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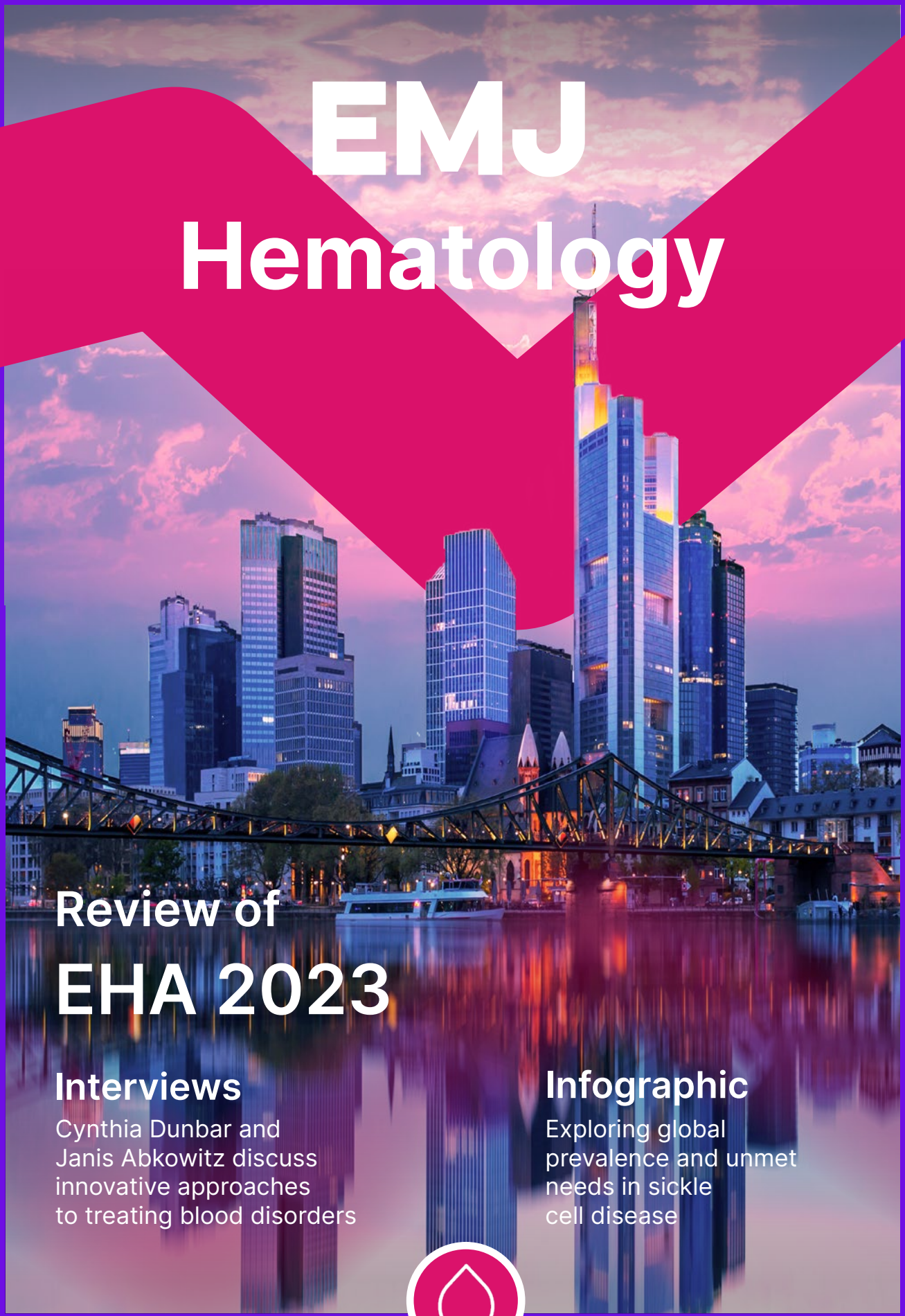

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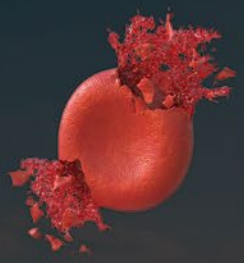

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References: 1. ENJAYMO Summary of Product Characteristics. Sanofi B.V; 2023 **2.** Röth A, Barcellini W, D'Sa S, et al. Sutimlimab in Cold Agglutinin Disease. *N Engl J Med.* 2021;384(14):1323-1334. doi:10.1056/NEJMoa2027760
3. Röth A, Berentsen S, Barcellini W, et al. Sutimlimab in patients with cold agglutinin disease: results of the randomized placebo-controlled phase 3 CADENZA trial. Blood. 2022;140(9):980-991. doi:10.1182/blood.2021014955

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Welcome letter

Koutsouki

Evgenia Koutsouki
Editor

Dear Readers,

Welcome to the 2023 issue of *EMJ Hematology*, bringing you our review of the 28th Annual Congress of the European Hematology Association (EHA), which this year took place in Frankfurt, Germany, in hybrid format.

We are delighted to be able to bring you our full, independent review of the congress, which hones into key topics, including current approaches to treatment of sickle cell disease and novel approaches to treating lymphoma, including immunotherapy and targeted therapy. We have handpicked a number of abstracts, summarised here, to give you a flavour of the research trends this year, which range from novel chimeric antigen receptor therapies for acute myeloid leukaemia to a potential one-time cure for patients with transfusion-dependent β-thalassaemia.

Our interviews feature thought leaders in haematology, who discuss groundbreaking research in the field and provide insight into key topics. Finally, we feature an article describing a case of steroid toxicity in immune thrombocytopenia, which I am certain will be of interest to many of you.

I would like to thank the journal Editorial Board, and of course our contributors, interviewees, and peer reviewers, who have helped bring this great content to you. I hope you enjoy reading this issue and we are excited to see next year's developments.

