CLL ALLIANCE INAUGURAL SCIENTIFIC MEETING 2025

Strand Hotel, Limerick
Friday 7th February 2025

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HAEMATOLOGY ASSOCIATION OF IRELAND

Contents

Inaugural CLL Alliance Conference

Hosted by Pharmatek Conferences Ltd

Date: Friday, 7th February 2025

Venue: Strand Hotel, Limerick

(CPD Pending)

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	Nursing management of rapid dose escalation of Venetoclax in CLL patients – A patient Case Study Melissa Martin, CNS, St James's Hospital, Dublin
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	Novel drug combinations strategies for chronic lymphocytic leukaemia Julie David, John Durkan Leukaemia Laboratories, Trinity Translational Medicine Institute
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16:30	**Tea/Coffee & Meet the Sponsors and Poster Walk/Adjudication**
17:00	**Keynote Speaker:** ***Introduced by Prof. Ruth Clifford*** ***The Changing Landscape of CLL Therapy*** **Prof Susan O' Brien**, Haematologist, UCI Medical Centre, California
17:45	**Closing Comments**

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Guest Speaker Bios

Wen Yuen Lim

Wen Yuen Lim (known as Yen Lim) is the lead haematology pharmacist and deputy team manager of the cancer pharmacy team in Oxford University Hospitals NHS Foundation Trust in Oxford. She has been part of the CLL multidisciplinary team as a prescribing pharmacist for the past 5 years. Her other specialist interest areas are TTP, myeloid disorders, CAR-T therapies and health economics. Yen has recently completed an MSc in Precision Cancer Medicine with the University of Oxford.

Anita Dowling

Anita graduated from DIT Kevin Street with a Bachelor of Biomedical Science in 2009 and her Master's in Clinical Laboratory Science degree in 2012.
She began her career in St. James Hospital where she worked in both routine & specialised laboratory areas. She also did a sabbatical in the lymphoma section of CMD before moving on to St. Vincent's University Hospital in 2018 as a Specialist Medical Scientist setting up the Immunophenotyping laboratory.

Jan Rynne

In 2011, at the age of 39, Jan was diagnosed with CLL.Jan had an opportunity to participate in a clinical trial in the UK for a novel therapy in 2014 and is presently doing well on continuous treatment. In 2017, she and her husband Michael founded Chronic Lymphocytic Leukaemia Ireland, a patient-led advocacy group and registered charity that aims to support others in Ireland impacted by a diagnosis of CLL. Jan sits as the chairperson of the CLL Ireland trustee board, and manages operations for CLL Ireland in a voluntary capacity. More broadly, Jan is an active member of Precision Oncology Ireland's Governance Committee, the overall oversight board for the POI programme and a graduate of IPPOSIS's patient education programme. In 2023, Jan graduated with a first-class honours degree in the Health and Society programme from Dublin City University. Jan now works with CLL Advocates Network, a global umbrella group representing International CLL Patient Advocacy Groups ,in a project and stakeholder relations role. Jan is passionate about patient advocacy and believes that collaboration, connection and communication can affect positive change for CLL patients.

Ferran Nadeu

Dr. Ferran Nadeu did a bachelor in Biotechnology (University of Barcelona), a master of science in Bioiformatics (Pompeu Frabra University), and a PhD in Biomedicine (University of Barcelona, Dr. Elías Campo lab). He is currently a post-doctoral researcher at the Fundació Recerca Clínic Barcelona-Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS, Barcelona). He has published 84 articles in top journals in the field of hematology and cancer genomics including Nature Medicine, Nature Genetics, Blood, Nature Communications, among others (times cited: 2,877; H-index: 28). Dr. Nadeu has participated as invited speaker, oral presenter, and poster presenter in national and international meetings, has received 14 national and international awards for young investigators, and his research has received the financial support of the EHA, AACR, and Lady Tata Memorial Trust, among others. His research focuses on understanding the (immuno)genomic determinants of leukemia and lymphoma initiation, diversification, and progression before and after therapy through the use of novel methodologies and bioinformatic tools.

Enhancing Access to Dermatology Care for CLL Patients: A Multidisciplinary Approach Using Clinical Photography and Advanced Nurse Practitioner Collaboration.

Hackett F[1]. , Clifford, R.[1], O'Leary H.[1], Ahmad, K.[2], Power E.[2]
[1]Haematology, Cancer Services, UHL
[2] Dermatology, UHL

Background

Individuals with chronic lymphocytic leukaemia (CLL) are at a heightened risk of secondary malignancies, particularly melanoma and non-melanoma skin cancers, which are already common in the general population. Contributing risk factors for CLL patients may also include the use of immunosuppressive medications, fair skin, frequent recreational or occupational sun exposure, and advanced age. Standard care incorporates patient education, opportunistic and focused skin cancer screenings, and urgent dermatological evaluations for suspicious lesions to facilitate diagnosis and improve prognostic outcomes. However, timely access to dermatology services was a challenge, necessitating targeted interventions.

Aim:

To enhance access to dermatology care for CLL patients through multidisciplinary collaboration and advanced nurse practitioner (ANP) co-ordination.

Methods:

Haematology and dermatology ANPs collaborated to share clinical expertise, identify challenges, and establish best practice. The haematology ANP undertook training in the dermatology department and subsequently integrated focused skin cancer screening into routine clinical assessment. A streamlined referral pathway was created, incorporating email referrals from the haematology ANP, with clinical photographs of suspicious skin lesions. Upon receipt, dermatology consultants reviewed and triaged the referrals based on clinical urgency. All referred patients were scheduled for dermatology clinic appointments, with expedited prioritisation for those presenting with high-risk lesions to minimise delays in care.

Results

Twelve haematology referrals received priority dermatology appointments leading to diagnosis of actinic keratosis, non-melanoma skin cancer and malignant melanoma. These cases were managed with timely interventions, including cryotherapy, surgical excision and radiotherapy.

Discussion

Clinical photography as a triage tool has proven effective in enhancing care for CLL patients requiring urgent dermatology evaluation, improving access to dermatology care, streamlining referrals and ensuring prompt identification and prioritisation of high-risk cases. Similar approaches in the UK demonstrate the value of such innovations in diagnosing and managing skin cancers effectively.

Conclusion

This collaboration between ANPs in hematology and dermatology has successfully enhanced access to urgent dermatological care for CLL patients. This demonstrates the value of multidisciplinary partnerships in addressing care gaps, improving patient outcomes, and provides a model for similar innovations in other specialties.

“Nursing management of rapid dose escalation of Venetoclax in CLL patients – A patient case study.”

M. Martin, C. Waldron, E. Vandenberghe
St James’s Hospital, Dublin

We present a case of a 66-year-old male with standard risk CLL with progressive lymphadenopathy and a lymphocyte doubling time of less than six-months requiring treatment after a long period of active surveillance with the fixed duration Venetoclax-Obinutuzumab regimen. This gentleman and his partner underwent extensive nurse-led counselling on the potential risks and benefits of the regimen as well as on the two different modes of venetoclax administration i.e., as a slow ramp-up in the outpatient setting (approx. 6 weeks) or as a rapidly ramped-up as an inpatient (approx. 10 days).
This patient was very anxious about starting treatment and the notion of accelerating the dosing of venetoclax was particularly worrisome for him, moreover he had never been an inpatient in hospital in his adult life. The nurse-led counselling sessions were critical for him in his decision making and also to allay fears regarding the rapid venetoclax ramp-up. The emotional support provided a space for him to express his concerns and freely ask questions. Form a practical stand-point it was important that he knew the steps involved in treatment as this regimen can be confusing for patients that are not adequately counselled.

