a salvage haplo-identical transplant from a variant-negative son.

Finally, we report a case of AML arising 15 years ago in a 25 year-old man who has since been diagnosed with biallelic mutations in *MBD4* - a gene involved in DNA repair.[3] He received myeloablative conditioning with total body irradiation. While in leukaemic remission, he has suffered significant toxicity including severe GVHD, ischaemic heart disease, renal impairment and avascular joint necrosis. This year he underwent a subtotal colectomy due to *MBD4*-driven gastro-intestinal polyposis.

Conclusion: Our limited series certainly underestimates the true number of germline cases transplanted since the inception of our national programme. Our data nonetheless supports:
(i) Germline *RUNX1* mutations conferring an adverse prognosis. Patients may benefit from treatment intensification where possible. This may influence transplant timing.
(ii) Germline *DDX41*-mutant AML havng a low risk of post-transplant relapse, but a higher risk of treatment-related complications.
(iii) Aberrant DNA repair in *MBD4*-disease possibly sensitizing patients to alkylator/radiation-induced toxicity. Close patient observation in survivorship clinics is warranted.

As experience with hereditary AML increases, peri-transplant decisions can be tailored to optimize patient outcomes. There is a need for haematology-focused cancer geneticists to better serve patients and their families as novel germline variants of concern steadily emerge.

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AN AUDIT OF COMPLIANCE WITH THE BRITISH SOCIETY FOR HAEMATOLOGY GUIDELINES ON THE DIAGNOSIS AND EVALUATION OF PROGNOSIS OF ADULT MYELODYSPLASTIC SYNDROMES

F O'Flynn[1], D Fitzgerald[1], V Mykytiv[1]
[1]Department of Haematology, Cork University Hospital, Cork, [2]Department of Haematology, Cork University Hospital, Cork, [3]Department of Haematology , Cork University Hospital, Cork, Cork

Introduction: Myelodysplastic syndromes (MDS) are a group of clonal haematopoeitc stem cell disorders characterised by cytopenias, dysplasia and bone marrow failure, with a median survival time of 30 months. (1–4) Appropriate diagnosis and prognostication are essential to ensure patients are suitably treated and have appropriate expectations. (5)

In order to achieve this, the British Society for Haematology (BSH) guidelines recommend the use of the World Health Organisation (WHO) classification system (based on morphology and cytogenics), and Revised International Prognostic Scoring System (IPSS-R score). (3,6,7) When morphology and cytogenetics are outstanding/indeterminate, flow cytometric scoring systems, e.g., the Ogata score, can be used as co-diagnostic tools. (1,6,8) This audit aims to assess compliance with the BSH guidelines on the diagnosis and prognostication of MDS.

Methods: This audit was conducted as a retrospective chart review from a pre-established database of patients diagnosed with MDS in Cork University Hospital from the period 03/12/2021-21/11/2022. Data on WHO classification, IPSS-R and Ogata scores, cytogenetics and patient demographics were collected.

Data was analysed using *Jamovi 2.3.21.* software system. Descriptive statistics were produced regarding the proportion of patients whose documentation was compliant with BSH guidelines as well as the nature of their disease. Pearson's Chi-squared tests were used to assess differences in proportions between groups.

Results: 84 individuals were analysed in this study, 67.9% of which were male. The mean age of the sample at diagnosis was 73 years. The mean Haemoglobin at time of bone marrow biopsy was 9.75g/dL, while the mean Absolute Neutrophil Count and Platelet Count were $3.41x10^9$/L and $191x10^9$/L respectively.

71.4% individuals had a documented diagnosis of MDS according to the WHO classification system and 32.5% individuals had a documented IPSS-R score. The median IPSS-R score was 2.0 (low risk). 43.3% of those with a documented WHO classification had a documented IPSS-R score.

82% of individuals had documented cytogenetics, 50.7% of which were normal. A higher proportion of those with documented normal cytogenetics (associated with a favourable prognosis) had documented IPSS-R scores (9), however this difference was not significant (40% vs. 20.6%, p=0.08).

100% of individuals had a documented Ogata score, with a median score of 1.0. The sensitivity of the Ogata score in predicting MDS in our sample was 45.2%, i.e., 54.8% of those ultimately diagnosed with MDS had Ogata scores of 0 or 1, usually suggestive that an individual is unlikely to have MDS.

Conclusion: This audit assessed compliance with BSH guidelines for the documentation of MDS diagnoses and prognoses. Areas of highest compliance were in documentation of cytogenetics and WHO classification, with a notably lower proportion of patients having a documented IPSS-R score. Those with a potentially better prognosis (e.g., by means of normal cytogenetics) were more likely to have an IPSS-R score documented (although this difference was not significant). All patients diagnosed with MDS had a calculated Ogata score, however the Ogata score alone proved a poor predictor of ultimate MDS diagnosis in our sample (with a sensitivity of 45.2%).

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IMPLEMENTATION OF THE OGATA SCORE AS A COMPANION TOOL FOR THE DISCRIMINATION OF MYELODYSPLASTIC NEOPLASMS FROM NON-CLONAL CAUSES OF CYTOPENIA.

J Patterson[1], K Clarke [1]
[1]Haemato-oncology Laboratory, Belfast City Hospital, Belfast Health and Social Trust, Belfast, Northern Ireland

Introduction: Myelodysplastic Neoplasms (MDS) consist of a group of heterogeneous clonal bone marrow disorders predominating in the elderly. Patients with MDS usually present with unexplained cytopenias with single or multilineage morphological dysplasia. Non-neoplastic causes of these, such as viral infections and nutrient deficiencies must therefore be initially excluded before a diagnosis of MDS is investigated(Marques and Sabina, 2022). Distinguishing MDS from other, non-clonal causes of cytopenia is therefore challenging using conventional diagnostic methods. There are common aberrant phenotypic manifestations of cell proliferation, maturation and function, which are detectable, by immunophenotyping by multicolour flow cytometry, therefore its use has been recommended in recent European LeukemiaNET (ELN) guidelines (Porwit et al, 2023). The Ogata score is a simple flow cytometry scoring system that has been extensively discussed in the literature and has been shown to be technically robust in distinguishing MDS from non-clonal causes of cytopenias.

Aims/objectives: The aim of this work was to validate the Ogata score for use as a companion tool for MDS diagnosis by adequately differentiating between MDS and non-clonal causes of cytopenia in a cohort of patients from Northern Ireland.

*Methods/*Results: Retrospective immunophenotyping data from a total of 43 patients were reviewed and scored using the Ogata FCSS. The sensitivity of the Ogata score in this cohort was 78.6%, specificity was 66.7%, PPV 81.5% and NPV 62.5%. The AUC value was 0.726. Independent t-test analysis showed a significant difference in our cohorts in two of the four parameters: myeloblast related cluster size and the CD45 MFI ratio between lymphocytes and myeloblasts showing p values of p=0.009 and p=0.048 respectively. The remaining two parameters constructing the Ogata score are the Ogata score are the B-progenitor-related cluster size and SSC peak channel ratio between total granulocytes and lymphocytes.

Conclusion: In our hands, the Ogata score performed consistently with previous publications and is feasible to implement in our small laboratory. However, our study design may have introduced bias into our cohort through the inclusion of significantly more high-risk patients. Two of the parameters did not perform as well as expected, some mechanisms behind this may be through haemodilution of BM samples, contamination of cell populations through our gating technique or through the effect of therapeutics on the BM microenvironment.

Porwit, A., Béné, M. C., Duetz, C., Matarraz, S., Oelschlaegel, U., Westers, T. M., Wagner-Ballon, O., Kordasti, S., Valent, P., Preijers, F., Alhan, C., Bellos, F., Bettelheim, P., Burbury, K., Chapuis, N., Cremers, E., della Porta, M. G., Dunlop, A., Eidenschink-Brodersen, L., … van de Loosdrecht, A. A. (2023). Multiparameter flow cytometry in the evaluation of myelodysplasia: Analytical issues. Cytometry Part B: Clinical Cytometry, 104(1), 27–50. https://doi.org/10.1002/cyto.b.22108 Marques, F. K., & Sabino, A. de P. (2022). Myelodysplastic neoplasms: An overview on diagnosis, risk-stratification, molecular pathogenesis, and treatment. Biomedicine & Pharmacotherapy, 156, 113905. https://doi.org/10.1016/J.BIOPHA.2022.113905

LENALIDOMIDE MAINTENANCE THERAPY PRESCRIBING POST-AUTOLOGOUS STEM CELL TRANSPLANT FOR MULTIPLE MYELOMA AT IRISH TERTIARY HOSPITAL

J Potocka[2], C Duane[1], P Murphy[1,2], D Swan[1], P Thornton[1,2], J Sargent[1], S Glavey[1,3], J Quinn[1,2]
[1]Department of Haematology, Beaumont Hospital, Dublin, Ireland
[2]School of Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland
[3]Department of Pathology, Royal College of Surgeons in Ireland , Dublin, Ireland

Introduction:
While multiple myeloma (MM) remains an incurable malignancy, there have been significant therapeutic advances in the most recent decade, resulting in vastly improved survival rates. In particular, lenalidomide maintenance therapy (LenM) following autologous stem cell transplant (ASCT) in younger and fitter MM patients has now become standard care, given the survival benefits associated with it. In 2017, the EHA-ESMO clinical practice guidelines recommended LenM therapy post-ASCT, based on a large meta-analysis published by McCarthy et al, which demonstrated significantly prolonged overall survival (OS). Thus, we carried out an audit in one Irish tertiary hospital to evaluate LenM therapy prescribing in patients post-ASCT over a 10-year period. We also assessed the prevalence of adverse effects associated with LenM in our cohort to evaluate safety and tolerability in this clinical setting.

Methods:
We completed a retrospective audit of MM patients attending an Irish hospital who underwent ASCT from 2012 – 2022. Endpoints included the rate of lenalidomide maintenance (LenM) over that time period and the prevalence of associated adverse effects. A combination of medical chart and electronic record review was used to obtain key clinical information.

Results:
172 patients who underwent ASCT during the specified timeframe were identified, with median age 61. 79 patients were included in the audit, while 93 were excluded due to insufficient patient information, or the delivery of post-ASCT medical care at an alternative clinical centre. Within the cohort, 60% received LenM post-ASCT. Of note, there was a significant increase in the use of LenM from 41% between 2012-2017, compared to 86% in the period 2018-2022.

Of the 51 patients who received LenM, 8% of patients experienced adverse effects requiring dose reduction, including cytopenias (2%), respiratory tract infection (2%), diarrhoea (2%) and deranged liver function tests (2%). LenM was discontinued in 16% of patients due to serious adverse events such as pulmonary embolism (4%) and recurrent severe infections (2%), as well as drug intolerance (2%), and disease relapse (8%). Within the cohort, there were 12 events of neutropaenia grade 3 and 11 events of grade 4 neutropaenia.

An important potential adverse effect associated with LenM for MM is the increased risk of developing a second primary malignancy (SPM). In this audit there were 3 reports (5.9%) of second primary malignancies (SPMs), specifically lung adenocarcinoma, squamous cell carcinoma in-situ, and head and neck carcinoma.

Conclusions:
Our findings demonstrate increased prescribing of LenM post-ASCT in the 10 year period studied. This coincides with the publication of large trial data supporting its use. The results demonstrate compliance with EHA-ESMO Clinical Practice guidelines. Associated adverse events are an important consideration in patients on maintenance therapy and requires frequent monitoring. However, our data suggests overall good tolerability and a reasonable safety profile associated with LenM.

High Grade T Cell Lymphoma and Treatment Outcome. Single Centre Retrospective Study

S Samuel[1], B Hennessy[1], S Kumar[1], A Bannaga[1], M Griffin[2], M Nur[2], E Elhassadi[1,2]
[1]Haematology, UHW, Waterford,
[2]Haematology, UHW, Waterford,
[3]Haematology, UHW, Waterford,
[4]Haematology, UHW, Waterford,
[5]Pathology, UHW, Waterford,
[6]Pathology, UHW, Waterford,
[7]Haematology, UHW, Waterford,

Mature T-cell lymphomas comprise 15% to20% of all aggressive non-Hodgkin lymphoma(NHL) and all 5% to 10% of all NHLs. Peripheral T-cell lymphomas(PTCL) are a biologically diverse and uncommon group of diseases compared to their B-cell counterparts. CHOP type chemotherapy has been the mainstay of therapy for PTCL with some exception in NK/T cell lymphoma, but with the nootable exception of ALK positive ALCL, outcome has been uniformly disapointing.

This study is a single centre, retrospective study on aggressive T-cell NHL patients treated over the study period(2010-2020). Treatment response, progression free survival(PFS) and overall survival were evaluated using KM curves. Multivariant (age,gender,stage and disease subtype) impact on treatment outcome were analysed using long-rank (Mantel-Cox) test for statistical analysis. Twenty-seven patients weere included in this study, with male predominance, median age 69 years and the majority with advance disease. The common histology subtype was ALCL, followed by PTCL. Chemotherapy (CHOEP, GDP based) was the main initial treatment modality and complete response(CR) was achieved in 16 patients and 8 disease progression. At relapse GDP and Brentuximab Vedotin were used in 8 and 3 patients respectively resulted in CR in 2 patients and progression disease in the remainder. Autologous bone marrow transplant consolidation was used in 3 patients and radiotherapy in 5 patients.