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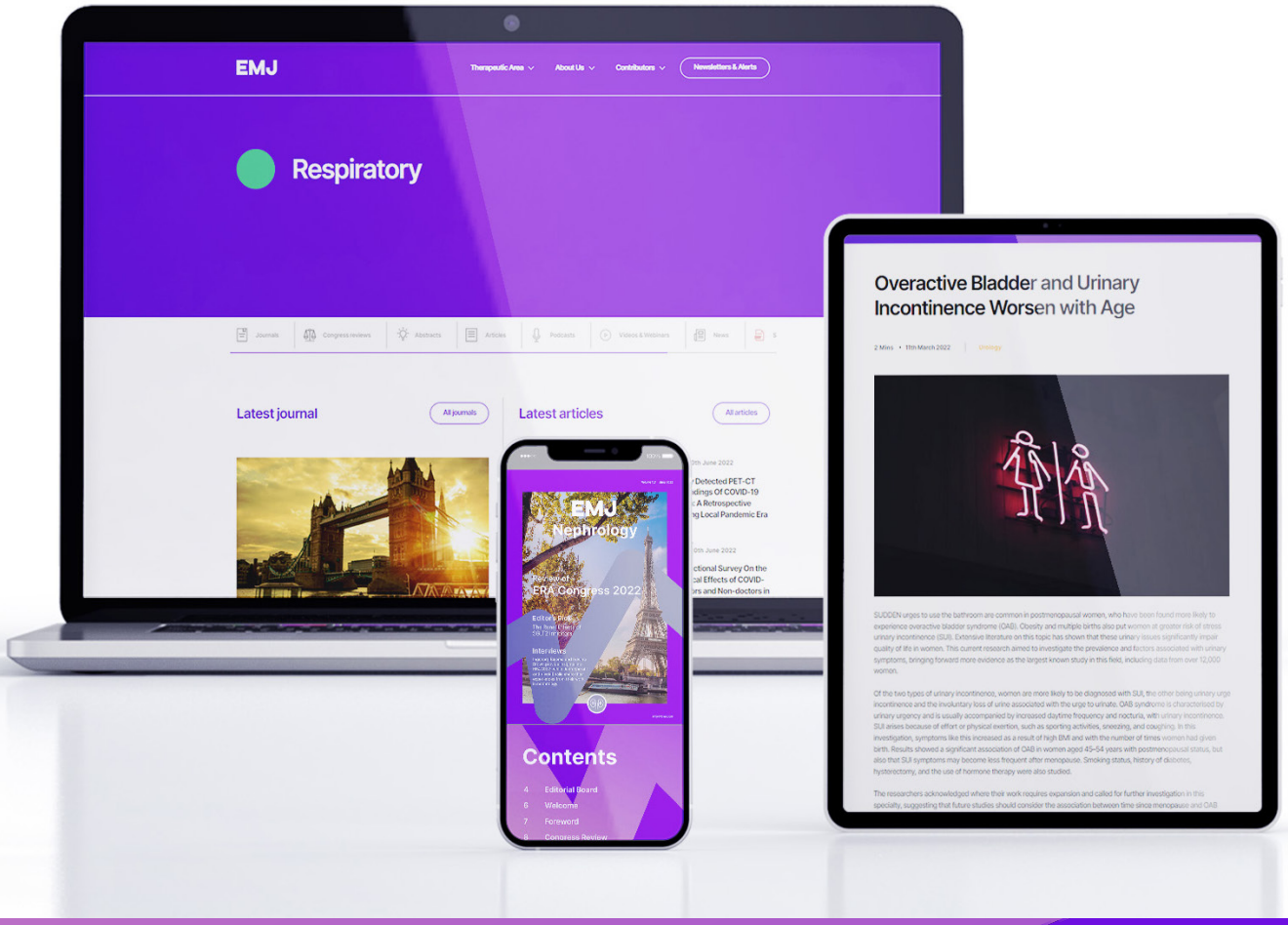

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EMJ

Foreword

Dear Colleagues,

Welcome to *EMJ Hematology 11.1*, which features a plethora of content from this year's European Hematology Association (EHA) Congress, which took place between 8th–11th June in Frankfurt, Germany, as well as online. EHA 2023 gave haematologists from all over the world the opportunity to meet and collaborate in person, and was the Association's second hybrid congress following the COVID-19 pandemic.

Covered in this issue are congress review highlights on combination therapy in the treatment of acute promyelocytic leukaemia, the promise of gilterinib as a maintenance therapy post-transplant, and the potential of exagamglogene autotemcel as a one-time cure for patients with transfusion-dependent β-thalassaemia. We also feature a congress interview with EHA's Jean Bernard Lifetime Achievement Award Winner 2023, Irene Roberts, Emeritus Professor of Paediatric Hematology, Department of Paediatrics, Medical Research Council (MRC) Weatherall Institute of Molecular Medicine, University of Oxford, UK.

On the subject of interviews, EMJ also sat down with Cynthia Dunbar, Secretary, American Society of Hematology (ASH); Chief, Translational Stem Cell Biology Branch; and Head, Molecular Hematopoiesis Section, National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, USA; and Janis Abkowitz, Head, Division of Hematology, University of Washington, Seattle, USA, and Adjunct Professor of Genome Sciences, University of Washington School of Medicine, Seattle, USA.

As well as our comprehensive congress coverage from EHA 2023, you can also find some fantastic abstracts and articles in *EMJ Hematology 11.1*, which investigate a wealth of topics in our specialty.

As ever, I extend my thanks to all of the authors and interviewees who contributed to this journal, our Editorial Board members and reviewers, and to you for reading this issue. I hope that our featured content provides a lot of food for thought, and that you find it as engaging as I certainly have.