He opted to have venetoclax ramped-up rapidly as an inpatient. He remained an inpatient for 12 days by which time he had to reached the full (400mg) dose of venetoclax. He remained well through-out and was reviewed by a haematology CNS throughout his inpatient stay. He was discharged on venetoclax 400mg and had completed the first dose of Obinutuzumab as an inpatient. He did not experience TLS or any other complications during his inpatient stay.

The haematology unit in St James’s hospital has adopted a strategy of inpatient rapid venetoclax dose-escalation since 2022. Venetoclax doses are escalated every 48 hours if tolerated and tumour-lysis risk is managed with continuous monitoring, IV fluids, rasburicase and 6 hourly TLS bloods. All of the patients that have undergone this regimen have been treated successfully with high satisfaction levels reported by patients.

Case Study: CLL/SLL associated renal disease, rapid venetoclax escalation and TLS prevention

Sam Grennan*, David Parfrey*, Elisabeth Vandenberghe*†
* Department of Haematology, St James's Hospital, Dublin, Ireland. † School of Medicine, Trinity College Dublin, Ireland

Renal insufficiency occurs in 7.5% of patients with Chronic-Lymphocytic Leukaemia (CLL) at diagnosis and can be caused by immune-mediated glomerulonephritis, interstitial nephritis, direct tumour infiltration, ureteric obstruction and treatment-related tumour lysis syndrome (TLS). I am presenting a patient with CLL-associated interstitial nephritis treated with steroids and Venetoclax-Obinutuzumab (Ven-O) therapy using a rapid dose-escalation.

A 69-year-old gentleman presented with widespread bulky lymphadenopathy. Core lymph node biopsy and bone marrow assessment was consistent with small lymphocytic lymphoma (CLL/SLL), Binet stage B. His prognostic risk assessment confirmed CD38+, CD49d+, unmutated IGHV, unmutated TP53 and FISH analysis demonstrated del (11q). Co-morbidities included ischaemic heart disease, hypertension and dyslipidaemia.

The patient was observed for 9 months, but progressed and developed an acute kidney injury (AKI). A renal biopsy confirmed severe tubulointerstitial nephritis and multiple small aggregates of CLL cells. The AKI was attributed to immune-mediated CLL-associated nephritis and treated with prednisolone 100mg for 10 days with some renal function recovery (eGFR 17ml/min to eGFR 48ml/min). The CLL/SLL was treated with venetoclax induction, with dose escalation every 48 hours unless biochemical TLS developed in which case dose escalation was delayed until biochemistry returned to baseline. TLS risk was mitigated by aggressive intravenous hydration and rasburicase. The patient achieved the target dose of 400mg in 17 days, despite an 8-day period where venetoclax was held due to a temporary worsening of renal function with an associated rise in serum phosphate and coexistent COVID infection. This occurred at dose level 200mg but did not meet the laboratory TLS *Howard* criteria as the remainder of TLS biochemical markers were normal.

This outcome was consistent with a cohort of 16 patients admitted to our hospital for a similar rapid venetoclax inpatient dose-escalation. All achieved target-dose venetoclax 400mg with a median inpatient stay of 10.5 days. No patients in the cohort had TLS by *Howard* criteria, although 4 (25%), including our patient, demonstrated laboratory TLS by *Cairo-Bishop* criteria.

Ultimately, the patient achieved MRD-negativity after Ven-O treatment but has ongoing chronic kidney disease (stage 3A) caused by CLL associated immune dysfunction which emphasises the importance of recognising CLL-associated renal disease.

Richter's Transformation: BiTEs to the Rescue?

Ellen O'Rourke (1), Grainne Young (1), Ezzat Elhassadi (1)
1 Haematology Dept, University Hospital Waterford
Ellen O'Rourke, 1st year Haematology SpR, University Hospital Waterford

Richter's Transformation (RT) describes the abrupt progression of chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) into an aggressive high-grade lymphoma. This transformation is frequently linked to high-risk genetic abnormalities and resistance to chemoimmunotherapy, resulting in a poor prognosis. In clonally related RT, responses to conventional chemotherapy are often transient.

A 76-year-old male presented with inguinal lymphadenopathy and constitutional symptoms. Lymph node biopsy confirmed SLL with a proliferation index of 10–15% and no TP53 mutation. Bone marrow flow cytometry identified a minor population of CD5/CD19 kappa-restricted B cells, and fluorescence in situ hybridization (FISH) revealed no 11q, 13q, or 17p deletions. Persistent B symptoms prompted the initiation of continuous Bruton's tyrosine kinase inhibitor (BTKi) therapy during the COVID-19 pandemic, resulting in complete resolution of lymphadenopathy and symptoms.

Three years later, the patient presented with rapidly enlarging adenopathy and thrombocytopenia. Biopsy confirmed RT to diffuse large B-cell lymphoma (DLBCL) without TP53 mutation, and molecular analysis demonstrated a clonal immunoglobulin gene rearrangement related to original SLL biopsy. He received six cycles of R-mini-CHOP. While interim imaging suggested complete response, end-of-treatment PET scans revealed Deauville 4 residual disease, necessitating consolidative radiotherapy. The patient achieved a six-month remission before relapse, with biopsy again confirming RT without TP53 mutation. Progression occurred despite treatment with Obinutuzumab-Venetoclax and subsequent escalation to Rituximab-Polatuzumab-Bendamustine, leading to obstructive uropathy due to bulky intra-abdominal disease.

Compassionate access to Epcoritamab, a CD3xCD20 bispecific T-cell engager (BiTE), was granted. After dose escalation, the patient experienced resolution of B symptoms and a reduction in adenopathy, with re-staging imaging pending.

This case underscores the aggressive course of RT and the challenges in achieving durable responses. Prognosis is particularly poor for clonally related RT, with treatment strategies often extrapolated from other B-cell malignancies. While allogeneic transplantation and Chimeric Antigen Receptor (CAR) T-cell therapy offer potential for long-term survival, their use is limited. BiTEs, such as Epcoritamab, provide a promising targeted, less toxic alternative. Results from the EPCORE™ CLL-1 trial demonstrate significant efficacy in RT, particularly in untreated cases, suggesting early use could obviate the need for toxic conventional chemotherapy.

Audit of Immunoglobulin levels in Altnagelvin Area Hospital patient CLL cohort: compliance with BSH guidance for the treatment of chronic lymphocytic leukaemia (published 21st March 2022)

Dr Adam Waterworth[1], Dr Feargal McNichol[1], Dr Patrick Elder[1], CNS Sylvia Cole[1], Dr Conal McConville[1]
Department of Haematology, Altnagelvin Area Hospital, Northern Ireland

Introduction

Hypogammaglobinaemia is a commonly seen phenomenon in patients with chronic lymphocytic leukaemia (CLL). The British Society of Haematology (BSH) guidance for the treatment of CLL was updated in 2022. In this audit we analysed our local department's compliance to the recommendations regarding Immunoglobulins.