The median survival for AITL, ALCL-ALK Neg, EATL and PTCL-NOS were 19,46,26 and 4 months respectively. The median OS was longer for early stage disease (Stage I,II) (26 months) when compared with advanced stage (III,IV)(11.5 months). This study reflects real world data on high grade T-cell lymphoma and the impact of patient age and disease subtype. High grade T-cell lymphoma continue to be challenging disease to treat and unmet clinical needs with a short lived treatment response and frequent relapses.

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Whole Genome Sequencing Reveals Spatial Heterogeneity of Extramedullary Disease at Diagnosis and Relapse in Multiple Myeloma Patients

S Sarihan[1], R McAvera[1], T O'Grady[2], I Drozdz[1], D Swan[3], J Sargent[3], P Murphy[3], J Quinn[3], S Glavey[1,2,3]
[1]Multiple Myeloma Research Group, Royal College of Surgeons in Ireland, Dublin, Ireland
[2]Department of Pathology, Royal College of Surgeons in Ireland, Dublin, Ireland
[3]Department of Haematology, Beaumont Hospital, Dublin, Ireland

Introduction

Extramedullary disease (EMD) is an aggressive manifestation of multiple myeloma (MM) that occurs when malignant plasma cells become independent of the bone marrow (BM) microenvironment and infiltrate other organ systems. EMD may occur at diagnosis or relapse, and is associated with reduced overall survival (OS) and suboptimal responses to novel therapies. The unprecedented increase in OS in this disease has resulted in EMD becoming a relevant clinical issue rather than an end stage manifestation of disease, as was once thought. Recent data has demonstrated that EMD is associated with 1q and del17p but genomic drivers of EMD are not well defined and specific therapies to target EMD are lacking. To enhance understanding of genomic drivers in EMD we performed Whole Genome sequencing (WGS) and RNA sequencing from paired sequential samples (BM and EMD) at MM diagnosis and relapse.

Methods

Following written informed consent MM samples from BM and EMD biopsies from 13 individual patients underwent DNA and RNA extraction. EMD samples include biopsy tissue from rib, colon, pituitary, neck, skin and pleural effusion. CD138 staining was used to mark tissue as involved or uninvolved for tumour selection from Formalin-fixed paraffin-embedded (FFPE) tissue, and macrodissected based on CD138 positivity. DNA and RNA were independently sequenced on an Illumina NovaSeq 6000 platform with paired-end 150 bp (PE150) reads. Data was analysed with following steps; Quality checks done with FastQC and Trimmomatic and reads that passed quality filters aligned to human genome version GRCh38 with BWA-MEM. After aligning reads sorting, indexing and other post processing steps done according to GATK best practices with SAMTools, Picard and GATK4. Lastly, variant calling done with Mutect2 with respectively post processes quality steps. Clinical data from patients, including therapy resistance data was collected by retrospective chart review.

Results

For patients presenting with EMD at diagnosis, comparison of spatial genomic heterogeneity reveals an accumulation of single nucleotide variants (SNVs) at the EMD site vs the BM site. This was evaluated by chromosome revealing additional variants clustered to chromosome 1. When comparing the EMD site to the BM site in a patient who had bone marrow based disease at diagnosis along with EMD a significant accumulation of chromosome 1 SNVs and intronic variants were evident indicating this may be a driver region. Analysis of copy number abnormalities and somatic mutations between and within patients over time is ongoing.

Chimeric antigen receptor (CAR) T cell therapy for high risk B cell haematological malignancies: a single centre audit of patient outcomes and toxicity

S Toolan[1], C Browne[1], I Hughes[1], E Higgins[1], G Lee[1], C Degay[1], U Rathnam[1], N Gardiner[1], O Crehan[1], F Dowdall[1], D Byrne[1], C Waldron[1], E O'Connor[1], E Doran[1], R Henderson[1], E Vandenberghe[1], CL Bacon[1]
[1]Department of Haematology, St. James' Hospital, Dublin, Ireland

Introduction: Chimeric antigen receptor (CAR) T cell therapy using engineered cytotoxic T cells has shown promising responses in High grade B Cell Lymphoma and B Cell Acute Lymphoblastic Leukaemia (B- ALL) (1,2,3). Two products are funded in Ireland for use: Kymriah© produced by Novartis and Yescarta© manufactured by KITE/Gilead. In this audit, we assessed patient characteristics, outcomes and complications of CAR-T cell manufacture and reinfusion performed in SJH from Dec 2021 (first registered patient) until March 2023 (36 patients). We report for the first time the outcomes for this patient cohort.

Methods: This was a retrospective electronic chart review of patients undergoing CAR-T therapy within our institution from December 2021 March 2023. Statistical analysis for progression free survival (PFS) and overall survival (OS) was performed via the Kaplan-Meier method.

Results: In this time period, 36 CAR T-eligible patients were reviewed. 34 (94%) patients proceeded to T cell apheresis and CAR T manufacture. 28 (78%) patients proceeded to CAR T infusion. The median age of the cohort was 59.5. The oldest patient reinfused was 76yr (DLBCL) and the youngest 17yr (B- ALL). 28 patients (78%) were male.

As per eligibility criteria for CAR T cell therapy, all patients had failed at least 2 lines of therapy. From a disease perspective, 25 (69%) patients had relapsed / refractory diffuse large B cell Lymphoma (DLBCL), 2 (5%) had relapsed refractory primary mediastinal B Cell Lymphoma (PMBL) and 1 (3%) had relapsed refractory B ALL. Of note, 18(64%) patients were reinfused with Kymriah© and 10 (34%) with Yescarta©. 26 (72%) patients required bridging therapy.

Of the 8 patients who didn't proceed to CAR T infusion, 2 (25%) did not proceed to apheresis due to disease progression and clinical deterioration. The remaining 6 (75%) had apheresis performed and CAR T cells manufactured. 5 (83%) of these patients deteriorated clinically with progressive disease during Car T cell manufacture and were not infused. 1 (13%) patient obtained a CR with bridging therapy and proceeded to allograft following discussion in clinic. 5 (18%) patients proceeded to CAR T cell therapy in complete remission post bridging therapy.

9 patients in the entire cohort (32%) required Intensive Care Unit (ICU) admission; of these, 4 (44%) admissions were due to Immune Effector Cell Associated Neurotoxicity (ICANS) and 5 (56%) due to cytokine release syndrome (CRS). The average length of stay in ICU was 2 days. Reassuringly, there were no toxicity-related deaths in this cohort.

Overall survival (OS) for the infused cohort was 81% at 1 year with PFS of 53% at 1year. These figures are at least equivalent to outcomes in the Juliet1 , Eliana2 and Zuma 13 registration trials.

Conclusions: Car T cell therapy in SJH is now a well established programme delivered in the national stem cell therapy unit. Importantly, in the establishment and delivery of a new service, the outcomes and toxicities demonstrated were consistent with international best practice and outcomes.

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Invasive fungal disease in acute myeloid leukaemia patients: a 5 year review in the Mater Misericordiae University Hospital, Dublin, Ireland.

S Toolan[1], S Ni Bhaoill[1], N Scanlon[1], C Quinn[1], S Lapthorne[1], A Page[1], D Mangon[1], G Dornikova[1], M Hannan[1], D Brady[1], S Maung[1], M Fay[1], A Fortune[1], M Lynch[1]
[1]Mater Misericordiae University Hospital, Dublin, Ireland.

Background

Acute myeloid leukaemia (AML) is a haematological malignancy with a poor prognosis. Invasive fungal disease (IFD) occurs more often in patients with prolonged neutropenia, placing AML patients among the highest risk group. Prophylaxis with a triazole anti-fungal is recommended during induction treatment, with posaconazole being the drug of choice.
Novel target agents for AML have become available, expanding treatment options in older or relapsed AML patients. The metabolism of these newer agents interacts with that of of triazole antifungals - the cytochrome P450 enzyme pathway - and guidance on anti-fungal prophylaxis in these patients is scarce (Stemler 2022).

Methods

A retrospective analysis of 91 AML patients over a 5 year period was conducted. Evidence of IFD was identified as per EORTC guidelines using a combination of mycological, clinical and radiological data obtained from the electronic patient record. Previous anti-fungal prophylaxis, treatment and clinical data were cross-referenced using data obtained from the Microbiology, Haematology, Radiology and Pharmacy departments.

Results

We reviewed data on 91 patients diagnosed with AML from January 2018 to November 2022. 50 (55%) had uninterrupted posaconazole prophylaxis without clinical suspicion or investigation for IFD. 3 (3%) had delayed commencement of antifungal prophylaxis.
8 patients (9%) did not receive posaconazole therapy. 1 (1%) developed possible IFD and was treated with voriconazole and commenced posaconazole prophylaxis thereafter. Another patient in this group, with a primary diagnosis of HIV-associated lymphoma, developed invasive pulmonary aspergillosis following a subsequent diagnosis of therapy-related AML one year later.
Posaconazole prophylaxis was interrupted for 30 patients. Indications included azaole or AML treatment related adverse effects, clinical deterioration or escalation from anti-fungal prophylaxis to treatment. Of these, 1 (1%) patients had possible IFD which was successfully treated. 8 (9%) patients were switched to caspofungin or ambisone while receiving treatment with a novel targeted agent for AML. 1 (1%) patient in this group developed invasive fungal endopthalmitis. Schizophyllum species was identified on broad range PCR.

Conclusion

AML patients are at high risk of IFD. Posaconazole is an effective anti-fungal agent for prophylaxis with low levels of IFD identified in our patient cohort. As we increasingly incorporate novel therapeutic agents into our treatment pathways, echinocandins may be a useful alternative to azoles in this setting.

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QUALITY IMPROVEMENT: A RE-AUDIT OF THE CURRENT TREATMENT OF MULTIPLE MYELOMA-RELATED BONE DISEASE AT GALWAY UNIVERSITY HOSPITAL IN ACCORDANCE WITH THE 2021 INTERNATIONAL MYELOMA WORKING GROUP RECOMMENDATIONS

S Vieno[1], C O'Sullivan[1], O Esezoobo [1], C Meyer[1], T Meenaghan [1], D Cox[1], A Hayat[1], J Krawczyk[1], S Ni Loingsigh[1], Y Nunez[1], N Keane[1]
[1]Hematology-Oncology, University Hospital Galway, Galway, Ireland

In 2021, the International Myeloma Working Group (IMWG) reviewed all currently available evidence on Multiple Myeloma-related bone disease and published updated recommendations for its management. (1) In order to ensure that clinical practice at Galway University Hospital was in accordance with the IMWG guidelines, this audit reviewed the management of Multiple Myeloma-related bone disease in 20 patients with Multiple Myeloma attending our Haematology Day Ward. Sixty percent (N=12) of total patients received bisphosphonate treatment monthly. Of the patients on monthly zoledronic acid, 75 % (N=9) received the appropriate dosage schedule according to IMWG guidelines. Twenty-five percent (N=5) of total patients received three monthly bisphosphonate treatments. Of these patients, 60% (N=3) followed IMWG recommendations regarding the administration schedule. One-hundred percent (N=2) of the patients on denosumab therapy were following IMWG guidelines. In conclusion, this audit demonstrates that the current management of Multiple Myeloma-related bone disease in GUH has improved since its original audit according to the 2021 IMWG guidelines.

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RELEVANCE OF CD56 EXPRESSION IN THE DIAGNOSIS OF PLASMA CELL MYELOMA: 134 BONE MARROWS REVIEWED TO DETERMINE IF CD56 CAN EXPLAIN THE DISCREPANCY BETWEEN ASPIRATE AND TREPHINE PLASMA CELL COUNTS.

D Waddell[1], A Niblock[1,2]
[1]Haematology department, Antrim Area Hospital, N. Ireland
[2]School of Medicine, Ulster University, N. Ireland

Importance

Plasma Cell Myeloma PCM is a disorder caused by malignant plasma cells. One of the most important diagnostic tests is the bone marrow aspirate and trephine. Greater than 10% clonal plasma cells is diagnostic of PCM[1]. CD138 is used on the bone marrow trephine to help quantify the percentage of plasma cells and has been well documented that it is common to have a difference in the percentage of plasma cells seen on bone marrow aspirate and flow cytometry compared with the percentage of CD138+ve cells seen in the trephine[2]. Malignant plasma cells within the bone marrow have different patterns of infiltration and appear to have a different affinity in their adhesion abilities. Therefore cases can have a wide variation between aspirate and trephine plasma cell counts. This can be concerning as on occasions a patient may not have had a successful trephine.