Emanuele Angelucci

Chair, Hematology and Cellular Therapy Unit, Ospedale Policlinico San Martino; Transplant Program Director, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Genova, Italy

EHA 2023

Review of the 28th Annual Congress of the European Hematology Association (EHA)

Location:	Frankfurt, Germany
Date:	8th–11th June 2023
Citation:	EMJ Hematol. 2023;11[1]:10-18. DOI/10.33590/emjhematol/10301337. https://doi.org/10.33590/emjhematol/10301337.

MALIGNANT haematology and haemoglobinopathies were among the themes of the 28th Annual Congress of the European Hematology Association (EHA), which aims to "elevate progress towards a cure for all blood disorders." In the welcome speech, Elizabeth Macintyre, EHA President, recognised the balanced representation EHA was proud to showcase at this meeting, in the forms of diversity, equity, and inclusion, as well as a hybrid attendance model.

As artificial intelligence continues to play a greater role in modern healthcare, Macintyre fittingly joked that they had written their speech using the famous ChatGPT (OpenAI, San Francisco, California, USA) software. Macintyre was joined by Konstanze Döhner, EHA President Elect and Scientific Committee Chair, to open the annual meeting taking place between the 8th–11th June 2023, in the vibrant city of Frankfurt, Germany.

Located by the River Main, a major financial hub in central Germany, this city provided the perfect setting for a community of haematologists to gather and exchange knowledge in order to "ignite the spark of innovation that drives our profession," as Macintyre put it. Frankfurt's Römerberg Square, famous for hosting bustling Christmas markets, is a short trip on the subway from Messe Frankfurt, one of the largest trade fairs in the world, where EHA 2023 took place.

Döhner introduced the scientific programme available for attendees to access, hoping that it proved both "stimulating and enriching." They drew attention to the YoungEHA and poster sessions as particular highlights, stating: "Together we have created an extraordinary platform," covering a broad spectrum of the specialty, and filled with "a balance of benign and malignant haematology." Alongside these, EHA2023 was packed with over 180 sessions, including debates, workshops, and symposia, ranging in intimacy from large auditorium presentations to smaller case discussions, and spotlight talks featuring speakers from most continents in the world. There were more than 15,000 registrations for this event, and a comprehensive abstract programme was selected, comprising over 2,750 oral and poster presentations combined.

"Located by the River Main, a major financial hub in central Germany, this city provided the perfect setting for a community of haematologists to gather."

"EHA2023 was packed with over 180 sessions, including debates, workshops, and symposia, ranging in intimacy from large auditorium presentations to smaller case discussions."

Jean-Pierre Bourquin, Chair of EHA Fellowship and Grant Committee, was on hand to introduce the 34 researchers from 13 different countries who were awarded EHA Research Grants for their outstanding proposals, more than half of whom were female candidates. These included the Physician Scientists' Research Grant, which was awarded to Jana Ellegast, University Hospital Zürich, Switzerland, and the Topic-in-Focus Research Grants that went to Alkmini Anastasiadi, University of Patras, Greece, and Annamaria Aprile, Fondazione Telethon ETS, Italy, for their projects on haemoglobinopathies. Kick-Off Grants were given to support the initiation of novel concepts, alongside Research Mobility Grants. The coveted Education and Mentoring Award was credited to Gianluca Gaidano, University of Eastern Piedmont, Italy. The David Grimwade Award honouring basic and translational haematology research was given posthumously to Pieter van Vlierberghe, Ghent University, Belgium, who sadly passed away in early 2023. Van Vlierberghe's wife accepted the award on their behalf and gave an emotional speech. A long-time collaborator with van Vlierberghe, Steven Goossens, Ghent University, Belgium, presented some of the work from their research group in an honorary lecture on T cell acute lymphoblastic leukaemia. The José Carreras Award was accepted by Robin Foà, Sapienze University, Rome, Italy, delivering their honorary lecture on Philadelphia chromosome-positive acute lymphoblastic leukaemia.

In one of the final sessions of the in-person congress sessions, António Almeida, Hospital da Luz, Lisbon, Portugal, took over from Macintyre as EHA President, and will guide the association as it focuses now on the EHA2024 meeting that will take place in Madrid, Spain, between the 13th–16th June next year.

This issue of *EMJ Hematology* contains our scientific highlights from the 28th congress of EHA, including a review summarising the cutting edge press releases shared, and abstracts from presenters on topics such as patient blood management and 'haemovigilance', as well as severe haemophilia.

Luspatercept Superior in Treating Anaemia in Lower-Risk Myelodysplastic Syndromes

RESULTS from a Phase III study suggest that patients with lower-risk myelodysplastic syndromes (LR-MDS) suffering from chronic anaemia could benefit from luspatercept therapy. Patients with LR-MDS with chronic anaemia experience iron-overload, increased morbidity, and reduced survival. Furthermore, the current standard of care, erythropoietin-stimulating agents (ESA), produce suboptimal results in these patients. In a pre-planned interim analysis of ESA-naïve patients with LR-MDS, luspatercept demonstrated substantial clinical benefits when compared to the standard treatment, epoetin alfa.

Phase III of the COMMANDS study examined the safety and efficacy of luspatercept and epoetin alfa in 356 ESA-naïve, transfusion-dependent patients with LR-MDS. Primary outcomes investigated during the first 24 weeks include the achievement of red blood cell transfusion independence for ≥12 weeks with a concurrent haemoglobin increase of ≥1.5 g/dL.