Methods

Retrospective data collection from electronic care record on all patients diagnosed with CLL, since publication of the 2022 BSH guidance. This data was analysed with the BSH criteria for consideration of immunoglobulin replacement therapy : Immunoglobulin (Ig) replacement therapy is advised for patients who: (1) suffer recurrent or severe bacterial infections despite six months of continuous oral antibiotic therapy; (2) have a total IgG <4 g/l; and (3) have documented failure to respond to polysaccharide vaccine challenge.

Results

Of our cohort of 49 patients, in the final analysis, 95.9% of patients (47/49) had their baseline IgG levels checked. The median and mean IgG levels were 9.65 g/L and 9.51 g/L. The median igG levels of patients on treatment were 6.20 g/L, and for patients not yet received treatment 10.18 g/L. 2 patients had an IgG level less than 4g/L. None of the patients have received immunoglobulin prophylaxis.

Discussion

It is pleasing that the great majority of patients had their baseline immunoglobulin levels checked. The median and mean total IgG levels were within our laboratories normal reference range (6-16 g/L). The median IgG level was seen to be lower in patients on treatment than those who have not yet required therapy. Of the 2 patients with IgG levels less than 4 g/L, one patient had a history of severe bacterial infection which was not recurrent. No patients had a documented pneumococcal infection or antibody titre after vaccination.

Effective Management of Disease Relapse in TP53-Mutated Chronic Lymphocytic Leukemia.

Ali Al-Baghdadi, Ruth Clifford
Department of Haematology University Hospital Limerick

Background:

Chronic lymphocytic leukemia (CLL) is a heterogeneous malignancy often complicated by genetic abnormalities, including TP53 mutations, which are linked to a poor prognosis. Targeted therapies like Bruton's Tyrosine Kinase inhibitors (BTKi) and BCL-2 inhibitors have significantly improved outcomes for patients with relapsed and refractory CLL. This report discusses a case of TP53-mutated CLL, illustrating disease progression following BTKi therapy and the subsequent effective management with BCL-2 inhibition and an anti-CD20 monoclonal antibody.

Case Presentation:

A 77-year-old male was diagnosed with Stage A CLL with a TP53 mutation in October 2017. His initial management involved active surveillance until progression to Stage C in August 2018, marked by severe anaemia and lymphadenopathy. He was treated with continuous ibrutinib, achieving complete remission until September 2023. In July 2023, after losing response to ibrutinib, he was switched to Acalabrutinib. While there was an initial reduction in lymphocytosis, complications arose by September 2024, including anaemia, thrombocytopenia, and the discovery of a new BTK mutation, leading to resistance to both therapies. He experienced neutropenic sepsis and life threating fungal pneumonia, necessitating 6 weeks of hospitalization. This highlighted the need for antifungal prophylaxis in neutropenic patients. Subsequently, he was transitioned to Venetoclax combined with Obinutuzumab, resulting in a complete response. Antifungal prophylaxis was discontinued once neutropenia resolved with no evidence of disease progression .The patient has since remained on 400 mg Venetoclax, maintaining a good quality of life without significant treatment-related toxicities.

Discussion:

This case underscores the complexities of managing TP53-mutated CLL, particularly regarding treatment resistance. Molecular testing for BTK mutations can help guide therapy. Continuous BTKi is the recommended treatment for patients with high risk, TP53 disrupted CLL .Current evidence suggests continued, not fixed-duration, BCL-2 inhibition with Venetoclax may be a reasonable alternative option for these patients[1].

Conclusion:

This case underscores the importance of genetic and molecular testing in CLL to identify mutations that inform therapeutic decisions. It also illustrates an increasing number of for this high risk group but this requires further investigation in clinical trials.

A complex case of Atypical CLL and CHAD

James Dillon, Elisabeth Vandenberghe, Melissa Martin, Carmel Waldron
St. James's Hospital

In Feb 2022, a 73-year-old male was referred with lymphocytosis (10.8 x 10^9/L), mild neutropenia (1.5 x 10^9/L) and macrocytosis (MCV 101 fl). His only co-morbidity was dyslipidaemia. His family history was significant for VTE. He had a normal examination.

Peripheral blood morphology confirmed mature small lymphocytes with clumped chromatin and a rim of cytoplasm consistent with CLL. These cells were kappa restricted and expressed CD5, CD20 (MFI 32.9), CD49d, CD38, ROR1, CD200 and negative for CD23, CD43, sIgM and CD79b. Due to CD23 negativity and strong CD20 expression he was classified as having atypical CLL. FISH confirmed the presence of trisomy 12, while t(11:14) was not detected by PCR or FISH.

A CT TAP, performed 3 months later, identified multiple enlarged lymph nodes (up to 1.8cm) and hyperenhancement within the left femoral vein, was confirmed to be an extensive femoral thrombus by doppler. He was commenced on therapeutic anticoagulation.

With worsening cytopenia, a bone marrow examination confirmed a markedly hypercellular marrow (80%) due to an extensive infiltration by CLL. Dysplasia was not reported and a myeloid NGS out-ruled pathogenic myeloid variants.

By October 2024 treatment was indicated due progressive cytopenia - WCC 13.3, neutrophils 0.9, lymphocytes 11.8, haemoglobin 11.5, platelets 96. A molecular work-up confirmed: Unmutated TP53, unmutated IgVH (no stereotyped subset), unchanged FISH (trisomy 12) and a karyotype identified: 48XY, +12, del (14)(q21q32), +18.

Two days following the commencement of Venetoclax-Obinutuzumab he was admitted with worsening anaemia (Hb 11.2g/l to 7.2g/) due to severe haemolysis secondary to cold agglutinins - hyperbilirubinaemia, C3b/C3d+++, MCHC >300. He was transfused via a blood warmer while further doses of Obinutuzumab were held. He completed a rapid venetoclax ramp-up which was followed by normalisation of Haemoglobin, neutrophils and platelets (WCC 5.3, neutrophils 4.0, lymphocytes 0.3, haemoglobin 14.2, platelets 227)

This is a complex case of atypical CLL with significant karyotype findings and features of CHAD.

A Tale of Two Clones - TP53-Mutated CLL pre and post Allogeneic Stem Cell Transplant

Conal Houstoun[1], Kanthi Perera[2], Elisabeth Vandenberghe[1]
1. Department of Haematology, St James's Hospital
2. Department of Haematology, Midland Regional Hospital Tullamore

Case:

Our patient was initially diagnosed with CLL with unmutated IGHV in 2009, aged 50. She was treated with FCR in 2010. She developed a NOTCH1-associated Hodgkins Richter transformation in 2012 and was treated with 6 cycles of ABVD, to complete remission.
In 2014 the CLL relapsed with biopsy-proven nodal disease. Progression of this disease was treated with ibrutinib in 2016. In 2019 she had further disease progression with lymphadenopathy and thrombocytopenia. She was treated with single agent venetoclax. A TP53 deletion was detected at VAF 54%.

In August 2020, she underwent a matched sibling Fludarabine/Busulfan/ATG Allogeneic stem cell transplant. Her acute transplant course was uncomplicated. However she required donor lymphocyte infusions for mixed chimerism.

Her MRD analysis was positive in May 2021. She was commenced on venetoclax with the intention of completing 2 years of therapy as per local policy. Her MRD became negative in February 2022, and she developed full donor chimerism. Venetoclax was stopped in Jan 2023 during an admission with sepsis. MRD remained negative.