CD56 is expressed in 70-80% of patients with PCM and a recent meta-analysis has revealed that CD56 negativity is associated with a poorer overall survival[3]. CD56 is a neural adhesion molecule and it plays a role holding myeloma cells together and tethering them to the marrow stroma[4].

Do CD56+ve PCM have a greater discrepancy between trephine and aspirate plasma cell counts when compared with CD56-ve PCM?

Observation

A total of 134 patients were reviewed. 92 (68.7%) were CD56+ve and the rest were CD56-ve. The difference between the aspirate plasma cell percentage and the trephine CD138+ve percentage was assessed in both CD56+ve and the CD56-ve PCM groups. The mean difference between the aspirate plasma cell percentage and the percentage CD138+ve in the bone marrow trephine not significantly different in both groups. The trephine had a mean of 30% more plasma cells identified than the aspirate or the population seen with flow cytometry. This study did not assess the prognosis associated with CD56.

Relevance/ conclusion

As expected there was a wide variation in plasma cell population seen on bone marrow aspirate, flow cytometry and trephine. We found that the variation was similar in both CD56+ve and CD56-ve samples therefore the expression of the adhesion molecule CD56 did not directly account for differences between the trephine and aspirate plasma cell counts and adds no diagnostic predictive ability.

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Low ROR1 expression in newly diagnosed CLL predicts an indolent disease course.

C Waldron[1], E Jones[1], A Polion[1], B Cunningham[1], K Perera[2], GM Crotty[2], A Walsh[2], M Connolly[2], R Clifford[3], H O'Leary[3], R Mc Cafferty[1], D Waldron[1], AM McElligott[6], CL Bacon[1], F Quinn[5], E Vandenberghe[1,5]
[1]Haematology, Trinity St James's Cancer Centre, Dublin, [2]Haematology, Midland's Regional Hospital, Tullamore, [3]Haematology, University Hospital , Limerick, [4]Flow Cytometry Laboratory, Trinity St James's Cancer Centre, Dublin, [5]Cancer Molecular Diagnostics Laboratory, Trinity St James's Cancer Centre, Dublin, [6]John Durkan Leukaemia Laboratories, Institue of Molecular Medicine, Trinity St James's Cancer Centre, Dublin, Ireland

Introduction: Chronic Lymphocytic Leukaemia (CLL) is the commonest leukaemia in the western world, with a median diagnostic age of 70 years and a variable clinical course, from indolent (never requiring treatment) to an aggressive, ultimately fatal disease despite multiple lines of therapy. CLL diagnosis is dependent on a characteristic immunophenotype and its variable clinical course is ascribed to genetic subgroups. We have focused on the role of an extended immunophenotype to cost effectively predict prognosis at diagnosis and reserve complex molecular assessment for patients requiring treatment.

The receptor tyrosine kinase-like orphan receptor 1 (ROR1) is expressed in >90% of CLL cases and increased expression is predictive of aggressive disease[1]. Under 10% of CLL patients express low levels of ROR1 (ROR1lo) and the limited clinical information on this subset suggest that it behaves indolently and is associated with an atypical immunophenotype[2,3,4].

The aim of this study is to assess the clinical and immunophenotypic profiles, *TP53* and *NOTCH1* mutational status and time-to-first treatment (TTFT) of newly diagnosed ROR1lo CLL.

Methods: Consecutive, newly diagnosed, consented CLL cases from 01-11-2017-to 31-09-2018 from the Trinity St James's Cancer Institute, University Hospital Limerick and the Midlands Regional Hospital were included. Ethics approval was obtained for demographics, extended immunophenotype, (including PE-conjugated anti-ROR1), mutational status (*TP53* and *NOTCH1*), biobanking and follow-up. ROR1lo was defined if <30% of CLL cells expressed ROR1. Clinical status was assessed on 01-03-23.

Results: ROR1lo was detected in12 (14%) of the 85-patient cohort; 8 (66.7%) were male, 7 (87%) had Binet A disease. At diagnosis, the median age was 63.5 (*range 50-77)* years*,* median absolute lymphocyte count was 9.63 *(range 6.0-16.24)* 10^9/L and median ROR1 expression was 11.3 *(range <1-24)* %. Five (41.7%) had atypical immunophenotypes; 4 expressed CD79b and 3 expressed high CD20 levels. The prognostic profile of the ROR1lo was CD38 positive(+ve) in 3/12 and 49d+ve in 4/12 cases, IgVH analysis was available in 5 cases of whom 4 (80%) had a mutated profile, no patient had a *TP53* or *NOTCH1* mutation.

The median time from diagnosis to census date was 60 *(range 53-65)* months, during which time 2 patients required treatment; patient 7 received FCR at 12 months and remains in MRD-ve remission at 47 months and patient 12 was treated with R-Chlorambucil a month after diagnosis and died of progressive disease 2 years later. A further treatment-naïve patient died 2 years after diagnosis from pneumonia.

Conclusion: This small ROR1lo cohort were younger, had indolent disease and displayed atypical immunophenotypic profiles which may have therapeutic implications (CD20 high, absent ROR1 for BiTE/CAR-T); 10 (83%) patients have not been treated at a median of 5 years from diagnosis, 3 treatment-naïve patients have been discharged to primary care follow-up and one patient has died of disease. We have validated extended immunophenotypes (CD38, CD49d, CD20 expression level, ROR1) as a cost-effective prognostic assessment tool, reserving molecular assessment (IgVH, FISH, mutation analysis) for patients requiring treatment. Diagnostic immunophenotypes should include ROR1 to risk-stratify patients, promote personalised patient care and target patients for clinical trials.

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Post-transplant lymphoproliferative disorder in paediatric patients: the Irish perspective

A Allen, A Malone, O Smith, L Storey, E Fitzpatrick, C McMahon, N Barrett, P McCarthy, A O'Marcaigh, P Evans, S Vandenberg, V Broderick
[1]Children's Health Ireland , Crumlin, Dublin.

Introduction: Post-transplant lymphoproliferative disorder is a heterogeneous group of disorders occurring after both solid organ and haematopoietic stem cell transplantation(HSCT)(1). The majority of PTLD are associated with Epstein Barr virus (EBV)(2). The incidence of PTLD is significantly higher in paediatric recipients, and has been as high as 19.5% in lung, heart and heart-lung transplants(3) Unfortunately, the mortality for PTLD, that fails to respond to a reduction in immunosuppression, is high(3) and an optimal therapy strategy remains controversial(4).

Methods: We retrospectively assessed presentation, investigations, management and outcomes of all patients who were treated in our center for PTLD between January 2004 and May 2023. Clinical and laboratory data were retrieved by retrospective review of patient medical records and hospital radiology management systems.

Results: There were 25 cases of PTLD identified over a 19 year period at our institution. There was a male predominance noted (68%, 17/25). The median age at diagnosis was 6 years (range 1-16 years). 4 patients had HSCT and 21 patients had solid organ transplants (SOT). The distribution of SOT types included: 14 liver transplants, 1 lung transplant, 2 renal transplant, and 4 cardiac transplants. The median time from transplant to PTLD diagnosis was 8.5 months (range 2 to 108 months)

Histologically the majority of cases were classified as monomorphic PTLD 48% (12/25), or polymorphic 44% (11/25). CD20 immunochemistry was positive in the majority of cases (92%, 23/25).EBERish was performed in the majority of cases and positive in 96% (23/24).

The median EBV DNA viral load prior to treatment measured by quantitative PCR was 40,076 copies/ml (range 2022–1,534,853)in patients treated in the last decade in comparison to 281,573 copies/ml (range 500–5,779,300) in patients treated 2004-2015. LDH was elevated in the majority of patients (13/23, 56%). Radiological staging methods at diagnosis and completion of therapy varied widely.

All patients had a reduction of immunosuppression. 7 patients received rituximab alone,13 received rituximab, low dose cyclophosphamide and steroid, 3 patients were treated with intensive multi-agent chemotherapy.

Overall survival at 1 year was 87.5% (21/24). Two patients died due to PTLD-related complications, highlighting the aggressive nature of certain PTLD subtypes. Another patient died due to a relapse of AML.

Conclusion: Treatment of PTLD following SOT and HSCT at our institution over a 19-year period has yielded excellent results. All patients had EBV viremia at time of diagnosis indicating the importance of vigilant monitoring although the optimal strategy for management of EBV viraemia in the absence of PTLD in the SOT population remains uncertain. The availability of commercial EBV-CTL products, such as Tabelecleucel (5), which has shown excellent outcomes in relapsed/refractory PTLD, is an attractive chemotherapy-free strategy with that may alter the therapeutic landscape of PTLD in the future. Finally, the variability in radiological investigations performed highlights the need for guidelines to address variability in clinical practice.

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NOVEL INSIGHTS INTO FACTOR VIII AND FACTOR IX LEVELS AMONG PAEDIATRIC HAEMOPHILIA CARRIERS

H Fogarty[1], **A Busher[1]**, S Ahmed[1], B Nolan[1]
[1]National Paediatric Haemophilia Centre, Children's Health Ireland, Crumlin, Dublin

Introduction: Given the X-linked inheritance of FVIII and FIX deficiency, it was traditionally assumed that female haemophilia carriers (HC) are asymptomatic. However, this misconception is challenged by recent evidence suggesting increased bleeding tendency in HC. Bleeding phenotype in HC remains poorly understood, especially in children. New HC nomenclature by the SSC of the ISTH suggests five categories: mild/moderate/severe haemophilia, symptomatic and asymptomatic HC (FVIII/IX ≥0.40IU/ml with/without a bleeding phenotype).[1] Whether these categories are appropriate in children is unknown.

Aims: To characterize FVIII and FIX levels among HC attending the National Paediatric Haemophilia Centre, evaluate bleeding phenotype and haemostatic treatment requirements.

Methods: A clinical data-set of HC attending CHI, Crumlin was established. FVIII/FIX levels were assessed and additional haemostatic assays performed as appropriate. Since genetic testing is not routine <16 years, females were classified as 'Obligate' HC with paternal history of haemophilia, as having a '50% chance' of being a HC with a maternal history of carriership or 'Possible' HC where factor deficiencies were identified *de novo* or haemophilia family history was unclear. Bleeding phenotype was evaluated via chart review.

Results: A total of 217 females (n=62 FIX, n=155 FVIII, median age 9.6 [IQR 7.3] years) were included; 47 (22%) 'Obligate' HC, 115 (54%) with '50% chance' of carriership and 53 (25%) 'Possible' HC. Median age at FVIII/FIX testing: 2.3 [IQR 5.4] years. Using paediatric age-specific reference ranges, 52% (113/217) had normal levels, 47.5% (103/217) had mild and 0.5% (1/217) had moderate FVIII/FIX deficiency. Conversely, using <40 IU/ml to define FIX/FVIII deficiency, 78.3% (170/217) had normal levels, 21.2% (46/217) mild and 0.5% (1/217) moderate FVIII/FIX deficiency. Overall, 16.5% had received haemostatic therapy; of these 64% tranexamic acid (TXA) only, 18% TXA+DDAVP, 7% TXA, DDAVP+Elocta, 4% TXA+Elocta, 4% Alprolix only and 4% DDAVP only. Recipients were significantly older than non-recipients (mean age 12 versus 9.6 years, p=0.01). Comparing FVIII and FIX, median levels were: FVIII 0.56 [IQR 0.36], range 0.02-1.91IU/ml and FIX: 0.58 [IQR 0.32], range 0.20-0.95IU/ml. There was no difference between FVIII and FIX HC regarding age, absolute levels or proportions with mild FVIII/FIX deficiency (48% and 45%, respectively). Significantly more FVIII HC received haemostatic therapy than FIX (20% versus 9%, respectively, $\chi 2$ 4.1, p=0.04). Commonest indications for treatment were mucosal bleeding; epistaxis and menorrhagia, and prophylaxis for surgical procedures.

Discussion: Mild FVIII/FIX deficiency is common in this cohort. Complexities inherent in evaluating paediatric HC include: variations in factor reference ranges with age and the fewer bleeding challenges faced by children versus adults. Furthermore, adolescents and young adults (AYA) likely experience greater haemostatic challenges than younger children, especially females. Accordingly, we observed haemostatic therapy recipients were older, likely attributable to menorrhagia among AYA. Interestingly, FIX HC received less haemostatic therapy than FVIII HC, consistent with studies suggesting FIX deficiency may be associated with a less severe bleeding phenotype than FVIII deficiency with the same plasma level.[2]

Conclusion: Our novel data from a large paediatric HC cohort highlight a significant bleeding phenotype and treatment burden in these children, worthy of further study.