Analysis suggested luspatercept outperformed epoetin alfa, as patients treated with luspatercept more commonly achieved red blood cell transfusion independence (59%) than patients treated with epoetin alfa (31%; $p<0.0001$). Further analysis also demonstrated that patients with specific MDS-associated gene mutations, such as *ASXL1*, *SF3B1*, *SF3B1a*, and *TET2*, had superior responses to luspatercept than epoetin alfa. Importantly, luspatercept also exhibited a more favourable safety profile, with patients only reporting mild to moderate treatment-emergent adverse events. These events did not lead to treatment discontinuation, and were generally non-serious. Finally, both treatments resulted in similar overall death rates.

Overall, the results from the COMMANDS study suggest luspatercept may be the more superior treatment option for patients with LR-MDS with anaemia, who require transfusions. Luspatercept's improved outcomes, favourable safety profile, and broad applicability across a range of genetic profiles is encouraging. The research team from Humanitas University and Research Hospital, Milan, Italy, hope these results have the potential to establish a new standard of care for patients with LR-MDS who have not yet received ESAs. ●

"Phase III of the COMMANDS study examined the safety and efficacy of luspatercept and epoetin alfa in 356 ESA-naïve, transfusion-dependent patients with LR-MDS."

Targeting ADGRE2 and CLEC12A as a Novel Therapy for Acute Myeloid Leukaemia

AT EHA 2023, Sascha Haubner, Memorial Sloan Kettering Cancer Center, New York City, USA, presented promising preclinical outcomes for a novel combinatorial chimeric antigen receptor (CAR) concept called ADCLEC.syn1 for the therapy of acute myeloid leukaemia (AML).

ADCLEC.syn1 utilises cooperative receptors that target *ADGRE2* and *CLEC12A* to efficiently eliminate AML, while minimising haematologic toxicities. This has been demonstrated in a comprehensive series of *in vivo* efficacy and toxicity models, prompting the development of a Phase I clinical trial for ADCLEC.syn1 in AML.

CAR therapies for AML face challenges due to clonal heterogeneity and similarities to normally early haematopoiesis, potentially resulting in antigen escape and haematological toxicities.

Haubner and colleagues performed a quantitative analysis of target expression profiling on the surface of AML and normal tissues to determine therapeutic avenues for novel combinatorial CAR designs. The unique CAR therapy, ADCLEC.syn1, was developed to simultaneously target *ADGRE2* and *CLEC12A* for selective elimination of AML cells with low levels of *ADGRE2*, while preserving normal haematopoietic stem and progenitor cells.

The research team correlated target antigen expression with efficacy and CD33-CAR T cells, using patient-derived or humanised AML xenograft models. This demonstrated a high expression of ADGRE2 and CD33 within the AML fraction enriched for leukaemic stem cells. Comparatively, *ADGRE2* expression was significantly less abundant in normal haematopoietic cells compared with CD33.

ADCLEC.syn1 induced durable remissions in multiple human AML cell line xenograft models representative of phenotypes found in patients with relapsed/refractory AML. A control CD33-CAR also demonstrated effectiveness against AML cell lines in engrafted mice. However, when AML-engrafted mice were reconstituted with normal human haematopoietic cells, only ADCLEC.syn1 exhibited a response, not CD33-CAR. In an AML patient-derived xenograft model, mice treated with CD33-CAR experienced relapse with functional leukaemic stem cells, which were effectively eliminated by ADCLEC.syn1.

The findings emphasise the importance of quantitative CAR target profiling in AML and normal tissues to guide CAR design, and highlight the need for further investigation into how antigen expression on normal bystander cells can impact CAR therapy efficacy. Notably, ADCLEC.syn1 is set to undergo a first-in-human Phase I clinical trial for relapsed/refractory AML.

"ADCLEC.syn1 utilises cooperative receptors that target *ADGRE2* and *CLEC12A* to efficiently eliminate AML."

Combination Therapy Improves Survival Rate in Acute Promyelocytic Leukaemia?

STUDY findings presented at EHA 2023 in Frankfurt, Germany, discussed overall survival (OS) outcomes in patients with acute promyelocytic leukaemia (APL) treated with all-trans retinoic acid and arsenic trioxide (ATRA-ATO) combination therapy.

Maria Teresa Voso, Department of Biomedicine and Prevention, University of Rome Tor Vergata, and Neuro-Oncohematology Unit, Istituto di Ricovero e Cura a Carattere Scientifico (IRCSS) Fondazione Santa Lucia, Rome, Italy, and colleagues, used data from the HARMONY registry to retrospectively assess OS in patients with APL treated with chemotherapy-free regimen, ATRA-ATO, compared with those treated with ATRA-idarubicin (AIDA).

The HARMONY registry comprised 1,868 patients with a diagnosis of APL who had been involved in two clinical trials (n=536), UK AML-17 and GIMEMA APL0406, as well as patients with APL from national registries in six countries (n=401) who had received diagnosis between 2007–2020. A total of 937 of these patients met the data quality criteria for inclusion in the study; 380 (40.6%) received ATRA-ATO, 509 (54.3%) received AIDA, and treatment received was not available for 48 patients. The cohort consisted of 483 males (51.5%) and 454 females (48.5%), and the median follow-up was 5.66 years.

Following data analysis, researchers found that 10-year OS rate was significantly improved in patients treated with ATRA-ATO at 92% compared with 75% for those treated with AIDA ($p<0.001$). Despite this, early death rates, defined as death within 30 days of diagnosis, were similar between both groups (3.4–5.7%). Following risk stratification using the Sanz risk score, the survival benefit was seen across risk groups. Additionally, the authors also found that age had a significant role in OS, with patients <50 years of age experiencing better outcomes.