Disease relapsed with bulky lymphadenopathy in April 2024. Lymphocyte count was normal. Bone marrow showed an 80-90% infiltrate of CLL. The TP53 variant c.1024C>T; p.Arg342Ter was detected with a VAF of 39%. This clone was present at 1% in 2020, and the original dominant TP53 clone was not detected.

Obinutuzumab and venetoclax was commenced in May 2024. Bone marrow in October 2024 showed CLL burden remained 70-80%, and she had developed a complex karyotype.

Our patient's original CLL was treated with 3 years of BTKI with subsequent progression. However, due to the post-transplant CLL having a different TP53 clone, we theorised that the disease may have a distinct biological profile and be sensitive to BTKIs. She was started on Zanubrutinib in Jan 2025. She has had a lymphocyte flair to 35 x109/L, which we feel may be an encouraging sign of some disease response. BTKI mutation analysis from 2020 and 2024 is pending. Our options from here include compassionate access pirtobrutinib or a second stem cell transplant, but this is dependent on patient fitness.

Stereotyped subset 2 (IGHV3-21/IGLV3-21) display a shorter TTFT compared to non–subset #2/IGHV3-21

Andrew Hindley[1], Julie McGimpsey[1], Clare Crean[1], Sarah Lawless[2], David Donaldson[2], Mark Catherwood[1]
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[2] Haematology Department, Belfast City Hospital, Belfast Health and Social Care Trust, Northern Ireland

Approximately 40% of all patients with chronic lymphocytic leukaemia (CLL) express stereotyped B-cell receptor immunoglobulins (BcR IG) and can be assigned to distinct subsets, each with a particular BcR IG.

Stereotyped subset 2 (IGHV3-21/IGLV3-21, ~3% of all cases of CLL) is an aggressive disease variant, irrespective of the somatic hypermutation (SHM) status of the clonotypic IGHV gene.
In this study we assessed the clinical value of subset 2 BcR IG in a real world cohort compared to non–subset #2/IGHV3-21.

Within our series, 102/1479 cases (6.9%) expressed IGHV3-21 BcR IG. Of these, 47(46%) were classified as subset #2 as they shared homologous VH CDR3 sequences of identical length.
No differences were observed between subset#2 vs non–subset #2/IGHV3-21 cases regarding age at diagnosis and gender distribution within the cohort.

Within subset #2, IGHV-mutated cases predominated, whereas non–subset #2/IGHV3-21 was enriched for IGHV-unmutated cases ($p<0.05$). Subset #2 cases exhibited significantly shorter time-to-first-treatment (TTFT) compared with non–subset #2/IGHV3-21 (21 vs 38 months ($p<0.05$).

In conclusion, we demonstrate that subset#2 patients have a shorter TTFT regardless of IGHV status compared to non–subset #2/IGHV3-21. Therefore, IGHV3-21 CLL should not be considered a homogeneous entity and the concept of stratifying CLL based of the features of the BcR IG determined by subset assignment may be more important in determining disease biology than IGHV mutational status in certain cases.

Investigation of Monocyte Subsets and Monocytic Trends in Chronic Lymphocytic Leukaemia Diagnosis

Michelle Nolan, Maureen O'Donnell
Department of Haematology, University Hospital Galway

Chronic Lymphocytic Leukaemia (CLL) is a prevalent lymphoproliferative disease with its pathophysiology thought to be strongly associated with its tumour microenvironment. Monocytes, immune cells of the tumour microenvironment, can be classified into at least three unique entities determined by their immunophenotype: Classical Monocytes (CM) (CD14++CD16−), Intermediate Monocytes (IM) (CD14++CD16+) and Non-Classical Monocytes (NCM) ($CD14^{dim}$CD16+).

19 anonymised peripheral blood samples with clonal B-lymphocytic populations having phenotypes consistent with CLL were analysed to identify the distribution of CMs, IMs and NCMs in their monocyte population by flow cytometry. These were compared to 10 normal controls without clonal populations. The median fluorescence intensity (MFI) of CD14, CD16, CD64 and HLA-DR was assessed on total monocytes, and CD14 and CD16 MFIs were calculated in monocyte subgroups and neutrophils.

CLL group patients had a statistically significant decrease in CMs ($p<0.05$) and increased NCMs ($p<0.05$) compared to normal controls. Downregulation of CD16 on total monocytes, CMs and IMs was noted along with upregulation of CD14 on total monocytes, all monocyte subgroups and neutrophils compared to normal controls.

A notable shift in subset distribution was seen, consistent with previous studies. Increased IMs and NCMs illustrates the immunological processes involved in CLL and overexpression of CD14 was also noted on neutrophils of the CLL group, reiterating the involvement of tumour microenvironment in CLL disease. As well as quantitative differences in monocyte subgroups, qualitative differences were also seen with upregulation of CD14 and downregulation of CD16 on cells - an area which has been scarcely reviewed in CLL previously but holding great potential clinical value.

A case of Richter's transformation in a diagnosed CLL patient

Isabelle Delachapelle, Senior Medical Scientist, Haematology Laboratory
Immunophenotyping, St James Hospital

An elderly lady presented with weight loss, night sweats and overwhelming fatigue. Her background is significant for CLL managed with active surveillance for 7 years. 18 months prior to this presented, she was diagnosed with high-grade transformation (Richter's syndrome and achieved remission with rituximab and ibrutinib combination treatment. Three months prior to presentation she was in clinical remission on zanubrutinib.

At presentation, an FBC counts were preserved (Hb of 12.6 g/dl, platelets 137 x 10^9/L and WCC of 10.7 x 10^9/L). A bone marrow aspirate revealed two different lymphocytes population: small mature lymphocytes (17%) and larger cells with nucleoli and cytoplasmic vacuolation (12%) (images will be presented).

The immunophenotyping analysis confirmed that both populations were mature B lymphocytes however, they differ in their size and immunophenotype (dot plots will be presented).
The first population (15% of of B cells) were small B cells (CD19+, CD20+w) displayed the same immunophenotype as at CLL diagnosis (CD5+, CD19 +, CD23+, CD79b-, IgM-, CD43+, CD200+ and kappa light chain restricted).

The second population (85% of B cells) was composed by larger cells (higher on the FSc vs SSc graph) and displayed a CD5-/CD10- DBLCL immunophenotype (CD19+w, CD20+s,) consistent with marrow-based Richter's transformation. The trephine histology and immunohistochemistry confirmed the diagnosis.

This case study highlights the importance of the provision of clinical details and close integration with morphology to guide identification of abnormal populations. Secondly, the case illustrates the necessity of to ensuring all cell population are identified in analysis.

All-Island Characterisation of CLL – Limerick Experience of eHealth Hub Project

Nkemdilim Anyaoku[1,2,3], Elzbieta KoronaAnsari[1], Michelle O'Sullivan[1], Hilary O' Leary[1], Mary Ryan[1], Aedin Culhane[2,3], Ruth Clifford[1,2,3]

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KEYWORDS: Chronic Lymphocytic Leukaemia (CLL), Real-World Data (RWD), Electronic Health Records (EHR), Health Information Systems (HIS), Data standards, Haematological cancers.

Introduction

The All-Ireland Characterisation of Blood Cancers project led by the eHealth-Hub for Cancer, in collaboration with Blood Cancer Network Ireland (BCNI), seeks to streamline data harmonisation across the island. This project is funded by the Higher Education Authority to train the next-generation of cancer data scientists. The objectives are - to implement a data collection system for national and international real-world data (RWD) studies, provide accurate data for clinical trial feasibilities, and link data with biobanks for pre-clinical research. In Phase I, five cancer centres are involved in data collection for CLL, AML and MM. University Hospital Limerick will lead on CLL, undertaking a pilot that will be expanded to include all ten cancer centres on the island.