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REVIEW OF THE POSTNATAL MANAGEMENT OF INFANTS FOLLOWING POSITIVE DIRECT ANTIGLOGULIN TEST

A Busher[1], S Costello[1], M Culliton[2], J Fitzgerald[2], MC Murphy[1]
[1]Neonatal Department , National Maternity Hospital, Holles Street, Dublin
[2]Haematology Department, National Maternity Hospital , Holles St, Dublin

Introduction: Haemolytic Disease of the Foetus and Newborn (HDFN) is caused by maternal alloimmunisation against red blood cell antigens[1]. The direct antiglobulin test (DAT) is used for identification.[2] Clinical outcomes vary, ranging from mild jaundice to kernicterus and death. Antenatal monitoring guidance is available[3] and includes the identification of antibody levels, referral to foetal medicine specialist, and review of Doppler ultrasound. Antibody quantifications and titrations are used to guide the management based on the risk of developing HDFN.

Methods: We wished to review our postnatal management of infants following positive DAT. We identified positive DAT results from laboratories in our tertiary maternity hospital over a 1-year period. We conducted a retrospective chart review of electronic medical records, and audited management against our protocol. Serum bilirubin measurements were interpreted using the NICE Guideline for Jaundice in Neonates.[4] From July 2021 – July 2022, 394 positive DATs were collected; 6 (2%) patients had DAT4+, 7 (2%) patients DAT3+, 85 (21%) patients DAT2+, and 296 (75%) patients DAT1+.

Results: From July 2021 – July 2022, 394 positive DATs were collected; 6 (2%) patients had DAT4+, 7 (2%) patients DAT3+, 85 (21%) patients DAT2+, and 296 (75%) patients DAT1+. Among the DAT4+ group (n=6), anti-D +/- anti-C antibodies were the most commonly identified. All infants had antenatal quantifications in the moderate-high risk levels (levels 5-160 iu); anti-c levels for one patient reached a level of 110iu/l. All of these infants were directly admitted to the neonatal intensive care unit and had an early bilirubin sent. All infants in this cohort had prophylactic phototherapy commenced. 4 of 6 infants received intravenous immunoglobulin, 5 of 6 infants received postnatal red cell transfusions, and no patient in this group received an exchange transfusion. All patients were prescribed folic acid postnatally. The mean (SD) duration of stay was 9.8 (2) days. Among the DAT3+ group (n=6), all patients had antenatal levels at low-risk range. Anti-D, anti-E, anti-c, anti-Cw, and anti-S antibodies were present. Two infants were admitted to the neonatal intensive care unit. All infants had serum bilirubin samples below the phototherapy threshold.

Among those with DAT2+ and DAT1+, phototherapy was commenced for 13 (15%) and 18 (6%) patients respectively. A positive DAT was due to ABO incompatibility in 10.7% (9) in the DAT2+ and 6% (18) in the DAT1+ group. Maternal anti-D immunoglobulin administration was found in 72.6% (61) in the DAT2+ group and 91.5% (271) in the DAT1+ group.

Conclusions: We found that newborns at greatest risk of HDFN were recognised antenatally and appropriately admitted to the neonatal unit. Those at greatest risk for HDFN all had moderate-high risk levels antenatally. Education on antibody significance may improve management in those with low risk levels. In our study, infants with a DAT3+ result had maternal antibodies present at a low risk level, though two were admitted to the neonatal unit for phototherapy, despite never reaching phototherapy threshold. Ongoing education is warranted.

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Megakaryoblasts in pleural fluid in neonate with transient leukaemia of Down's syndrome

K Chmielowiec[1], G Beattie[1], K Clarke[1], E McCloy[2], B Mitchell[2], C Macartney[2]
[1]Haematology, Belfast City Hospital, Belfast, Northern Ireland
[2]Paediatric Haematology, Royal Belfast Hospital for Sick Children, Belfast, Northern Ireland

Twin baby boy born at 35+2 weeks gestation with a birth weight of 2070 grams via emergency cesarean section secondary to abnormal CTG and foetal distress. Full blood count obtained at birth showed haemoglobin 159 g/L, total white cell count 99.54 × 109/L platelet count 779 × 109/L.Manual differential showed an absolute neutrophil count of 2.01 × 109/L absolute lymphocyte count of 45.27 × 109/L and blast count of 50.3 × 109/L (50%). Initial peripheral blood smear morphology review revealed a thrombocytosis, platelet anisocytosis and micromegakaryocytes. It also demonstrated neutropenia, myeloid left shift, large blasts with a high N/C ratio and nucleoli. Additionally, numerous nucleated red blood cells were seen with marked red cell dysplasia including binucleate forms and abnormal haemoglobinisation. There was no prenatal diagnosis of Down's syndrome (DS). The above blood results along with the baby's clinical signs raised suspicion of DS and subsequently transient leukaemia of DS. This baby was then transferred to the regional neonatal intensive care unit on day 2 of life.

On admission, he was noted to have bilateral pleural effusion, synthetic liver dysfunction with elevated creatinine and ammonia levels as well as ascites. He was intubated, and ventilated and required inotropic support. Due to adverse features of elevated white cell count, hepatosplenomegaly, pleural effusion as well as ascites [1] and following the multidisciplinary team (MDT) discussion and parental consent, the patient was commenced on lowdose cytarabine for 7 days. He tolerated that well, however, did experience mild cytopenias and pyrexic episodes, followed by recovery during the following two weeks with a reduction in pleural effusions, hepatosplenomegaly and reduction in oxygen requirement which enabled successful extubation and commencement of continuous positive airway pressure.

Unfortunately, on day 19 of life hewas noted to have slowly increasing oxygen requirements with re-accumulation of pleural effusions and increasing hepatosplenomegaly as well as increasing blast count in peripheral blood. He proceeded to require intubation and ventilation again as well as placement of a chest drain to remove pleural fluid to improve respiratory compliance. A review of pleural fluid morphology had shown frequent 'blast-like' cells; these were mediumsized with a high N/C ratio with finely condensed chromatin nucleoli and budded basophilic cytoplasm thought to most likely represent megakaryoblasts [2]. As a result of the deterioration, a decision by MDT was made to give another cycle of low-dose cytarabine on days 1 through 5. Following the second cycle of cytarabine, the patient again experienced mild cytopenias and pyrexic episodes, was treated with antibiotics and supportivemanagement and transfusions of packed red cells. He had complete count recovery and no blast population identified morphologically on peripheral blood film on day 26 of the second cycle of cytarabine. His GATA1 mutation was subsequently found to be positive. He continued to improve and was discharged home on day 67 of life.

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USE OF RECOMBINANT ACTIVATED FACTOR FVII IN THE NICU – A RETROSPECTIVE REVIEW

Ciara Dixon, Siobhan Coughlan, Sonia Varadkar, Jana Semberova
Dept of Neonatology, Coombe Women & Infants Hospital, Dublin

Background

Factor VII (FVII) is a vitamin K-dependent glycoprotein that binds to Tissue Factor in the setting of endothelial injury. This gives rise to activated Factor VII (FVIIa), which further activates Factors IX and X, promoting thrombin release, platelet activity and formation of a fibrin clot. Recombinant activated FVII (rFVIIa) (Novoseven) is a synthetic form of FVIIa that is licensed in cases of intractable bleeding in patients with haemophilia, congenital FVII deficiency, and Glanzmann's thrombasthenia. It is also used in severe postpartum haemorrhage. Off-label use of NovoSeven as a potentially effective haemostatic agent has been rapidly expanding, although its utility in the newborn population is under-investigated. In the neonatal intensive care unit (NICU), rFVIIa is most commonly used off-label as a rescue intervention in those with uncontrolled haemorrhage that is unresponsive to conventional treatment with fresh frozen plasma (FFP) and other blood products.
This paper outlines a cohort of critically ill patients at a tertiary neonatal centre who received rFVIIa, and evaluates indications for treatment, number of doses, and clinical outcomes.

Methods

A retrospective chart review was carried out on newborns who were administered rFVIIa in a tertiary NICU from January 2008 to January 2022. Demographic, clinical and laboratory data was collected from charts and the laboratory computer system.

Results

10 infants were identified as having received one or more doses of rFVIIa between January 2008 and January 2022. The median birth weight was 2630g, with a median gestation of 37^{+6}/40. Precipitating diagnoses included pulmonary haemorrhage (n=4), subgaleal haematoma (n=2), superficial skin haemorrhage (n=1), and severe disseminated intravascular coagulation (DIC) (n=2). Two patients were identified as having specific factor deficiencies causing bleeding. One infant was treated for DIC with hypovolaemia following a maternal antepartum haemorrhage. Between one and thirteen doses of rFVIIa were administered. 70% of patients (n=7) received a single dose, one patient received four doses, and two patients received thirteen doses. The median prothrombin time prior to rFVIIa was 29.1, and the median after treatment was 18.1. Four (40%) infants survived to discharge. Two infants died within 72 hours of rFVIIa treatment, and four died more than three days after. Overall hospital mortality was 6/10 (60%).

Conclusion

Use of rFVIIa in our NICU is infrequent, and is reserved for critically unwell infants with a high risk of mortality. Early consideration of rFVIIa may be an effective addition to current treatment modalities for refractory haemorrhage in infants.

HIGH-CONTENT DRUG SCREEN IDENTIFICATION OF ALBENDAZOLE AS A NOVEL COMPOUND WITH EFFICACY IN PAEDIATRIC ACUTE MYELOID LEUKAEMIA *IN VITRO* AND *IN VIVO*

SM Lynch[1], R Wilson[2], T Ní Chonghaile[3], A Thompson[4, 5], K Mills[4], R Levine[6], KB Matchett[1]
[1]Personalised Medicine Centre, School of Medicine, Ulster University , Derry/Londonderry, UK
[2]Department of Natural Sciences, University of Bath, Bath, UK
[3]Department of Physiology and Medical Physics, Royal College of Surgeons in Ireland, Dublin, Ireland
[4]Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, Belfast, UK
[5]Centre for Cancer Sciences, The Biodiscovery Institute, Faculty of Medicine & Health Sciences, University Park, Nottingham, UK
[6]Department of Medicine, Memorial Sloan Kettering Cancer Centre, New York, United States

Introduction: Acute myeloid leukaemia (AML) is a leading cause of leukaemia death in children. Indeed, only 60% of children diagnosed with AML will survive >5 years. These poor outcomes are further complicated by severe and toxic side effects that children experience during treatment regimens, these include hair loss, nausea, bone pain, memory and attention problems, heart muscle damage, decreased lung function and tooth decay (1-6). Therefore, there is a clear urgent clinical need for novel therapies that will provide efficacy against paediatric AML, whilst also reducing therapy-associated side effects.

Methods: A single agent in-house screen was performed to identify potential novel hits using the Screen-Well® FDA drug library in primary murine cells, representative of MLL-AF9-driven paediatric AML and normal karyotype HOXA9-Meis1 driven AML. A novel hit from this screen was then evaluated for anti-leukaemia efficacy in murine and human models of childhood AML using *in vitro* and *in vivo* assays.

Results: The anthelmintic agent albendazole (ABZ) was identified as a novel drug candidate. Low dose ABZ (IC50 <300 nM at 72 hours) reduced viability in human AML cell lines, while having minimal effect on normal mouse and normal human peripheral blood cells. ABZ caused G2/M arrest and PARP cleavage (at 4 hours following 100 nM ABZ treatment), leading to apoptosis as confirmed by PI and Annexin V-based flow cytometry and Western blot. RNA-seq analysis of ABZ-treated AML cells identified 98 genes with increased expression, and 14 downregulated genes. *IL1B*, *P38 MAPK* and *NF-kB* were identified as key perturbed networks following ABZ treatment. Moreover, *SELPLG* was found to be top ranked upstream regulator of the ABZ gene signature. The *SELPLG* gene encodes a glycoprotein that functions as a counter-receptor for the cell adhesion molecules P-, E- and L- selectin expressed on myeloid cells and T lymphocytes (7). Finally, luciferase expressing THP-1 childhood AML cells were generated and pre-treated with either vehicle or ABZ and an untreated group included. Live tracking of pSLIEW-transduced AML cells in NSG mice showed ABZ decreased leukaemia burden and extended lifespan (median survival; Control (30 days) vs ABZ (53 days)).

Conclusion: The novel drug candidate ABZ was found to have remarkable anti-leukaemia efficacy in murine and human models of childhood AML *in vitro* and *in vivo* while having negligible effects in normal cells. Based on our data, the effective anti-leukaemic concentrations of ABZ is clinically achievable (8) and ABZ has an excellent toxicity profile (9). Current work entails evaluating if this novel drug ABZ has potential to progress to clinical trial as an age-tailored therapy for paediatric AML.

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PAEDIATRIC BONE MARROW TRANSPLANT: IMPROVING THE PATHWAYS OF CARE INNOVATION WORKSHOP

R Ruddock, J McGarrity, M O'Brien, K Murray, C Besani, R Long, P Evans, V Broderick
[1]HSCT and Cellular therapy Department, Children's Health Ireland at Crumlin, Dublin, Ireland

Background: The Haematopoietic Stem Cell Transplant (HSCT) and Cellular Therapy Department in Children's Health Ireland, Crumlin held a workshop titled '*Improving the Pathways of Care Innovation*' in June 2023. The aim of the workshop was to collect feedback from patients and parents on the transplant journey for the purpose of quality improvement and service development.