> **"Researchers found that 10-year OS rate was significantly improved in patients treated with ATRA-ATO."**

The researchers concluded that the findings confirm, in a large international cohort, that chemotherapy-free ATRA-ARO combination treatment confers a survival advantage in patients with APL, and that this survival advantage is consistent irrespective of risk profile. In terms of limitations, high-risk patients were under-represented in the analysis, and therefore the findings will need to be confirmed in this cohort in the future. ●

Effective Treatment Found for Chronic Lymphocytic Leukaemia

A LONG-TERM study has confirmed that an effective treatment for chronic lymphocytic leukaemia (CLL) has been found in venetoclax-obinutuzumab. Researchers from the CLL14 study, a prolonged and groundbreaking investigation into the treatment of CLL, presented updated evidence on long-term outcomes of this drug combination at EHA 2023, held in Frankfurt, Germany, and online.

The aim of the CLL14 study is to investigate the long-term safety and efficacy of fixed-duration B-cell lymphoma 2 inhibition with venetoclax when combined with the CD20 antibody obinutuzumab, in previously untreated patients with CLL. Results showed evidence of sustained efficacy, as well as safety, and potentially pave the way for venetoclax-obinutuzumab to become a preferred therapy option for patients with CLL, including those who have co-existing conditions.

"The study, which is ongoing, included 432 patients with CLL who were previously untreated."

The study, which is ongoing, included 432 patients with CLL who were previously untreated. The group were randomly assigned either venetoclax-obinutuzumab or chlorambucil-obinutuzumab. After the median follow-up period (76.4 months), venetoclax-obinutuzumab demonstrated higher progression-free survival (PFS) rates in comparison to chlorambucil-obinutuzumab (median PFS: 76.2 versus 36.4 months, respectively), and a significantly longer time-to-next-treatment (6-year time-to-next-treatment: 65.2% versus 37.1%, respectively). Researchers estimated that PFS after 6 years would be 53.1% for venetoclax-obinutuzumab versus 21.7% for chlorambucil-obinutuzumab.

Results were replicated across all risk groups, which included patients who had high-risk characteristics for CLL. Venetoclax-obinutuzumab also showed excellent minimal residual disease response; 7.9% of patients had undetectable levels of minimal residual disease after a 5-year follow-up, compared with 1.9% of patients treated with chlorambucil-obinutuzumab.

The CLL14 study has shown convincing evidence thus far regarding the long-term benefits of using venetoclax-obinutuzumab in patients with CLL, including those who are defined as high-risk. It offers patients high rates of undetectable minimal residual disease, prolonged time-to-next-treatment, and sustained remission; over half of patients treated with venetoclax-obinutuzumab in this study remained in remission for 5 years following treatment completion. The majority of patients also did not require any second-line treatment.

Venetoclax has been approved to treat patients who are previously untreated and who have been diagnosed with CLL or small lymphocytic lymphoma, by the U.S. Food & Drugs Administration (FDA, 2019), and the European Medicines Agency (EMA, 2020). To conclude, researchers believe that a treatment regimen of venetoclax-obinutuzumab for a 1-year period is an effective option for patients with CLL.

Potential One-Time Cure for Patients with Transfusion-Dependent β-Thalassaemia

EXAGAMGLOGENE autotemcel (exa-cel) has potential as a one-time cure for patients with transfusion-dependent β-thalassaemia, according to interim findings presented at EHA 2023. Franco Locatelli, Catholic University of the Sacred Heart, Bambino Gesù Children's Hospital, Rome, Italy, revealed the results of CLIMB THAL-111, a Phase III study.

Exa-cel is a non-viral cell therapy that uses *ex vivo* clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 gene editing. This targets *BCL11A* in autologous CD34⁺ haematopoietic stem and progenitor cells, and reactivates synthesis of foetal haemoglobin.

"Only 27 could be evaluated during the pre-specified interim analysis for study endpoints."

While the study included 48 patients with transfusion-dependent β-thalassaemia, only 27 could be evaluated during the pre-specified interim analysis for study endpoints. Of these, 88.9% maintained an average weighted haemoglobin of ≥9 g/dL, without the need of transfusion for ≥12 months. After exa-cel infusion, patients who were transfusion-independent for ≥12.0 months remained transfusion-free for up to 40.7 months, and had a mean time to last transfusion of 37 days.

Edited *BCL11A* alleles in the patients' bone marrow CD34⁺, haemoglobin levels, and peripheral blood nucleated cells remained stable. Furthermore, exa-cel's safety profile proved to be consistent with autologous transplantation procedures and the myeloablative busulfan-based conditioning regime.

No patients discontinued the study or died, all serious adverse events were resolved, and there were no malignancies. Locatelli also reported that the study showed significant improvements in patient quality of life. Moreover, the CLIMB THAL-111 study observed successful neutrophil and platelet engraftments in all patients.

The results of the CLIMB THAL-111 study indicate that exa-cel has potential as a one-time cure for patients with transfusion-dependent β-thalassaemia. It shows that patients can achieve transfusion independence, thus improving their quality of life and haemoglobin levels. This marks a significant advancement in treating transfusion-dependent β-thalassaemia.

Gilterinib Promising as Post-transplant Maintenance Therapy

TREATMENT with tyrosine kinase 3 inhibitor gilteritinib has shown potential as a post-transplant maintenance therapy in patients with acute myeloid leukaemia with an internal tandem duplication mutation of *FLT3*. The MORPHO study, which investigated whether this treatment would improve relapse-free survival, was presented by Mark Levis, John Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland, USA, at EHA 2023.

In this Phase III, randomised, double-blind, placebo-controlled trial, participants were randomised to receive either 120 mg of gilteritinib daily for 24 months, or a placebo. The primary endpoint was relapse-free survival, while secondary endpoints included overall survival; graft-versus-host-free relapse-free survival; event-free survival; non-relapse mortality; incidence of infections; acute and chronic graft-versus-host disease; and effect of pre- and post-haematopoietic cell transplantation with detectable measurable residual disease on relapse-free survival and overall survival. Results showed that patients receiving gilteritinib had a higher 2-year relapse-free survival rate (77.2%), compared with the placebo group (69.9%); however, this was not statistically significant (p=0.0518). Overall survival rates were similar in both groups, but in patients with detectable measurable residual disease, gilteritinib had a more pronounced effect, suggesting that the treatment could be beneficial for this population.