Methods

A data dictionary was developed to represent 95 prerequisite data fields, detailing four categories - diagnosis, therapy, supportive care and clinical reviews. The data standards were defined and validated to include ontologies (SNOMED, LOINC, ICD-10).

A relational-database schema was designed on MicrosoftAccess consisting of 20 tables using hospital chart number and biobank-ID as primary keys to collate data from iLab, MedOnc and Integrated Patient Management System (IPMS).

Data quality was interrogated by audits using a sample size of 15 random patients verified through paper clinic files, MedOnc and iLab.

Results

174 CLL patients diagnosed before 01 January 2023 have been characterised at the time of reporting. General lab reports and demographics have the highest level of completion at 100% and 86%, respectively. Incompleteness of data was noted for data not stored on electronic systems.

Gap analysis identified key data-fields that were consistently omitted. Consequently, an electronic case report form (eCRF) was implemented to retrieve data on CLL patients, which feeds directly into the database.

Conclusion

Execution of these beneficial and robust RWD processes is limited by the absence of an interactive multidisciplinary electronic health system causing significant gaps in treatment status, genomics reports and supportive care that hamper the quality of longitudinal research. Hence, synchronisation of data from EHRs and CLL-eCRFs presents a viable opportunity to develop and contribute RWD as a standard to optimise clinical outcomes through pragmatic data analytics.

Novel drug combinations strategies for chronic lymphocytic leukaemia

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Introduction

Chronic lymphocytic leukaemia (CLL) is an incurable B-cell malignancy, accounting for over one-third of all leukaemia cases in the developed world, with Ireland reporting among the highest incidence rates globally. CLL cells interact intricately with the tumour microenvironment through the B-cell receptor (BCR) signaling pathway, which has driven the development of therapies targeting critical components of this pathway, such as Bruton's tyrosine kinase (BTK).

Despite the significant advancements achieved with these targeted therapies, including BTK inhibitors, challenges persist. Resistance to therapy, off-target effects, and low rates of complete response underscore the need for novel combination treatment strategies. As CLL cells exhibit characteristic cytoskeletal abnormalities, with tubulin closely associated with BCR-mediated signaling molecules, one such strategy is to investigate the use of microtubule-targeting agents in combination with BTK inhibitors.

This preliminary study explores a potential therapeutic approach combining the BTK inhibitor ibrutinib with the MTA vincristine, aiming to leverage their complementary mechanisms of action to improve treatment outcomes in CLL.

Materials & Methods

The cytotoxic effect of ibrutinib and vincristine on a panel of CLL cell lines were determined using MTT proliferation assays. Drug-induced modulation of the cell cycle was assessed by flow cytometry following propidium iodide staining. The levels of apoptosis induced by these agents individually and in combination was determined by annexin-V/propidium iodide staining and flow cytometry in cell lines and in *ex-vivo* patient-derived CLL cells in co-culture with the human stromal cell line HS5. Drug synergism was determined using CompuSyn software.

Results

CLL cell lines and patient-derived samples demonstrated sensitivity to both ibrutinib and vincristine. Combination treatments with ibrutinib and vincristine resulted in significantly greater apoptosis compared to either agent alone across all tested concentrations and treatment durations in CLL cell lines, exhibiting a synergistic effect in three cell lines. Preliminary findings suggest that vincristine enhances ibrutinib-induced apoptosis in patient-derived CLL cells, indicating a potential for improved therapeutic efficacy with this combination approach.

Conclusion

This work demonstrates that the use of ibrutinib in combination with the microtubule targeting agents may show promise as a novel treatment strategy in CLL.

Analysis of the single cell transcriptome of peripheral blood monocytes in Chronic Lymphocytic Leukaemia to gain insight into innate immunity

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Background: Chronic lymphocytic leukaemia (CLL) is a haematological cancer characterised by the uncontrolled proliferation of CD5+ B lymphocytes. Up to 60% of patients display compromised immune function, leading to frequent and sometimes fatal infections. Monocytes are innate immune cells with important roles in fighting infection. Recent single cell sequencing studies have postulated that there are 5-6 monocyte subtypes in cancer patients, each with different roles. Our aim in this study is to determine the distribution of these newly defined monocyte subsets in CLL and if differential gene expression can provide insight into potential defects in monocyte function.

Method: Two single cell RNA-seq (scRNA-seq) datasets of peripheral blood monocytes (PBMCs) in CLL pre-treatment patients, GEO accession codes: GSE161610 (n=5) and GSE111014 (n=4), and one scRNA-seq dataset from healthy patients, pbmc3k (n=9), were analysed using Seurat package in R version 4.3.3. First, data was clustered to identify which immune cells were present in each dataset. Then, the monocytes were identified and mapped onto the MoMacVerse to annotate these into the monocyte subgroups. Lastly, differential expression analysis was conducted to find key markers that could distinguish each subset.

Results: In CLL, monocyte frequency was around 5-10%, like healthy individuals. The analysis revealed four distinct monocyte subsets, the three traditional ones (classical, non-classical and intermediate), but also IL-1B monocyte subset, that notably was present in some CLL patients and absent in healthy individuals. The differential expression analysis revealed enrichment of HLA genes in the intermediate subset, genes involved in immunity such as S100A8, S100A9 and LYN, genes involved in innate immune response in non-classical monocytes such as IFITM2, SIGLEC10 and HLA-E and genes involved in inflammation in IL1B monocyte subset such as IL1B, CCL3 and CCL4.

Conclusion: We identified a panel of key markers that can distinguish the monocyte subsets, and we aim to evaluate, through flow cytometry, the monocyte population phenotype in CLL and whether presence of IL1B monocytes may have implications for the ability of patients to fight infection. This research could provide valuable insights into the mechanisms underlying immune suppression in CLL and potentially give rise to improved patient outcomes.
This project is funded by the All-Ireland Cancer Research Institute (AICRI).

(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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CLL Transformation to Richter's Syndrome.

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Case Study:

In 2011, a 70 year old male presented with a lymphocytosis of 26.1 x10^9/L. Blood film review showed an atypical lymphocytosis with prominent smear cells. Peripheral blood flow cytometry revealed a $CD5^+$, $CD19^+$, $CD23^+$, $FMC7^-$ monoclonal B-cell proliferation that was $Lambda^{+\ weak}$ light chain restricted confirming a diagnosis of B-CLL. These cells were also $CD38^+$. Cytogenetics found a 13q deletion. Initial treatment was watch and wait.

In 2014, due to a rising lymphocyte count and worsening pancytopenia a bone marrow biopsy and aspirate were taken. The biopsy revealed extensive effacement of marrow with 85% of B-cells consistent with marrow involvement by CLL. FISH showed no evidence of adverse CLL markers ATM (11q22.3) or TP53 (17p13.1). The bone marrow immunophenotype was the same as the diagnostic peripheral blood sample in 2011. Treatment with Rituximab and Bendamustine commenced.

In 2019, the lymphocyte count progressed resulting in a drop in haemoglobin and a positive Coombs test with no evidence of haemolysis. The patient had been treated with Ibrutinib for 4 years but due to a history of chronic sinus bradycardia 3 cycles of Chlorambucil were given instead.