Materials and Method: Of the 51 patients who underwent an allogeneic HSCT between 01/01/2019 and 31/01/2023, 15 families were invited to attend the workshop via email. Separate patient and parent focus groups were led by a facilitator and explored the below three topics. Field notes of the focus group discussion were taken by scribes, and supplemented by visual representations created by focus group participants. A thematic analysis was performed on data collected.

Results: 16 parents and 8 patients participated on the day. The mean age of the patients was 16 years old.

1. *'The road through treatment – filling the potholes'.*The main themes from the parent group were: the need for better communication, the need for a conversation at the start of the journey on how and when the information will be provided & how this can be individualised based on the families wishes. The need for peer support for families, more age appropriate play therapy for the teenagers and increased support from psychology/physio/OT/complementary therapy. At diagnosis, the need for a social worker. From the patient group the main themes were: timely and flexible access to psychology, the importance of peer support, awareness in schools, the need for information on side effects of treatment. At diagnosis, information on available charity support and access to dietetics and physiotherapy.
2. '*Survivorship and Transition: Road to New Discovery'* . The main themes from the parent group were: the need for more information and support regarding fertility, side effects of treatment, the re-integration to school and the need for a key worker. From the patient group the main themes were: more engagement from the wider team including psychological support to cope with triggers and the highs and lows after transplant, the need for more discussion about fatigue associated with treatment, use of age appropriate language and the long waiting times.
3. *'Enhancing care through digital innovation'* . The main theme that arose was the need for digital solutions to streamline and advance the paper based information already provided. An app to record medical history, allergies and side effects of treatment, screening of patient recorded symptoms and/or symptom tracker, provide support through moderated peer-to-peer individual and group chats, sharing of information about transplant including video demos of central line/NG care, available charity supports. Parents also thought it would be useful for coordination of appointments. The need for delivery of healthcare supports such as therapeutic interventions on a virtual platform and educational podcasts was also explored.

Conclusion: Feedback from the workshop has resulted in the decision to develop a patient care app to meet the needs highlighted. We anticipate further quality improvements, after consultation with the multi-disciplinary team.

AN AUDIT OF THE FERTILITY PRESERVATION PRACTICES IN THE HAEMATOLOGY-ONCOLOGY DEPARTMENT AT CHI CRUMLIN

M Shah[1], C O'Sullivan, J Fay, P McCarthy, S Alken, N Barrett, P Evans
[1]Haematology/Oncology, CHI at Crumlin, Dublin, Ireland

Introduction In Ireland, the 5-year survival rate in Paediatric Cancer is greater than 80%.[1] With increasing survival rates, there is a focus on cancer survivorship care, of which fertility is an important aspect. Fertility preservation is an essential component of cancer care as many treatment regimens are gonadotoxic. At present, gamete preservation techniques are the only fertility preservation service available in Ireland. As such, prepubertal patients are not offered fertility preservation despite ovarian tissue cryopreservation now considered a standard of care for prepubertal female patients who will receive treatment with moderate or high-risk gonadal toxicity. In this audit, we examined the current fertility preservation practices at CHI Crumlin for all patients newly diagnosed with cancer/referred for Hematopoietic Stem Cell Transplant (HSCT) from January 1st to March 31st, 2023.

Methods Retrospective chart review of 57 patients referred to the service from Jan 1st - Mar 31st for diagnosis and consideration of chemotherapy/HSCT. A proforma was used to collect the data, which included diagnosis, age, pubertal status, treatment and gonadal toxicity of treatment, documentation of discussion of risks of fertility treatment, fertility preservation options and if the patient was referred for and underwent fertility preservation. Gonad toxicity of treatment was classified as High, Moderate, Low or Unknown according to the Royal Children's Hospital Melbourne guidelines.[2]

Results 57 patients were referred to the service during the study timeframe. 14 of these patients were excluded as either they did not have a malignancy (N=8) or were treated with surgery alone (N=5) or were treated outside of Ireland (N=1). Of the patients who met the inclusion criteria (N=43), 63% were male and 37% female; ages ranged from 10 months to 15 years. Pubertal status was documented in 16% of patient charts. 0% of the prepubertal group (N=31) were referred to fertility preservation services, of which 29% received high risk treatment. 14% of patients were in early puberty (N=6) and 100% of these patients who received high risk treatment were not referred for fertility preservation. 100% of post pubertal adolescents were referred to fertility preservation services (N=6), of which 50% received high risk therapy. In total, 47% of patients received highly gonadotoxic chemotherapy yet only 15% were referred to fertility preservation services. 9% of patients were prepubertal/early pubertal females who received highly gonadotoxic treatment and were not offered any fertility preservation due to lack of available service in Ireland. The risk of gonadotoxicity of treatment was either not discussed or not documented in 53% of all patients. Of the cohort of patients referred for HSCT (N=10), only 1 patient (post-pubertal) was referred for fertility preservation. Discussion regarding sexual activity/contraception was documented in only 17% of post pubertal patients' charts.

Conclusion Current fertility preservation practices offered in Ireland are suboptimal especially for prepubertal children. Documentation in patient notes regarding the risk of treatment on fertility needs improvement. Following this audit, we have introduced a fertility preservation proforma for all patients to be completed at the time of treatment discussion. We will perform a re-audit to complete our Quality Improvement cycle.

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A novel discovery at the interface of metabolic medicine and haematology

P Behan[1], D Swan[1], J Quinn[1,2], P Murphy[1,2], P Thornton[1,2], S Glavey[1,2], J Coll[1], J Sargent[1], K Ewins[1,2]
[1]Department of Haematology, Beaumont Hospital, Dublin 9, Ireland
[2]School of Medicine, Royal College of Surgeons in Ireland, Dublin 2, Ireland

We present the case of a 38 year old gentleman initially referred to us by our neurology colleagues who was found to have a novel red cell pathogenic variant never before reported in scientific literature. He was diagnosed with Niemann Pick type C (Gln922X1/Val378AL8) at the age of the age of 27, an autosomal recessive storage disorder typically associated with neurological sequelae and lipid deposition within the liver, spleen and brain.

Our particular patient had presented to neurology with phenotypically characteristic findings of a supranuclear gaze palsy, vertical saccades, reduced downward gaze, upper limb dystonia and splenomegaly. He was commenced on the disease modifying agent miglustat (200MG PO OD), a glucosylceramide synthase inhibitor, which improved symptomatology and maintained independent activities of daily living. He has a strong family history of storage disorders and his sister sadly passed away from NPC Type C in her early thirties due to oropharyngeal lipid deposition leading to progressive dysphagia.

In the summer of 2022, this gentleman presented to our hospital's emergency department, following referral by his General Practitioner with symptoms of a lower respiratory chest infection, scleral icterus and left upper quadrant abdominal pain. His haematological indices were abnormal with a haemoglobin of 10.1g/dl (baseline 12.5g/dl), a normal MCV of 85.9fl, decreased platelets of 79 x 10^9/l (baseline approx. 150 x 10^9/l, a raised absolute reticulocyte count of 242 x 10^9/l, a raised direct bilirubin of 10.9umol/l, indirect bilirubin of 17.1umol/l and decreased haptoglobin of <0.03g/l. Of note, the lactate dehydrogenase was normal at 167IU/l and the direct antiglobulin test was negative. The peripheral blood film demonstrated anisopoikilocytosis and elliptocytosis.

At this time, the haematology service became involved and our aim was to elucidate the aetiology of this likely non-immune haemolytic anaemia. Bone marrow aspirate demonstrated unremarkable trilineage haematopoiesis. The bone marrow trephine biopsy demonstrated a hypercellular sample with no overt evidence of infiltration or abnormal maturation. Radiology investigations included cross sectional computed tomography of the thorax, abdomen and pelvis which showed marked splenomegaly with the spleen measuring 24cm in craniocaudal dimension but no evdidence of lymphadenopathy or other potentially malignant features.

This gentleman was commenced on folic acid and was managed for his lower respiratory tract infection. His symptoms resolved and his red cell indices returned to normal within 2 weeks. During subsequent investigations for red cell disorders, he was investigated for a potential membranopathy, haemoglbobinopathy or enzymopathy using Nonacus enrichment technology (RCGPv5) and Illumina DNA sequencing. The reported variant was confirmed by Sanger sequencing. Analysis revealed a heterozygous pathogenic variant known as SPTA1 c.476_488del; p.(Lys159fs) which has never been previously reported in the literature and is not present in the general population (gnomAD database). It causes a frameshift in the mRNA and is therefore predicted to be pathogenic. It is known that SPTA1 is a spectrin alpha gene known to be associated with elliptocytosis and pyropoikilocytosis but this particular variant has never before been recorded in the human population. With this in mind, this patient was commenced on folic acid 5MG PO OD for life and has been counselled on potential haemolytic triggers. He remains well at the time of publication.

The supply of appropriate blood for Sickle Cell Disease (SCD) patients in Northern Ireland

H Caldwell[1], A Rainey[2]
[1]Haematology and Blood Transfusion, Belfast Health and Social Care Trust, Belfast , N. Ireland
[2]Blood Group Reference Laboratory, Northern Ireland Blood Transfusion service, N. Ireland

Guidelines recommend that blood for SCD patients should be Haemoglobin S (HbS) negative and ABO-compatible, extended Rh- and Kell-matched units provided & antigen negative for any developed clinically significant red cell antibodies. Patients with SCD must also have extended red cell antigen typing performed (Davis, B.A et al, 2017).

Although some other transfusion centres in the UK have already introduced sickle cell screening for donors and provision of HbS negative blood NIBTS to date does not perform HbS screening. As the NI population becomes more diverse, there have been recent increasing numbers of SCD patients being admitted/treated within BHSCT. It is important that NIBTS can provide these patients with the appropriate blood especially given the recent blood shortages in the UK.

This study aims to investigate the use of Sickledex as a screening method to identify HbS negative donors to enable provision of safe blood for SCD patients in Northern Ireland. It also aims to implement a molecular red cell extended genotyping test kit to allow NIBTS to retain an accurate genotyping record when extended RBC phenotyping is not possible, in keeping with guideline recommendations and aid with appropriate selection of blood for transfusion purposes.

One hundred samples were tested for HbS using the sickle solubility test (Sickledex) , which included; random EDTA donor samples, random donor units, and EDTA samples from known SCD patients. Ten samples from known SCD patients were also tested using the Inno-train PCR (qPCR) molecular testing platform and had red cell genotyping performed using the FluoGene vERYfy eXtend kit to accurately determine the genotype of these multiply transfused patients ensuring appropriate blood selection for future transfusions.

A number of important mutations in these SCD patients were identified including absence of U antigen, U variant and GATA-1 mutations. There were also partial antigens identified which had not been previously detected via standard serological methods. These findings are significant for donor and recipient transfusion purposes as they can lead to patients being immunised and can cause difficulties with the provision of blood for further transfusions.

Davis, B. A., Allard, S., Qureshi, A., Porter, J. B., Pancham, S., Win, N., Cho, G., & Ryan, K. (2017). Guidelines on red cell transfusion in sickle cell disease. Part I: principles and laboratory aspects. British Journal of Haematology, 176(2), 179–191.

ROUTINE GROUP AND HOLDS IN GUH HAEMATOLOGY DEPARTMENT - AN AUDIT AND QI PROJECT

J Fitzgerald[1], Y Nunez[1]
[1]Haematology Department, Galway University Hospital, Galway,

Background: Routine bloods are used to track the clinical progress of patients, and in haematology patients in Galway routine group and holds (G+H) are performed to allow patients with standing orders for blood products to receive them. This audit aims to examine use of routine G+Hs to develop parameters for which haematology patients should have them to reduce the number of unnecessary blood tests performed, reducing unnecessary phlebotomy on patients not needing it, and reducing strain on hospital money and resources. An audit and quality improvement model was used for this analysis.

Methods: All patients admitted under haematology on Claddagh ward in Galway University Hospital were included in this audit. Initially two weeks at the end of February 2023 were selected when the team had not used any parameters for routine G+Hs. Data was retrospectively collected using the EVOLVE electronic record system, including how many patients had routine G+Hs performed, and which had subsequently been transfused blood products. Department policy is to perform routine G+Hs on Mondays and Fridays, G+Hs performed by phlebotomy during those days are considered to have been "routine" for this audit.

Parameters that were used to analyse if the G+Hs were appropriate are as follows:

1. Hb<9.5
2. Platelets<50
3. Required transfusion of blood products

If patients' bloods before the G+H met parameter 1/2, or if the patient retrospectively required transfusion (parameter 3), then the G+H was deemed "appropriate" in analysis.

A second set of data was collected in March 2023. For this, parameters 1 and 2 were used to actively guide which patients received routine G+Hs during the two weeks analysed. Data was then retrospectively collected in the same way.