There was a higher incidence of treatment-emergent adverse events, such as chronic graft-versus-host disease and myelosuppression, in those treated with gilteritinib, with a higher number of dose interruptions and reductions.

> **"In patients with detectable measurable residual disease, gilteritinib had a more pronounced effect."**

The team concluded that gilteritinib should be a standard-of-care for patients with measurable residual disease pre- or post-haematopoietic cell transplant. These results could improve outcomes for these patients, and aid the challenges of relapse. Further research will need to optimise patient selection and refine treatment protocols. ●

Transplantation Versus Gene Therapy for Sickle Cell Disease

Authors: Jivitesh Newoor, EMJ, London, UK

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https://doi.org/10.33590/emjhematol/10301924.

PRESENTED during the European Hematology Association (EHA) Congress 2023, held at the Messe Frankfurt Exhibition & Congress Centre, Frankfurt, Germany, between 8th–11th June, a captivating session on sickle cell disease (SCD) explored the role of allogeneic stem cell transplantation in this condition, as well as gene therapy and gene editing in treating patients with SCD. The session was co-chaired by Anna Sureda, Blood Cell Barcelona Hematology Institute, Spain, along with John Gribben, Barts Cancer Institute, London, UK.

ALLOGENEIC STEM CELL TRANSPLANTATION IN SICKLE CELL DISEASE

Sureda introduced Jean-Hugues Dalle, Robert Debré Hospital, Paris, France, who discussed the role of allogeneic stem cell transplantation in SCD. They explored the prevalence of SCD, describing it as the "most frequent rare disease" worldwide, with over 120 million carriers across the globe. Additionally, Dalle examined the pathophysiology of SCD, a monogenic disease characterised by the polymerisation of deoxygenated haemoglobin, resulting in the sickle-shaped red blood cells. Dalle affirmed that the erythrocyte alteration leading to haemoglobin S polymerisation is just one aspect of the complications associated with SCD, while a significant portion of the problem remains hidden, involving a complex and multi-step process that affects multiple cell types.

Dalle proceeded to discuss the clinical manifestations of SCD, which evolve with age, detailing the acute and chronic phases. In cases where the acute and chronic phases overlap, the initial approach focuses on symptomatic relief. However, chronic transfusion may be considered, particularly for patients with cognitive and cerebral impairments. More recently, drug therapies such as voxelotor and crizanlizumab have shown promise. Nonetheless, Dalle emphasised that these treatments primarily address the symptoms rather than providing a cure. Excluding gene therapy, haematopoietic stem cell transplantation (HSCT) is recognised as the only curative approach among the available treatment options.

The session then focused on various publications centred around transplantation in SCD. A prominent article by Walters et al.,[1] published in 1996, which defined the eligibility criteria for transplantation in children with SCD, was explored. Dalle highlighted that literature indicates young patients with symptomatic SCD and a human leukocyte antigen (HLA)-matched sibling donor should undergo transplantation at the earliest opportunity. Transplantation using related bone marrow or cord blood donors should only be considered if at least one of the indicators suggested by Walters et al.[1] is present, and such transplants should be performed within controlled trials in experienced centres.

Dalle detailed a study conducted by Gluckman et al.,[2] which included over 1,000 patients who underwent HLA identical sibling donor HSTC in 94 centres across two countries between 1986–2013. Most patients (87%) received a bone marrow transplant after a conditioning regimen. The 5-year overall survival rates were 96% for patients who received a bone marrow transplant

(n=835), 100% for those who received sibling cured blood (n=75), and 79% for patients who underwent peripheral blood transplantation (n=73). Additionally, 5-year event free survival was reported as 81%, 90%, and 73%, respectively.

The literature indicates that allogeneic HSCT from sibling donors has yielded successful transplant outcomes; however, several challenges and questions still remain. These include strategies to reduce toxicity, mitigate long-term side effects in children, enable HSCT in adults with comorbidities, expand indications for transplantation, and offer HSCT to patients without sibling donors. Lastly, a significant question remains regarding how to overcome the exclusion criteria established by Walters et al.[1] in 1996, mainly how indications can be expanded to minimise toxicity in children, and provide HSCT to older patients with comorbidities who have available matched sibling donors.

Dalle discussed the encouraging results of HSCT using a healthy sibling donor without the need for total body irradiation-free conditioning regimen, which is considered the gold standard for young patients without significant comorbidities.

Other forms of allogeneic HSCT are still in the developmental stage; however, the balance between potential benefits and risks must be carefully evaluated by a multidisciplinary team.