In 2024, the patient presented to ED in SVUH with SOB and pancytopenia but with a normal lymphocyte count. Bone marrow aspirate immunophenotyping revealed a $CD5^+$, $CD19^+$, $CD38^+$ monoclonal proliferation however, these B-cells demonstrated weak CD45 expression and had high side scatter properties which was suspicious of a potential Richter's transformation. The CD38 expression had also increased in intensity from the diagnostic flow report in 2011. The bone marrow biopsy demonstrated an extensive infiltrate of large mononuclear atypical lymphoid cells with rare binucleate forms concerning of Richter's Syndrome. Molecular and cytogenetic analysis subsequently showed a TP53 mutation (variant c.716A>6; p.Asn239Thr in Exon 7 at a variant allele frequency of 34%) and an ATM (11q22.3) abnormality.

Conclusion: This case demonstrates the prognostic significance of CD38 expression by flow cytometry and how the antigen is associated with an increased risk of CLL transformation and lower sensitivity to treatment responses.

Flow Cytometry Case

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Abstract

I wish to present a case of bimodal CD49d expression in a patient with newly diagnosed CLL.
CD49d is now accepted as being the most reliable immunophenotypic marker in CLL and is associated with high-risk molecular features, reduced times to first treatment, shortened survival times and inferior responses to BTKis.

The standard threshold for positivity in immunophenotyping is ≥30%, however in cases with a bimodal distribution, a subpopulation of CD49 + cells are also clinically relevant and independently associated with poor outcomes and an aggressive clinical course.

We present a 75-year-old male who was referred by his GP with a mild lymphocytosis (10.1 X 10^9/L), and anaemia (Hb 11.5g/l) and otherwise normal blood counts. Peripheral blood immunophenotyping was performed which reported B Lymphocytes representing 48% of the total lymphocyte population. A diagnostic CLL panel found; CD5+/CD19+ 84%, CD23+ 93%, CD200+ 98%, CD20+ 88% (MFI 7), sIgM 1%, CD79b 2%, CD43 79%, and CD10 <1%. Low expression of CD49d was detected at 15%. However, CD49d expression was demonstrated as bimodal with twin peaks identifiable on histogram plots.

This case was reported as a Binet stage A and therefore based on the stage, routine immunophenotypic markers and blood counts, he would appear low risk. Due the lack of indication for molecular testing at diagnosis as well as its expense and the time-consuming nature, the inclusion of CD49d in the diagnostic CLL panel provides a valuable insight into the underling risk profile of the patient and the need for close follow up.

Gating for these important bimodal populations requires an experienced scientist in a high throughput immunophenotyping laboratory. Due to the clinical relevance of bimodal CD49d expression, we report CD49d expression as well as bimodal cases on all diagnostic CLL panels.

Breaking it down: Acalabrutinib; a tough pill to swallow
Elderly man with challenges to continuous BTK-inhibitor therapy

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Our patient is a 78-year-old man with chronic lymphocytic leukemia (CLL) on maintenance therapy with Acalabrutinib, a Bruton's tyrosine kinase inhibitor (BTKi), for the past four years. His medical history includes laryngeal carcinoma, treated in 1996 with laryngectomy and radiotherapy, diagnosed 15 years prior to his CLL in 2011. He speaks with an electrolarynx.
Upon disease progression in 2021, his CLL was characterized by CD38 negativity, 13q deletion, mutated IGHV, and unmutated TP53. He achieved remission with Ibrutinib in 2021 but transitioned to Acalabrutinib in 2022 to reduce cardiac toxicity. He remains in remission on BTKi therapy.
The patient disclosed crushing Acalabrutinib tablets due to swallowing difficulties. Crushing is not recommended by manufacturers, and its impact on drug pharmacokinetics is unclear.

Current clinical practice is continuous long-term administration of BTKi[1]. Real-world evidence suggests continuous BTKi therapy may be challenging for some patients due to toxicity and potential acquired mutations at BTK or PLCG2 binding sites[2]. Intermittent dosing strategies are being evaluated in trials to mitigate cardiovascular and financial toxicities.

Emerging evidence supports exploring intermittent therapy for patients in sustained remission. Sub-analyses of the FLAIR trial demonstrated stable or decreasing residual disease levels in patients who ceased BTKi within 12 months. These findings have informed the design of ongoing randomized controlled trials, such as the STATIC trial.
However, data on the pharmacokinetics of crushed BTKi is sparse. In a phase 2 trial for Zanubrutinib during the COVID-19 pandemic, a subset of intubated patients received crushed Zanubrutinib via nasogastric tube, but pharmacokinetic analyses were limited. Similar data exists for acalabrutinib. No data on long-term administration of crushed tablets is available. This raises concerns about drug efficacy and the potential for adverse effects.
Considering our patient's favourable molecular risk profile, he may be a candidate for an intermittent dosing strategy to maintain remission while minimising risks associated with both continuous therapy and altered pharmcokinetics. Further research is warranted to guide practice for patients with similar challenges.

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Emerging targeted therapies and the role of Allogeneic Stem Cell Transplant in refractory Chronic Lymphocytic Leukaemia

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A 43 year old woman was referred to clinic in 2012 with constitutional symptoms, small volume lymphadenopathy, lymphocytosis of $23x10^9$/L and a diagnosis of CLL was confirmed by immunophenotyping. She was managed from February 2012 with a watch and wait approach until June 2015. She presented with worsening fatigue, progressive lymphadenopathy and a new breast mass necessitating biopsy. This confirmed CLL/SLL.

Peripheral blood FISH was carried out which showed intact TP53 and del 13q and NGS testing confirmed unmutated TP53 (exon 2-11) and unmutated IGHV status. Treatment with Fludarabine, Cyclophosphamide, and Rituximab (FCR) was initiated in early 2016, but she relapsed within 6 months of completion, as evidenced by elevated lymphocyte count in January 2017, peaking at $108x10^9$/L in July 2017 with associated lymphadenopathy.

Single agent Ibrutinib was commenced in July 2017 following with which best response was partial haematological and clinical remission (PR). Ibrutinib therapy was complicated by thrombocytopenia to a nadir of $16x10^9$/L. In December 2018, she transitioned to Venetoclax as a third-line therapy, but experienced significant bone marrow suppression, requiring dose reductions despite support with Eltrombopag, Aranesp, and G-CSF.

She was referred for opinion regarding allogeneic stem cell transplantation August 2020. In January 2021, she underwent a matched unrelated donor transplantation following Flu/Bu/ATG conditioning. Complications included skin graft-versus-host disease (GVHD). She achieved minimal residual disease (MRD) negativity at day 100 post-MUD and ongoing MRD assessment continued.
In November 2021 the detection of MRD positivity led to recommencing Venetoclax. 10 months post-transplant she maintained total donor chimerism. A donor lymphocyte infusion (DLI) was administered in November 2021. Venetoclax was continued for 2 more years, with close monitoring of MRD and clinical response, until November 2023.

This case highlights the challenges of managing refractory CLL, the importance of monitoring MRD, and the use of both targeted therapies and allogeneic transplantation in achieving long-term disease control. While targeted therapies have transformed CLL treatment and improved outcomes, allo-SCT remains a crucial treatment option for fit young patients with relapsed and refractory disease, particularly in the setting of suboptimal response or failure of 3 lines of therapy, including BTKI and BCL2 inhibitors.