Results: In the initial audit an average of 90.4% of patients had the test performed on each Monday/Friday. 68% of these on average were deemed appropriate within the parameters. An average of 35.4% of the patients who had routine G+Hs performed required transfusion.

On review, with parameters guiding the use of routine G+Hs, an average of 68.2% of patients had G+Hs. An average of 91% of those performed were appropriate within the parameters. An average of 50.6% of the patients who had routine G+Hs performed required transfusion.

Conclusions: The total % of patients on the ward who required transfusion was similar between the two datasets (average of 32% on initial audit and 33.6% on review). The use of simple parameters to guide which patients received routine G+Hs reduced total G+Hs on the ward by an average of 22.2% in this analysis. This equates to 12-14 blood tests per week. In addition, the average number of G+Hs used for cross match and transfusion increased by 15.2% on repeat audit. In summary the parameters used effectively reduced the number of unnecessary routine G+Hs, they can be further refined as per the limitations section to save on further patient procedures and money.

Fisher A, Katumba A, Musa K, Wijethilleke S, Khan Z, Chung Y, Akhtar W. Reducing inappropriate blood testing in haematology inpatients: A multicentre quality improvement project. Clin Med (Lond). 2021 Mar;21(2):142-146. doi: 10.7861/clinmed.2020-0250. PMID: 33762376; PMCID: PMC8002792.

THE APPROPRIATNESS OF PLATELET TRANSFUSIONS IN HAEMATOLOGICAL PATIENTS AND THE POTENTIAL FOR IMPROVEMENT

E O'Shea[1], D Ritchie[1], K Mason[1], AW Roberts[1]
[1]Clinical Haematology, Royal Melbourne Hospital, Melbourne, Australia

Background: Platelet transfusions play a critical role in the supportive treatment of haematology patients with thrombocytopenia[1]. Despite prior studies that have tried to determine safe pretransfusion platelet count thresholds, and the generation of multiple guidelines interpreting those data, many platelet transfusions are administered outside of these guidelines[2]. This audit aimed to assess the application of transfusion guidelines in haematological patients and identify variances from guidelines.

Materials and methods: A two week retrospective audit was conducted on all platelet transfusions in adult haematology inpatients at an Australian Academic centre. Episodes were assessed as either compliant or non-compliant based on Australia's national guidelines for platelet transfusion, the Patient Blood Management Guidelines[3]. Findings were also compared against guidelines from the British Society for Haematology (BSH)[4]. Patient demographic, clinical, and transfusion data were collected from hospital electronic medical records where the indications for transfusion are routinely recorded.

Results: 116 platelet transfusion episodes in 24 patients, predominantly with acute leukaemia (n=50) or undergoing allogeneic transplant (n=66), were audited. Overall, 38.8% (45) transfusions appeared non-compliant with Australian national guidelines; 31% (13/42) of therapeutic transfusions, 44.8% (30/67) of prophylactic transfusions and 28.6% (2/7) of pre-procedure transfusions. According to BSH guidelines, 43.1% (50) of platelet transfusions appeared non-compliant (p=0.5). A common non-compliance feature from was the absence of a platelet count prior to 14% (16) of transfusions, due to the administration of 2 pools of platelets consecutively. Other major reasons for non-compliance included the use of a threshold platelet count > 10×10^9/L in 25% (29) of transfusions without additional risk factors indicating the need for a higher threshold. This included 10.3% (12) of transfusions being given to patients with mucositis in the absence of active bleeding and 5.4% (6) of transfusions to patients on the day of discharge.

Conclusion: Our audit found a large discrepancy between platelet transfusion practice and published platelet transfusion guidelines. The large proportion of non-compliant platelet transfusion in haematological patients highlights both a need to understand if the guidelines are fully fit-for-purpose in busy acute haematology units and the need for educational and system changes at prescriber level. Variation from guidelines might represent anticipation of symptomatic thrombocytopenia in the absence of transfusion or bridging anticipated thrombocytopenia from the time of discharge to the time of next clinical review. More detailed guidelines may need to be developed for platelet transfusions in haematological patients in order to optimise transfusion practises and patient outcomes.

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REDUCING RED CELL TRANSFUSIONS IN HAEMATOLOGY INPATIENTS IN BELFAST CITY HOSPITAL

D WADDELL, J COSTELLO, D DONALDSON, G BENSON
[1]DEPARTMENT OF HAEMATOLOGY, BELFAST CITY HOSPITAL, BELFAST, NI

Introduction: Belfast City Hospital is the tertiary referral centre of Haematology in Northern Ireland. It also carries out all autologous stem cell transplants as well as sibling donor stem cell transplants. This unit is one of the biggest users of blood products in the region. The current Haemoglobin (Hb) threshold for Packed Red Cell (PRC) transfusion was $80x10^9$/L. NICE published guidelines in 2015 (NG24)[1] recommending a restrict transfusion threshold of $70x10^9$/L. Since then, there have been further randomised controlled trials[2] and systematic reviews[3] demonstrating that this is a safe threshold and does not affect the patient's quality of life.

Following discussions within the Haematology team, it was decided to adopt this restrictive policy. Therefore, during the department's patient safety meeting a presentation was given, as well as further education sessions within the nursing teams, to encourage restrictive transfusion practice. The date of implementation of the new Hb threshold of $70x10^9$/L was 1st May 2023. We therefore analysed the number of red cell units transfused for the three months preceding the change and compared this with the months after the change in threshold.

This analysis only looked at red cell transfusion data and didn't perform any patient symptom surveys. However, given that this intervention was on inpatients who have daily reviews any who are still symptomatic of their anaemia will have a higher transfusion threshold set.

Results: We observed that the weekly mean number of red cell transfusions decreased from 31 to 26 units per week. A monthly mean reduced from 131 units to 117 units. There was an unusual usage in May (163 units) compared to other months therefore longer analysis time will be required to see the full benefit of reducing the Hb threshold.

Given the ongoing pre-amber alert by the regional transfusion service there is a need to reduce PRC usage. From a patient safety point of view, blood transfusions come with risks such as infections, reactions or even development of alloantibodies therefore a reduction in transfusions could help to minimise these risks.

Other advantages are: less bed/chair time for the patient to be connected to transfusions that reduces mobility and more time available for nursing staff for other clinical duties. With an average cost of £158.18[4] per PRC unit this could lead to a weekly saving of more than £790 per week (or >£41,000 per year).

Conclusion: We can see that by reducing the Haemoglobin transfusion threshold from $80x10^9$/L to $70x10^9$/L there has been a 16% reduction in the number of red cell units transfused weekly. This was observed over a short period of three months therefore further monitoring will be useful to see if this average drops further given that May has an unusually high red cell usage. We can be reassured of the safety of this reduction given the results of recent RCTs showing no clinical concerns identified and no reduction in the patient's quality of life.

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NURSING & AHP DISPLAY POSTER BOARD LISTING

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Haematology '*Crib Cards*'

C A Galligan [A], D Byrne[A], S Impey[B], F Dowdall[A], M Gillespie[A]
[1]HOPe Directorate, St James Hospital , Dublin , Ireland
[2]School of Nursing and Midwifery, Trinity College Dublin , Dublin , Ireland

The '*Crib Cards'* project was initiated and designed to support end to end learning pathways designed and planned by the development teams in the CAR T Nursing Education pathway and on the Transplant pathway. This project was designed following an extensive gap analysis of current training and documentation review across the Haematopoietic Stem Cell Transplantation (HSCT) setting in St James.

Although the *'Crib Card'* project had a separate development group and was a stand-alone project it also forms part of a planned education process and was initiated based on a need and underpinning standards. The need was to provide evidence based education to support staff and the underpinning standards were the JACIE 8th standards. JACIE applicable standards were B3.6.2 which states that nurses shall have received specific training and maintain competence in the transplant and cellular therapy related skills that they practice.

'Crib Cards' were developed to facilitate and aid nursing education locally as a requirement in our specialist areas and the wider hospital setting. *'Crib Cards'* disseminate expert knowledge to our colleagues locally in St James Hospital. *'Crib Card'* ideas initially were designed and placed in newborn cribs in maternity hospitals and disclosed information of the baby's demographics and the mother's demographics (Huggies, 2022). *'Crib Cards'* are also used within the academic and professional field to state important information which may be required by the person (KP Cross Academy, 2023).

An action research methodology was used to achieve the goal of providing evidence based education and ensuring the programme content supported other elements of bespoke education pathways designed by the development team. The *'Crib Cards'* were tailored to support developed and developing education pathways and included relvent haematology nursing topics.

The project roles included clinical, technical, education and quality components. Development meetings were planned to design the programme content as required. The evidence was compiled to gather current evidence based practice. Healthcare professionals are required to update their skills regularly and engage in continuous professional development (CPD). Mlambo, Silén and McGrath (2021) published a meta synthesis which looked into nurses' experiences of CPD, as every day in the nursing environment requires new skill sets and knowledge within the dynamic healthcare service we are all working in. Evidence in CPD research concluded that is peer to peer, i.e. nurse to nurse, education is most beneficial and effective (Clarke, 2005, and Zaleska and De Menezes, 2007).

'Crib Card' content was reviewed on an ongoing basis throughout the project from a clinical, education and quality perspective to ensure content was relevant and evidence based. Technical skills and the support of a skilled designer was key in achieving our project outcome in the form of well designed, referenced, document controlled electronic '*Crib Cards'* that were uploaded to the hospital intranet system to allow staff to access key *'Crib Card'* information on a 24 hour basis. A designer was involved in the publishing of the *"Crib Cards',* this addition ensured that the content was visible and effective to the reader. Funds for this quality improvement project were sourced locally through HOPe Directorate grant funds. All '*Crib Card'* documents were also included in the local QPulse quality management system to ensure regular review and updates of documents are completed as required.

Haematology Crib Cards were compiled to provide information, which is required for the nursing management of the haematology patient. CPD is an effective benefit for the patient, the individual nurse and the hospital (Balls, 2010).

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LYMPHOMA FOLLOW-UP IN THE MID-WEST: A 10 YEAR RETROSPECTIVE REVIEW TO GUIDE PRACTICE

C. Ryan, S. Baker, R.K. Gupta, H. O Leary, R. Clifford, D. Kelly, F. McKenna Beattie, A. Sheikhi, **F. Hackett**
Cancer Services University Hospital Limerick, University of Limerick

Background: Lymphoma survivors who have received curative intent treatment are currently followed up in medical and nurse- led clinics often indefinitely. Surveillance is important to detect relapse quickly and includes radiological imaging, biochemical analysis, physical examination and focused patient clinical history at defined time points. Due to limited evidence, the follow up protocol is at the discretion of the treating physician. The purpose of this study was to analyse the biochemical, radiological and clinical findings at relapse to evaluate their significance when detecting recurrence in patients post curative intent treatment. This information can be used to guide optimal follow up.

Aim:

3. To explore the clinical, biochemical and radiological presentation of patients with Diffuse Large B-cell Lymphoma (DLBCL) & Classical Hodgkin Lymphoma (CHL) treated with curative intent at the point of recurrence from first remission.
4. To identify the number of these patients attending for follow up, the percentage who recurred, the time to recurrence and if recurrence was detected at scheduled follow up.

Methods: Ethical approval was sought and granted from the Research Ethics Committee, University Hospital Limerick. A retrospective review of all patients with DLBCL and CHL who attended the Mid-Western cancer Centre over a 10 year period on a surveillance schedule was performed. Patients treated with curative intent treatment who achieved remission and subsequently relapsed were identified. Data collected related to diagnosis, treatment type, confirmation of remission and recurrence event information. Statistical analysis was performed.

Results: There was a substantial number of patients with DLBCL & CHL treated with curative intent on a surveillance programme (N=226). Small numbers of this patient group relapsed (17% DLBCL and 7% CHL). The majority recurred between scheduled visits (93%). Clinically, the majority reported a symptom at recurrence (97%). Radiologically, a small number showed abnormality on CXR at recurrence (10%). Biochemically, 47% had an abnormal ESR and 70% had an abnormal LDH at recurrence. The majority relapsed within 5 years (67% DLBCL & 66% CHL).

Conclusions: The benefit of routine follow-up, particularly longer term follow up > 5 years, for detecting recurrence is not supported. The resources utilised for routine follow-up must be balanced with the requirement for access for new patients and acute relapses.

Stratified follow-up with direct access for patients with red flag signs & symptoms is recommended. The multiple survivorship aspects of follow-up visits are acknowledged. Provision of an End of treatment Patient Treatment Summary and Care plan, Patient Passport and signposting to survivorship services should be considered in addition.

Next Steps: To present the study findings to Lymphoma clinicians at the Lymphoma Forum of Ireland Annual Conference & to establish a working group of Lymphoma nurses to develop survivorship services in collaboration with NCCP.