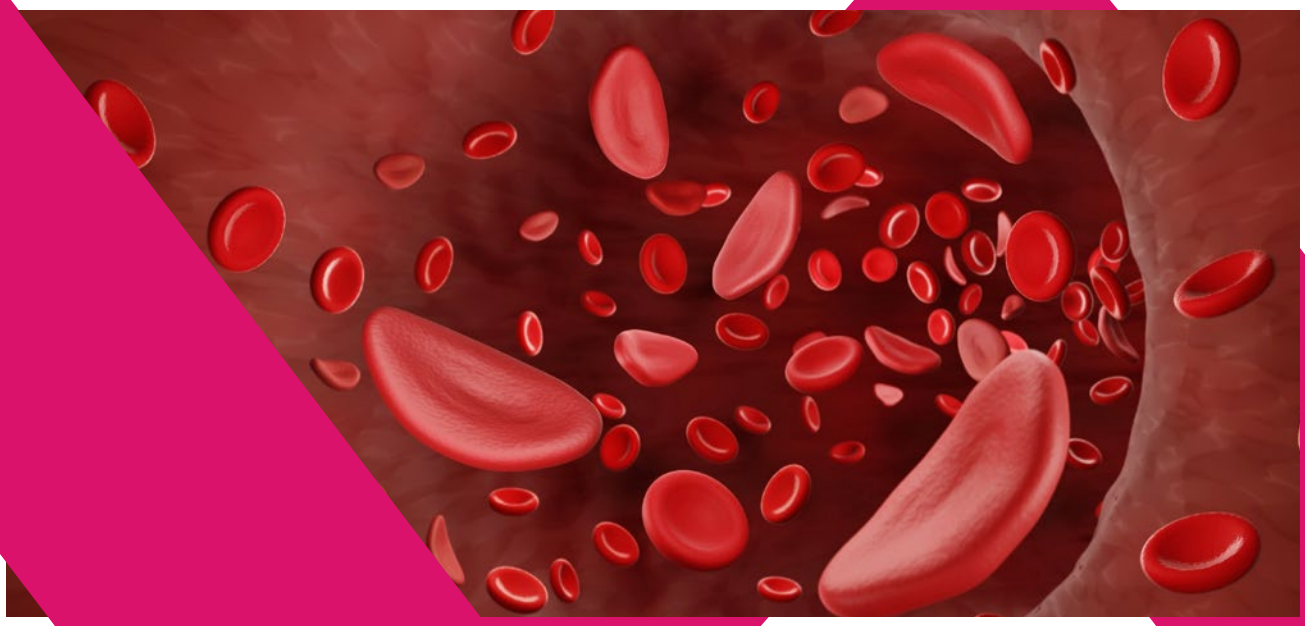
Regarding gene therapy, Dalle acknowledged its promising potential, but noted that it is still in the early stages of application. Many questions and uncertainties regarding its implementation and long-term outcomes remain to be addressed.

GENE THERAPY AND GENE EDITING IN PATIENTS WITH SICKLE CELL DISEASE

Gribben introduced Franco Locatelli, Catholic University of the Sacred Heart, Rome, Italy, who commenced by discussing the fundamental role of autologous stem cells in ongoing gene therapy and genome editing trials. The benefits of gene therapy were outlined, such as the ability for patients to serve as their donors, eliminating the need for an HLA-identical donor.

Locatelli listed the treatment-associated risks, which largely align with those typically associated with a myeloablative autograft. Therefore, this therapy can be considered for patients who are currently unsuitable candidates for allografts,

"The literature indicates that allogeneic HSCT from sibling donors has yielded successful transplant outcomes."



namely late adolescents and adults. However, there are certain limitations to this approach. It requires the use of a myeloablative regimen to eradicate the patient's haematopoiesis, resulting in inherent toxicity to the gonads and certain organs, predominantly the liver and lungs. Currently, this cannot be offered to patients with impaired haematopoiesis or pre-existing severe organ damage.

The presentation explored the use of betibeglogene autotemcel, which involves introducing modified copies of the *HBB* gene into the haematopoietic stem cells of patients with SCD using the BB305 lentiviral vector through transduction of autologous $CD34^+$ cells.

Locatelli discussed exagamglogene autotemcel (exa-cel) as a cell product consisting of autologous $CD34^+$ HSPCs modifying using non-viral, *ex vivo* CRISPR-Cas9 technology. Infusion of exa-cel increases foetal haemoglobin to levels similar to hereditary persistence of foetal haemoglobin, thereby preventing the need for red blood cell transfusions and eliminating vaso-occlusive crises (VOC). The benefits of elevated levels of foetal haemoglobin are associated with reduced morbidity and mortality in individuals with SCD.

CLIMB SCD-121, a pivotal Phase 3 trial aimed at evaluating the elimination of VOCs following exa-cel infusion in patients with severe SCD, was explored. The inclusion criteria included the diagnosis of severe SCD; age of 12–35 years; β^s/β^s, β^s/β^0, or β^s/β^+ genotype; and history of ≥2 VOCs per year in the 2 years prior to screening. Participants who completed the CLIMB SCD-121 trial were eligible for enrolment in the follow-up study, CTX001-131, which aimed to evaluate the long-term safety and efficacy of exa-cel.

"Among the participants in the primary efficacy set, 94.1% were VOC-free after exa-cel infusion."

The primary efficacy endpoint measured the proportion of participants free from severe VOCs for at least 12 months. The key secondary efficacy endpoint assessed the proportion of participants free from inpatient hospitalisation due to severe VOCs for at least 12 months. The results were based on a pre-specified interim analysis outlined in the protocol. The full analysis set included all enrolled participants who received exa-cel infusion. The primary efficacy set included all participants who were followed for at least 16 months after the exa-cel infusion, making them

assessable for the primary and key secondary endpoints. The pre-specified interim analysis was conducted when the primary efficacy set reached approximately 17 participants. Among the participants in the primary efficacy set, 94.1% were VOC-free after exa-cel infusion. For those who were free from severe VOCs for at least 12 months, the duration of VOC-free period ranged from 13.1–36.5 months, with a mean of 18.7 months.

There were early and sustained increases observed in total haemoglobin and foetal haemoglobin throughout the pancellular distribution, following the exa-cel infusion. At Month 3, the mean foetal haemoglobin level was 36.8%, which was subsequently maintained at approximately 40.0% during the follow-up period. The mean total haemoglobin level was 12.0 g/dL at Month 3, and remained at or above 11.0 g/dL throughout the follow-up period. Notably, Locatelli emphasised the significance of establishing comparable clinical endpoints when evaluating curative genetic therapies for SCD.

In their closing remarks, Locatelli underscored the promising and potentially curative nature of both gene addition therapy and genome editing for individuals with SCD.