Comorbidities Complicating CLL treatment Choice

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Treatment decisions for patients with CLL must be developed with consideration of the efficacy and side effect profile, which can be difficult in patients with multiple comorbidities and polypharmacy.

Mr. X, a now 77 year old man, was under active surveillance for CLL with a watch and wait approach for several years. He had a complex medical history including multiple hospital admissions for severe viral infections including disseminated herpes-zoster and Covid-19 infection with oxygen requirement. He also had a significant cardiovascular history with multiple PCIs and atrial fibrillation managed with rate control and anticoagulation. While anticoagulated he developed a left frontal intracerebral haemorrhage that was managed conservatively with input from neurosurgery and medicine for the elderly with significant resolution allowing anticoagulation to be restarted. Other co-morbidities included hypercholesterolemia, hypertension, impaired glucose tolerance, an elevated BMI, melanoma, SCC, and breast cancer treated by resection and radiotherapy. He had asymptomatic chronic thrombocytopenia, with platelets between 50 to 100, likely due to splenomegaly, marrow infiltration and/or immune causes. He continues intravenous immunoglobulin support for hypogammaglobulinemia with recurrent severe infections.

Thirteen years after his initial diagnosis he developed symptomatic anaemia, associated with a lymphocyte doubling time of 4 months. FISH revealed no deletion in 17p and no IGH rearrangement. There were several difficult considerations in deciding therapy for this gentleman given his medical history. Considerations included the risks of infection associated with Venetoclax Obinatuzumab in a person with a history of multiple, severe viral infections versus the bleeding risk of BTKI therapy given the history of intracranial haemorrhage, continued anticoagulation, and thrombocytopenia.

It was decided, with joint decision making and informed consent, to commence BTKI therapy with temporary cessation of anticoagulation, which has resulted in an improvement in both haematological parameters and in the patient's quality of life, without any significant adverse events to date. This case demonstrates the complexity of treatment decisions as well as some of the complications encountered in elderly patients with CLL.

Successful treatment of a case of Richter transformation complicated by Hemophagocytic Lymphohistiocytosis: A report on two decades of survival.

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Richter transformation is a devastating, and rare, but not uncommon development of aggressive lymphoma in patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma. We report a rare presentation of Richter transformation of CLL to high-grade B cell lymphoma driven by EBV virus, complicated by HLH, with successful treatment. Our patient was a known case of CLL 13 years prior to this presentation and required treatment with three lines for her CLL. She presented with progressive effusion, fever, thrombocytopenia, and elevated white count. Extensive investigation along with broad spectrum antibiotics was given. Her CT scan showed evidence of progressive disease and her biopsy confirmed the presence of high grade transformation, EBV PCR was positive, Soluble CD25 level was markedly elevated and her bone marrow biopsy had evidence of macrophage activity in keeping with HLH. We treated her with modified R-CHOEP. Our patient also received HLH-94 protocol therapy and she responded well to our treatment and remains well until now 8 year after. To our knowledge, such a combination of HLH and Richter transformation has been reported twice previously in the literature. Our case represents the first reported surviving patient with a rare complex presentation. This complex presentation is rarely described, with no consensus on the treatment approach, as the patients are generally unwell on presentation, and the symptoms overlap with infective symptoms, which is very common in this group of patients.

Richter's Syndrome with enduring remission post fixed duration Obinutuzumab, Ibrutinib and Venetoclax therapy with long term Ibrutinib maintenance

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Richter's Syndrome (RS) is a rare histological transformation of chronic lymphocytic leukaemia (CLL), most commonly to diffuse large B-cell lymphoma (DLBCL), which is clonally related in up to 80% of cases. It is characterised by an aggressive clinical course, rapid disease kinetics, high-risk genetic mutational profile, chemo-immunotherapy resistance, and consequent poor survival. Treatment is usually based on de novo DLBCL treatment regimens such as R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone); however, the outcomes with chemo-immunotherapy alone in Richter's Syndrome are poor. Clonally unrelated RS-DLBCL typically respond more favourable to chemo-immunotherapy and are generally managed as per de-nova DLBCL. Only 20-30% of patients of Richter's Syndrome patients achieve a complete response and median progression-free survival and overall survival are in the range of 6 and 12 months, respectively. Novel agents, such as BCL2 and BTK inhibitors, have been shown to have more favourable clinical outcomes in Richter's Syndrome patients; however, further study is needed.

A 72 year old lady with a history of 13q deleted CLL, previously treated with six cycles of Rituximab and Bendamustine, presented with increased frequency of infections, progressive lymphadenopathy and rising LDH. Background was significant for hypogammaglobulinaemia with recurrent chest infections and bronchiectasis. Left axillary core lymph node biopsy confirmed high grade lymphoma – diffuse large B-cell lymphoma with germinal centre subtype. Repeat peripheral blood analysis showed 17p deletion with IGHV unmutated status. Clonality studies confirmed that the DLBCL was clonally related to the prior CLL. The patient commenced fixed duration therapy with Obinutuzumab, Ibrutinib and Venetoclax. She achieved complete metabolic remission on end of treatment PET CT. She currently remains on Ibrutinib maintenance therapy and remains in remission two years later. This case highlights the enduring response of novel agents in the management of Richter's Syndrome.

A case of T-cell Waldenström Macroglobulinaemia.
A mistaken diagnosis or a nice Unicorn?

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Background. Molecular biology development has significantly contributed to achieving accurate diagnosis of chronic lymphoproliferative disorders. The recent discovery of MYD88 protein, for example, has become a paradigmatic tool for assessing Waldenström Macroglobulinemia (WM) diagnosis. We report on a case of WM which showed the presence of T cells only on flow cytometry with absent B-cells.

Case description#. An 80-year-old gentleman with a recent history of persistent lymphocytosis and chest infection, was referred to our clinic in December 2024. The examination was unremarkable except for splenomegaly (2cm). CT TAP was negative for masses or lymphadenopathy. Blood tests at presentation showed: WBC 8.0 (nv 4-11), Neutrophils 2.3 (nv 2.0-7.5), Lymphocytes 4.6 (nv 1.5-4.0) $X10^9$/L, Hb 11.3 (nv 13-18) g/dL, PLT $189X10^9$/L. Immunoglobulin test showed high IgM at 31.62 g/L (nv 0.35-2.42), free light chains study showed high K/L at 39.18 (nv 3/3-19.4). Molecular biology study (MLL Laboratory Germany) showed mutated IGVH and MYD88. BM aspirate was hemodiluted. Bone marrow (BM) biopsy showed 15% infiltration of CD138+ cells. All these findings were consistent with a WM diagnosis. However, flow cytometry showed T cells 88%, NK cells (CD3-, CD56+)10%; B cells (CD19+) 1%. Reversed CD4 to CD8 ratio. 70% of T cells were CD8+. The dominant presence of T-cell percentage on flowcytometry, was not compatible with a WM diagnosis, since this is a classical B-cell disorder. For this reason, a TCR rearrangement study was requested. This showed to be negative, out ruling the possibility of an underlying T cell clone, suggesting instead the possibility of a reactive T cell infiltration.

Conclusion. An accurate literature review showed that the presence of reactive clones of T-cells has occasionally been reported. We believe that this is a finding more likely during wintertime when influenza viruses may trigger such T cells proliferation. This case highlights that even in the presence of pathognomonic genetic markers, the presence of a clinical haematologist is relevant for ensuring accurate differential diagnosis.