IMPLEMENTATION OF A PATIENT–HELD MEDICINE LIST IN HAEMATOLOGY OUTPATIENT CLINICS

F. Hackett, M Whyte, S Lawlor, Eoin Barrett, S Carey
Cancer Services, University Hospital Limerick

Background: Medication reconciliation has been shown to be essential in medication safety in cancer patients with two information sources recommended, one of these being the patient or carer. The safe use of medicines requires knowledge and consideration of all the medications that the patient is taking in order to avoid omissions, duplications, dosing errors, and potential drug-drug interactions. There is extensive use of oral anti –cancer medications (OAM), often with concurrent intravenous regimens, across all haematology cancers. In addition many patients' with haematological malignancies attending outpatients (OPD) are taking medications for co-morbid conditions and supportive medications. Patient medications are variously prescribed by both hospital teams and GPs and dispensed from different pharmacies including clinical trials, hospital cytotoxic and community.

Aim: To implement and evaluate a patient- held medicine list as a means of enhancing medication safety within a Haematology department. The 'My Medicine list' tool developed by the HSE Medication Safety Programme (Safermeds) was chosen.

Methods: Haematology Health care professionals' (HCPs) (n=19) were asked their views on the value of utilising a patient-held medication list. The 'My Medicine list' was then initiated by the haematology nurse specialist team with patients attending haematology OPD. Patients were encouraged to fill out the list and take it with them to all healthcare appointments. The patients (n=30) were surveyed at the next clinic visit by an evaluation questionnaire with regards to their views on the use of 'My Medicine List'.

Results: Initial HCP views (n=19) indicated that the majority of HCPs carry out medication reconciliation with the main barrier being time limitations. The majority felt that generally patients do not remember their medications or keep an up to date medicine list. Almost all felt that the medicine list would be useful. The patient survey (n=30) post implementation indicated that the majority filled out the medicine list (80%) and brought it to the hospital appointment (80%). The majority felt that the list helped them remember their medications (73%) and felt it was useful (77%). Importantly a large number indicated that they will continue to use the list (77%). Barriers to use identified were taking a small number of medications, forgetting to bring list, alternative list in place, familiarity with medicines and concerns regarding the accuracy of patient list over pharmacy list.

Conclusions: The 'My Medicines list' was successfully implemented and positively evaluated by patients and HCPs. The use of a patient-held medicine list is a potential approach to improving medication safety by supporting self-management, patient empowerment and improving information transfer across care settings. The list can also act as a focus for medication discussions with HCPs while saving HCP time completing formal medicines reconciliation.

Next Steps: The 'My Medicine list' was implemented for all Haematology outpatients. This was achieved through outpatient communication, with a template medicine list posted with the appointment letter, requesting patients to complete and bring to their appointment.

INTRODUCING THE LEUKAEMIA CAST PODCAST SERIES WITH DEIRDRE O KANE

P Lannon, J Crowley, F McKenna, M Mannion, L Storey
Children's Health Ireland at Crumlin

Background/Objectives:

Children's Health Ireland at Crumlin (CHI), Dublin treats approximately 45 new children with Acute Lymphoblastic Leukaemia (ALL) per year. Treatment impacts on the social, emotional and educational development of patients. Treatment of ALL lasts for approximately 2 years for girls and 3 years for boys. What does life look like after a diagnosis and what should patients and their families expect and how can they prepare for this journey?

The podcast hopes to prepare the listener with practical advice on how best to navigate the cancer journey with a child or young person with ALL.

Method:

Hosted by Deirdre O'Kane Leukaemia CAST is a podcast series for parents of children and young people with Acute Lymphoblastic Leukaemia (ALL) in Ireland. Leukaemia CAST was developed by CHI@Crumlin with the support of Servier Laboratories, Ireland. This poster will highlight the availability of the podcast for families to use. It was launched in September 2022. Leukaemia CAST is a five part series getting insights from patients, their families and healthcare professionals through their personal stories. Getting a diagnosis of ALL is devastating for patients and their families. The schedule of treatment can be overwhelming but all cancer journeys are different.

The teaching programme for parents and families is carried out by the Haematology/Oncology Clinical Nurse Specialist (CNSp) team. We provide oral information, written information using a training booklet with a step by step guide for parents to follow at home. Visual information is provided by the use of a Hickman training App. Podcasts have had a rapid rise in popularity in recent years. Specifically, podcasts can be used as a teaching resource by educators and a learning resource by parents and children (Goldman, 2018). Having various digital tools and technology as part of the classroom environment is the new norm.

Results:

Approximately 92 children attend the Leukaemia clinic monthly. Children, young adults and their families have voiced wishing to hear from someone else going through treatment. Podcasts are a great way for this to happen.

We would like to evaluate the use of the podcast by children, young people and their families to see if they have found the CAST series valuable while attending CHI@Crumlin. We also plan to audit its use by healthcare professionals as there is valuable information for them in the series also, especially if they are new to Haematology/Oncology.

Conclusion:

The benefit of having numerous methods of teaching means that families can decide which they find the most helpful. As a CNSp team it allows us to offer various ways to learn a huge amount of new information at a pace which suits each family. Podcast can be listened to at any time. By reviewing how widely the podcast is used we will be able to see if it is helpful and also to find ways to ensure that families know that it is available to them.

FINDING FRAILTY IN THE HAEMATOLOGY CLINIC

L Lyons
[1]Haematology, Northern HSCT, Antrim, NI

Introduction

Frailty is a state of vulnerability initiated by disease, inactivity,inadequate dietary intake, stress, and/or the biology of ageing (Ahmend et al, 2007). Frailty is common in older adults and those with a blood cancer have been found to have a higher prevalence of frailty than those without a blood cancer (Atakul & Akyar 2019).

Frailty decreases the patient's physical and cognitive reserve and lowers patient's ability to cope with stressors such as cancer and its treatments. It is associated with poorer response to treatment, increased toxicity and worse survival for patients with blood cancer.

Current Practice

Treatment plans are based on performance status and chronological age. Frailty may be obvious when a patient attends the clinic however for some patients their levels of frailty can be subtle and easily missed in the routine haematology consultation. There is currently no frailty assessment to guide treatment decisions in the haematology clinic.

ANP led Frailty Clinic

All patients over 70 will have frailty screening carried out at diagnosis using a validated clinical frailty screening tool.All those identified as frail/at risk of frailty will be referred to the ANP led Comprehensive Geriatric Assessment (CGA). A CGA is a holistic review of functional status, comorbidities, mental health, social support, polypharmacy and nutritional status of older adults. It is hoped that early identification of frailty will lead to improved patient outcomes as information gained from CGA will inform treatment plans that consider frailty and physiological age as well as prompt early referral to a geriatrician if appropriate. The ANP led CGA will promote proactive referral to MDT for targeted treatment to address weight loss, decreased strength, polypharmacy, social support and cognitive impairment and low mood. Risk of treatment toxicity will be assessed using a validated geriatric assessment-based chemo toxicity calculator.

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PREDICTING THE DEPTH OF TISSUE TO THE POSTERIOR ILIAC CREST BY OTHER WEIGHT MEASUREMENTS TO IDENTIFY PATIENTS AT HIGHER RISK OF A BONE MARROW BIOPSY

L Lyons[1], KA Gillan[1], A Niblock[1,2]
[1]Haematology department, Antrim Area Hospital, N. Ireland
[2]School of Medicine, Ulster University, N. Ireland

Bone marrows biopsy's are a relatively safe procedure with a complication risk of around 0.4%. Complications can include haemorrhage, haematoma, neuropathy, chronic pain and infection. The majority of bone marrow biopsy's are achieved successfully first time however technical difficulties can arise if the patient has an increased amount of tissue overlying the posterior iliac crest.[1]

Obesity rates in the UK are increasing dramatically now with 63% of adults being obese or overweight.[2] This is concerning for many health reasons but also may be adding additional risk to the safety of bone marrow biopsy's.

A bone marrow biopsy requires palpation and identification of landmarks to ensure needle insertion is at the right location. If more tissue is present this is likely to make landmark identification more difficult. The more tissue present, the more vasculature will be penetrated potentially adding additional risk to the procedure. The bone marrow needles come in variable lengths and the majority are 4-6 inches. Occasionally the needles are not long enough to allow the procedure to occur.

Could a high risk cohort of patients be identified with body measurements prior to the procedure occurring to allow the option of a CT guided procedure?

Patients that attended the day unit for biopsy had their sex, BMI and waist circumference measured before biopsy. At the time of biopsy the depth of the needle from skin to the surface of the bone was recorded.

The study included 51 patients, 23 male and 28 female. BMI ranged from 19.3m^2 to 45m^2 with an average of 29.4m^2.The depth of the biopsy's had a wide range from 0.5cm to 11cm.

When comparing BMI to needle depth we found a spearman (r0.51) representing a moderate correlation. Waist circumference to needle depth had a weaker correlation (r 0.30). A patient with a BMI 23m^2 and another with a BMI 45m^2 both had a tissue depth of 4cm. The scattering of results were not robust enough to use as isolated parameters to predict difficulty of the procedure.

As obesity increases this will continue to be a problem practically for bone marrow biopsy's. The study population was not large enough to assess for complications and we could not identify a cohort that may require a CT guided approach.

1) Jennifer U Obasi, Adrian P Umpierrez De Reguero; Safety Profile of Bone Marrow Aspiration and Biopsies Performed By the Hospitalist Procedure Service at an Academic Center: An Observational Study. Blood 2019; 134 (Supplement_1): 5848. doi: https://doi.org/10.1182/blood-2019-121444 2) NHS Digital. Health Survey for England. Available from https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england(link is external). Accessed March 2020.

A Review of clinical frailty with patients with a haematological malignancy

KM Karena Maher[1], EE Ezzat Elhassadi[2], BH Brian Hennessy[2], SK Senthil Kumar[2], AB Ahmed Bannaga[2], AJ Alfred Jones[3], EB Emma Butler [3]
[1,2,3]Haematology, University Hospital Waterford, Waterford,

Background: Haematological malignanancies are beoming more prevalent. It is recognised that this prevalence increases with age. These malignancies include myleodysplasia,myeloproliferative neoplasms, lymphomas, chronic lymphocytic leukaemia and myeloma. Over the last 10 years the therapeutic options for these malignancies has improved with the advent of immunotherapies and small molecule drugs. However despite this they still remain largely incurable. These therapies also come with inherent toxities.

Clinical frailty is also exacerbated by cytopenias, infection and organ dysfunction. These are often caused and are compounded by both the haematological disease and the system anti-cancer treatments.

Clinical frailty is a recognised geriatric syndrome which is recognised as a marker of poorer outcomes in older adults with a haematological malignancy. Along with disease stratification and prognostic scores it is vital to assess the potential toxicity profile specific to each patient. Therefore estimating the risks of systemic anti cancer therapy and on an individualised basis.This should encompass assessments beyond chronological age, co-morbidities and performace status.

As well as aiding in clinical decision making frailty can also be an important discussion point for the patient and their significant others when considering treatment and consenting to treatment.

Aims: The purpose of this review is to get a statistical number of patients with haematological malignancies who have clinical frailty in University Hospital Waterford.

Methods: University Hospital Waterford (UHW) has 4 haematology consultants that all undertake haematology outpatients on a weekly basis. The clinical frailty score (rockwood score) has been chosen as the assessment tool due to its ease of application. Any haematology patient over 70 was included in this review. No patient specific details or identifiers were used on the CFS. If relevant for the patient a referral was made to geriatric services.

Results: Over a 2 week period 10 attendance haematology clinics were screened for patients with frailty. Of note all the haematology clinics are also using the virtual format for patient review. These patients were not included.

174 patients were reviewed, 56 patients were over 70 years of age. 32% of the patient cohort. Out of this the clinical frailty scale was used as a screening tool;

- 33.5% CFS 1
- 23% CFS 2
- 17.5% CFS 3
- 23% CFS 4
- 1.5% CFS 5
- 0.5% CFS 6
- 0.5% CFS 7

Conclusion: Frailty is present in patients with haematological malignancies. Using screening tools can assist with both decision making and further evaluation using geriatric assessment. This in turn can highlight specific patients that that require interventions tailored to their specific frailty issues.

Particularly in the context of systemic anti-cancer therapies to aid in decreasing toxicity and improving quality of life and adherence.

More research is required in this area specifically for patients with haematological malignancies.

Frailty and the management of haematological malignancies Gregory A. & Klepin D. Blood (2018), volume 13,no.5 pg 515-524 Frailty Assessment in the care of older people with haematological malignancies Golden V et Al. The Lancet (2021), volume 2,November, pg 736-745

WHAT IS THE IMPACT OF A MINDFULNESS-BASED INTERVENTION ON DEPRESSION AND BIOPSYCHOSOCIAL VARIABLES AMONG HAEMATOPOIETIC STEM CELL TRANSPLANT PATIENTS DURING HOSPITALISATION.

M Roche
[1]Denis Burkitt Ward , RCSI, Dublin 2,

Aim: To determine the impact of a mindfulness-based intervention on depression and biopsychosocial variables among haematopoietic stem cell transplant patients during hospitalisation.