Overcoming Resistance: A Challenging Case of CLL with a High Complex Karyotype

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In July 2013, a 58-year-old Russian gentleman was diagnosed with CLL, presenting with a lymphocyte count of 616×10^9/L, multi-station lymphadenopathy, and hepatosplenomegaly. FISH identified 13q and 11q deletions, unmutated *IGVH*, without *TP53*/17p deletion. Following one cycle of bendamustine, he developed severe red cell aplasia and was transitioned to weekly cyclophosphamide for four weeks, followed by six cycles of RCVP, achieving haematological remission.

In September 2014, he relapsed and was commenced on ibrutinib, achieving remission without adverse effects. He remained well until February 2020, when he presented with anaemia secondary to a gastrointestinal stromal tumour, which was surgically resected. Bone marrow analysis revealed low-level CLL involvement, and he remained off ibrutinib until July 2022.

In July 2022, treatment was restarted with venetoclax monotherapy maintaining remission until February 2024, when he presented with WCC 26.9×10^9/L, Hb 9.2 g/dL, and platelets 55×10^9/L. Bone marrow biopsy confirmed CLL infiltration (cellularity >95%). Repeat FISH/PCR analysis showed an unchanged *TP53*/17p status, but a high complex karyotype with ten chromosome aberrations (2,7,8,9,11,13,14,20,21 and 22) was detected in the marrow. PET-CT was not suggestive of transformation to a high-grade lymphoma.

Acalabrutinib was initiated in March 2024 but was ineffective, with persistent pancytopenia and reticulocytopenia. Subsequent addition of rituximab and two doses of obinutuzumab failed to improve counts. Idelalisib was initiated in July 2024 but yielded no haematologic improvement after six weeks. Bone marrow analysis showed heavy CLL infiltration (cellularity 95%) with NGS identifying an only an *ATM* variant.

Pirtobrutinib was introduced in August 2024, leading to reduced spleen size and bone marrow cellularity (30%), after 12 weeks of treatment. Despite these partial responses, the patient remains transfusion-dependent with persistent pancytopenia.

This is an unusual case of quadruple refractory CLL with no 17p, *TP53*, *BTK* or *PLCG2* aberrations. Compassionate access programmes and clinical trials are being pursued, including agents like bispecific T-cell engagers and BTK degraders with the goal of achieving adequate disease control to consolidate with an allogeneic stem cell transplant.

CLL in transformation- a case presentation

Tushar Pramod, Haematology Registrar, SVUH

Background: Richter's transformation (RT) in CLL reportedly occurs in 2% to 15% of patients[1]. This transformation presents significant therapeutic challenges and carries a poor prognosis, with median OS of 6-12 months[1].

Case Presentation: A 32-year-old male, diagnosed with high-risk CLL/SLL in 2008 (RAI stage III, CD38 positive, 17p deletion, and IgM paraproteinemia of 35.4 g/L requiring plasma exchange), was initially treated with FCR/R-CHOP followed by Rituximab maintenance. He achieved minimal residual disease (MRD) negativity in peripheral blood and complete response on PET-CT.

He remained in remission until 2021, presenting with a large intra-abdominal mass. Core biopsy and bone marrow demonstrated small mature lymphocytes with 53% CD38 positivity. Also present was a population of Hodgkin-like cells, noted to be negative for CD15, CD30, EMA expression, with reduced PAX5 compared to the CLL cells. Additionally, these were positive for MUM1, MYC, and TP53. The final pathology suggested CLL transformation, although not meeting WHO 2017 criteria for RT. The patient was started on ibrutinib and achieved complete metabolic remission (CMR) by PET. He continued ibrutinib and remained clinically stable after returning to Ireland in 2022.

In June 2024, he presented with abdominal pain. Imaging showed a pelvic sidewall mass with extensive PET-avid disease in the axillary, retroperitoneal nodes and spleen. An excisional biopsy of axillary nodes confirmed DLBCL, non-GCB subtype, with a Ki-67 index of 80%, consistent with RT. Cytogenetic analysis revealed persistent 17p deletion, and clonality studies indicated a clonal relationship to the original CLL.
Urgent treatment with R-CHOP and Epcoritamab was initiated, and the patient was referred for a potential allogeneic stem cell transplant. First dose Epcoritamab was complicated by grade 3 cytokine release syndrome, requiring ICU admission. Treatment was further complicated by pseudoprogression, leading to nodal capsular bleeding in retroperitoneal lymphadenopathy, and sepsis. Despite completing two cycles, there was no response to therapy. Unfortunately, the patient ultimately succumbed to his illness

Conclusion: This case highlights the challenges in treating patients with RT. It also demonstrates that 17p-deleted CLL can occasionally vary in its behaviour, with some cases showing a notably prolonged response to chemo-immunotherapy.

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Navigating Cytopenias in Chronic Lymphocytic Leukaemia: A Case Study Highlighting that CLL is not just a cancer but also an immune disease

Dr Jimmy William, Haem Registrar, Mater Hospital

Cytopenias are common complications in chronic lymphocytic leukaemia (CLL), often arising from disease-related immune dysfunctions or treatment toxicities. Autoimmune cytopenias (AIC) affect 4–7% of CLL patients. Understanding their aetiology and management is critical for improving outcomes.

Case Presentation:

In 2011, a 64-year-old male presented with DCT-positive haemolytic anaemia (Hb 4.5 g/dL) and leucocytosis (WBC 308 × 10^9/L) consistent with CLL (good risk). Due to the theoretical risk of haemolysis exacerbation, he was deemed fludarabine unsuitable. He completed six cycles of R-CVP with a durable response.

In 2014, he once again presented with severe haemolytic anaemia (Hb 5.9 g/dL, WBC 100 × 10^9/L), which was successfully managed with steroids. Later that year, Rituximab and Bendamustine were initiated for CLL management but discontinued after three cycles due to a severe drug-induced rash. One year later, he developed recurrent anaemia; however, on this occasion, there was no evidence of haemolysis, a bone marrow-confirmed pure red cell aplasia. Once again, he responded favourably to steroids.

In 2016, progressive leucocytosis (WBC 200 × 10^9/L) and worsening haemolytic anaemia (Hb 6.5 g/dL) again necessitated further steroids. Ibrutinib was also started but was discontinued due to a generalized pustular rash, later identified as Sweet's syndrome. As hematologic parameters improved (WBC 28 × 10^9/L, Hb 12 g/dL), he had a treatment-free interval for 14 months.

In 2019, WBC levels rose again to 130 × 10^9/L, with a stable Hb. Rechallenge with low-dose ibrutinib caused dermatologic and cardiac adverse effects, leading to prompt cessation. Venetoclax monotherapy was initiated that same month and has been well-tolerated till now. The patient achieved a sustained hematologic response with no further autoimmune cytopaenias or clinical evidence of CLL.

Discussion: This case highlights the multifactorial causes of cytopenia in CLL, including autoimmune and treatment-related effects. It underscores the need for differential diagnosis and individualized treatment. Advancements from chemo-immunotherapy to targeted agents have improved outcomes but introduced new challenges.

Conclusion: Managing AIC in CLL requires targeting the autoimmune process first, reserving CLL-specific therapies for refractory cases or progression. Understanding the interplay of disease biology and treatment side effects ensures optimized, individualized care.