Background: Hematopoietic stem cell transplant is an entrenched potentially lifesaving treatment option for haematological malignancies and bone marrow disorders. Psychological distress is identified as a major side effect of this treatment. Depression being the most prevalent symptom. Anxiety, diminished quality of life, physiological symptoms, fatigue, and poor concentration are also commonly experienced. Debilitating physical side effects that develop also during lengthy hospital stays in isolation can exacerbate these. Research studies suggest using alternative mental health options such as mindfulness-based interventions to help psychological anguish. Mindfulness-based interventions can help to combat depression, anxiety and overall emotional turmoil encountered during haematopoietic stem cell transplant. As treatments advance and expand in transplant, research suggests so too must the level of psychological care.

Design: Systematic review using narrative analysis.

Data Sources: Databases CINAHL, Medline, PubMed, Embase and PsycInfo were all searched between 12th of December and 4th of January 2023 for available evidence to answer the aim. Relevant reference lists of studies and relevant journals were hand searched and grey literature also searched for potential studies in January 2023.

Review Methods: The PICO (Population, Intervention, Comparison, and Outcome) mnemonic was used to formulate the review question. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to conduct the review. Out of 238 potential studies identified, six studies met the inclusion criteria. Within the six studies, a total of 270 patients were examined at different timelines during the haematopoietic stem cell transplant process. Quality appraisal of the included studies was carried out by using the evidence-based librarian critical appraisal checklist.

Results: Psychological distress was noted in all six studies as a harrowing side effect of haematopoietic stem cell transplant. Significantly a reduction in depression levels was reported in all six studies after the use of a mindfulness-based intervention. Notably, the response was higher with healing touch ($p=0.039$), and interventions based on mindfulness-based stress reduction ($p=0.04$) than with relaxation therapy ($p=0.824$). Timing was significant, noting an increase in psychological suffering at various points in the transplant process, questioning the need for intervention sooner. Mixed results were noted on biopsychosocial variables. By using elements of mindfulness, some significant responses were reported with anxiety ($p= <.05$) and conflicting results for fatigue.

Conclusion: Haematopoietic stem cell transplant, though lifesaving clearly comes with psychological risks. Mindfulness-based interventions appear to play a crucial role in assisting to cope and improve depression and biopsychosocial variables. Given the different types of hematopoietic transplant and accompanied side effects, further research is warranted in this area.

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CORRELATION OF THE IMMATURE PLATELET FRACTION WITH PATIENT OUTCOMES AND COMMON BIOMARKERS IN CRITICALLY ILL PATIENTS

A Spain[1], M Lyons[1]
[1]Haematology Laboratory, Galway University Hospital, Galway, Ireland

The immature platelet fraction (IPF) has utility in differentiating causes of thrombocytopenia and predicting platelet count (PLT) recovery in haemato-oncology cohorts. It has also shown promise in predicting infection and disease severity. Thrombocytopenia remains the most common haematological abnormality in critically ill patients, whilst severe infection is responsible for 1 in 5 Intensive Care Unit (ICU) admissions. No studies have yet evaluated the IPF in ICU patients; in terms of predicting platelet recovery, comparison to other patient cohorts, or correlation to biomarkers and patient outcomes. In this study, IPF, PLT, White Cell Count, Neutrophil Count, Nucleated Red Blood Cell Count (NRBC), C-Reactive Protein and Lactate data was compiled in 101 ICU patients. ICU patients were further subcategorised by their platelet count; Low PLT<150 x 10^9/l, Normal PLT 150-400 x 10^9/l and High PLT >400 x 10^9/l. ICU IPF (including subcategories) were compared to control and non-ICU groups, and correlation analysis was performed between ICU IPF and remaining parameters. IPF in ICU patients was significantly different to the control and non-ICU group. ICU patients with a Low PLT were responsible for the difference within the entire ICU cohort. A strong inverse correlation was found between IPF and PLT, with a weak positive correlation between IPF and NRBC. IPF measurement preceded PLT recovery in ICU patients with a low PLT by 3.7 days. No significant correlation was observed between IPF, and length of patient stay or mortality. The data shows the potential utility of IPF in thrombocytopenic ICU patients, although further studies are required for predicting PLT recovery.

PSEUDOMONAS AERUGINOSA OUTBREAK IN HAEMATOLOGY: SHARING BEST PRACTICE

J Stewart[1], D McKelvey[2], S Rainey[3], R Robb[3]
[1]10 North, Belfast Health and Social Care Trust, Belfast,
[2]Haematology, Belfast Health and Social Care Trust, Belfast,
[3]Infection Prevention and Control Nurse, Formerly Belfast Health and Social Care Trust, Belfast,

Introduction: Pseudomonas Aeruginosa is a bacterium that can cause infection mostly in hospitalised patients. A well-known risk factor is patients who are immunocompromised (Pathak, 2022). Pseudomonas Aeruginosa can be found in drains, water, clinical equipment and soil. It can infect any body part including the blood, gut, open wounds and urinary tract (United Kingdom Health Security Agency, 2018).

Background: In December 2021, following receipt of 4 positive clinical samples for Pseudomonas Aeruginosa within 10 North, Belfast City Hospital, the regional haematology and transplant centre for Northern Ireland, a request was made by the management team to have the water tested. All results were negative. In April 2022 the Infection Prevention and Control team noted a further 3 positive samples and sent all 7 samples for Variable Number Tandem Repeat (VNTR) typing; when the results were recieved all 7 samples had typed with a similar, very unusual VNTR type, WGS ST 168. At this point, an outbreak was declared.

Methods: Following the declaration of the outbreak, the following actions were implemented:
- Weekly patient screening and admission screening
- Mapping of patient journeys
- Enhanced ward cleaning/ review of cleaning practices, particularly water outlets
- Increased water testing and weekly testing of drinking water
- Increased drain cleaning
- Review of ventilation on unit
- Installation of self-flushing showers across the unit
- Environmental sampling/ auditing
- Increased practice audits
- VNTR typing of every positive Pseudomonas sample

The outbreak was reported to the Public Health Agency (PHA) who in turn escalated to the United Kingdom Health Security Agency (UKHSA). Following the introduction of the weekly screening a spike was noted of patients colonised with the same VNTR type. Despite regular environmental, drain and water testing the source of Pseudomonas Aeruginosa could not be located. Patient journeys identifed departments all patients attended. Those areas had water tested but the source remained undetected. Weekly practice audits for hand hygiene were 90-100%; therefore this was eliminated. Liquid mediations were also reviewed; no source as detected there either.

Results: UKHSA noted they had recieved reports of the same VNTR Pseudomonas Aeruginosa type from 12 other centres throughout the United Kingdom (UK) and Republic of Ireland (ROI), however 10 North had the largest number of positive patients. UKHSA declared a national outbreak and visited the ward to learn, as they were so impressed with the comprehensive response initiated by the team. UKHSA asked for numerous products to be tested, all were negative. In total haematology had 27 patients who isolated the same VNTR type. The isolates slowed, then stopped despite not locating the source. No patient came to harm during this outbreak with the majority of clinical isolates being colonisation rather than systemic infection. The 10 North outbreak closed on 22nd June 2023, however the national outbreak continues.

Conclusions: This is an issue of national significance. The action plan instigated by 10 North in response to the outbreak has been recognised by UKHSA as exemplary; therefore the team wish to share best practice with colleagues across UK/ROI to promote safe care to the vulnerable haeamatology population.

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AUDIT ON THE SCREENING AND MANAGEMENT OF LATE AND LONG-TERM CONSEQUENCES OF MYELOMA AND ITS TREATMENT.

K Sweeney[1], P Copeland[1], G Brown[1], A Niblock[1,2]
[1]Haematology department, Antrim Area Hospital, N. Ireland,[2]School of Medicine, Ulster University, N. Ireland

Advances in myeloma treatment have resulted in improved outcomes and prognosis for patients, with some now living with their condition for up to 20 years (National Institute for Health and Care Excellence, 2022). However complications from the disease, alongside toxicity from multiple lines of therapy, further impacted by increasing frailty, comorbidities and the psychosocial impact of living with myeloma, puts patients at risk of specific long-term consequences (Snowden *et al*., 2017).

Research is limited in relation to 'late effects' of myeloma, however there are studies that demonstrate myeloma patients face a wide range of long-term consequences, including cardiovascular and pulmonary toxicity, skeletal related events, renal failure, endocrine and nutritional abnormalities, increased susceptibility to infections, secondary malignancies, and psychosocial concerns.

It is recommended that screening to identify long-term consequences and allow for appropriate management is established. The British Society for Haematology (BSH) published 'Guidelines for screening and management of late and long-term consequences of myeloma and its treatment' (Snowden et al., 2017). However some studies suggest that levels of adherence to such guidance is suboptimal (Thompson *et al*., 2023; George *et al.*, 2020; Giri *et al*., 2019; Olszewski *et al*., 2019; Alemu *et al*., 2017).

An audit tool was developed, which was adapted from an existing tool published by the Royal College of Pathologists (2017), to assess compliance with BSH recommendations within a sample of 30 patients, in the Northern Health and Social Care, Northern Ireland. Following baseline audit, a screening checklist was developed and completed with each patient, to be used as an aide memoire for implementation of the screening recommendations. A re-audit, after three months was carried out to assess the effectiveness of the checklist.

Audit findings demonstrated several areas of good baseline practice: appropriate vaccinations; herpes prophylaxis; education of infection risk, dental assessment; regular bisphosphonate, calcium and vitamin D supplementation; and holistic needs assessments. However, others areas demonstrated gaps in practice including: monitoring of lipids; HBA1C; NT-proBNP; weight, height, BMI; endocrine screening post-transplant; calcium, vitamin D and parathyroid hormone in chronic kidney disease; education regarding secondary malignancy, and offers of a geriatric assessment in individuals aged over 75.

Findings from re-audit, after three months, following implementation of the screening tool, demonstrated that whilst offers of a geriatric assessment for appropriate patients still remains a gap in practice, all other remaining standards demonstrated high levels of compliance to the guidance, now ranging between 80 to 100% compliance.

Gaps were identified in meeting the recommendations for screening and management of long-term consequences of myeloma, however, utilisation of a screening checklist, as an aide memoire, has the potential to significantly increase compliance with recommendations. Early recognition of potentially reversible or manageable abnormities alongside education of patients and professionals on the importance of this key element of myeloma care is crucial to help improve outcomes for these individuals, and should be embedded into routine practice when caring for this patient group.

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Empowering Care: Advanced Nurse Practitioner led Oral Anti-Cancer Medication (OAMs) clinics leading the way in expansion of cancer care.

GW Walpole, Sligo University Hospital, Sligo

Introduction/Background: The use of SACT (systemic anti-cancer treatment) has increased significantly over the past 10yrs, with a variety of new therapeutic treatments which has led to improved cure rates, long term remission rates, better quality of life and longer survival (DOH, NCS 2017-2026). NCRI (2019) reports have projected increase by 51-81% demand for treatments nationally up to 2045.
National Cancer Control Programme recommended a model of care for the delivery of OAMS in 2018 and the need was identified locally. The Advanced Nurse Practitioners (ANP's) are central in the role of delivery of a service that sees a shift from IV SACT to oral drug treatments. This abstract discusses the evolution of an established nurse-led OAM in a Saolta Hospital.

Materials and methods: A service needs analysis was undertaken in 2017, which led to the development of an ANP-led OAM clinic. This was developed in a step-wise approach involving the relevant stakeholders and policy makers to ensure quality, safety and value for the service and patients.
Under agreed guidelines, patients are seen by the same person in a designated clinic at an agreed time which providing continuity of care. While managing the delivery of oral treatment and its complex side effects, the ANP provides holistic care, emotional support and education to patients, while liaising with consultant/nurse colleagues and other allied health professionals.
The OAM nurse led clinic has developed from 4 drug regimens to now encompassing all oral SACT up to 10 regimens, each with varying complexities. This is in line with the shift seen from IV to oral in the haematology setting.

Results: Feedback expressed from the clinic has been very positive, patient report feeling safe and supported, they enjoy the continuity of care received under this type of clinic, reports of time-saving for patients means greater quality of life overall. In liaising with the larger Haematology service improved adherence and early detection of relapse have been observed.
The complexities of running an OAM clinic, are not without challenge. The clinic has grown 4 fold in numbers. No additional resources have been put in place which restricts the addition of new patients. Additionally adding to this burden is a dearth of space and administrative support which provides a demanding environment for the haematology staff and patient which despite its demand has further potential to grow.

Conclusion: OAMs have the same potential for risk as parenteral SACT in terms of treatment-related toxicities and potential for serious medication errors leading to patient harm.
The growth of oral anti-cancer medications and the evolution of ANP led clinics for haematology patients is a positive step forward in enhancing patient care and provides a cost effective, holistic, patient centred service. The provision of necessary additional supports is required and will further enhance this service.

The future of oral anti-cancer medicines and ANP led clinics is promising. As drug therapies expand and increase, ANP's will continue to play a pivotal role in managing this patient cohort.