These approaches have the advantage of being applicable to any patient with a preserved haematopoietic reservoir and limited organ damage. The role of genome editing in paediatric patients will be further defined through future studies. It is crucial to thoroughly investigate the long-term safety profile of gene addition therapy and genome editing.

CONCLUSION

The session provided key insights on the role of allogeneic stem cell transplantation, gene therapy, and gene editing in treating patients with SCD, along with their advantages and challenges. Future studies are required to decipher the role of these therapies, explore their safety profiles, and expand on their indications.

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Immunotherapy, Targeted Therapy, and Novel Approaches to Treating Lymphoma

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LYMPHOMA experts presented an insightful exploration of clinical trial data on immunotherapy and targeted therapeutics for diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and mantle cell lymphoma (MCL) during a joint symposium session chaired by Elizabeth Macintyre, Université Paris Cité; Institut Necker-Enfants Malades (INEM); Institut national de la santé et de la recherche médicale (Inserm); and Laboratory of Onco-Hematology, Assistance Publique-Hôpitaux de Paris, Hôpital Necker Enfants-Malades, Paris, France; and Robert Brodsky, Division of Hematology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

INTRODUCTION

There have been several advances in the treatment of DLBCL, FL, and MCL, with the approval of targeted therapies and the advent of immunotherapy and chemoimmunotherapy, as well as promising new drug targets on the horizon. However, whilst there have been major advances, this progress has not been easy, and future progress in improving lymphoma treatment and patient outcomes will require ongoing research and dedication. When discussing lymphoma treatment, John Gribben, Barts Cancer Institute, Queen Mary University of London, UK, and past President of the European Hematology Association (EHA), spotlighted the vast number of clinical trials investigating immunotherapies for treatment of DLBCL. Gribben explained how understanding of the failed immune mechanisms, as well as tumour cell biology and the microenvironment involved in lymphoma pathogenesis, could enable us to harness the immune system to develop immune-based therapies to treat lymphoma, highlighting monoclonal antibodies, immunomodulatory agents, and chimeric antigen receptor (CAR) T-cell therapy as some of the key areas of interest. Gribben stated that in order to alter clinical outcomes, successful therapies need to target the 'Achilles Heel' of the tumour. This will be the ongoing focus and challenge for lymphoma therapeutic research and development.

> **"Successful therapies need to target the 'Achilles Heel' of the tumour."**

IMMUNOTHERAPY

Whilst stating that chemotherapy remains the backbone of treating lymphoma, Gribben explored chemoimmunotherapy as one of the first major advances in lymphoma treatment, which has now overtaken chemotherapy as the standard of choice in treating lymphoma. Gribben highlighted the rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) regimen success, which has shown significantly improved overall survival (OS) when compared to CHOP due to the synergy between the anti-CD20 monoclonal antibody, rituximab, and traditional chemotherapy. Following on from this research and discovery, Gribben discussed how, more recently, clinical trials have been investigating the use of antibody-drug

conjugates to improve on R-CHOP outcomes, which have shown positive results. These discoveries signify the importance of enhancing immune-mediated effector mechanisms in treating lymphoma.

Lenalidomide

Gribben explored the use of the immunomodulatory agent lenalidomide in treating lymphoma. Lenalidomide acts by enhancing immune synapse formation to enable effective phosphotyrosine signalling to improve the T-cell response. This is important, as lymphoma cells have been found to induce gene defects in T-cells and natural killer cells, resulting in impaired function, such as impaired actin polymerisation, immune synapse formation, phosphotyrosine signalling, cytotoxicity, motility, as well as cytokine and chemokine production. The effect of lenalidomide on malignant lymphoma is, however, modest. Gribben also discussed clinical trial evidence that led to the licensing of lenalidomide for FL.

Chimeric Antigen Receptor T-Cell Therapy

CAR T-cell has been one of the major successes in treating lymphoma. Gribben highlighted some of the key clinical trials involving CAR T-cell therapies in relapsed/refractory lymphoma and the impact to patient outcomes, including the ZUMA-1 trial. ZUMA-1 has >5 years of data, and took place in patients with relapsed/refractory DLBCL who had received ≥2 lines of prior therapy. The findings showed that 43% were alive at 5 years. However, the aforementioned studies used to approve CAR T-cell therapy were Phase II and not randomised, due to a lack of other effective therapies available at the time. Gribben further explored how this led to comparative analysis studies of confounder-adjusted OS retrospectively reviewing overall and progression-free survival in standardised treatment historical cohorts, compared to outcomes with CAR T-cell therapy. These comparative studies have shown that CAR T-cells have made a major advance in this patient population, Gribben stated.

In terms of second-line therapy, Gribben discussed the ZUMA-7 study, which looked at axicabtagene ciloleucel versus standard of care, followed by autologous stem-cell transplant (ASCT), in patients with relapsed/refractory large B-cell lymphoma. The trial results showed that CAR T-cells outperformed ASCT in the patient cohort. However, Gribben did note that many of the patients in the cohort failed to make it to ASCT, and the inclusion criteria had to relapse within 1 year of receiving frontline therapy or having primary refractory disease, and would therefore be expected to do less well with ASCT. Furthermore, Gribben highlighted that the TRANSFORM study showed improved event-free survival in the CAR T-cell arm compared to standard of care. However, the BELINDA trial showed no difference in event-free survival between the CAR T-cell arm and standard of care arms. Gribben commented that this could be explained by the difficulty in getting CAR

T-cell therapy to patients in a timely manner in the context of aggressive disease. They also discussed comparative analysis studies performed in relapsed/refractory FL, as well as data from other trials investigating CAR T-cell therapy in relapsed/refractory FL and MCL.

Additionally, Gribben discussed that many patients undergoing CAR T-cell therapy would be unfit for ASCT. They spoke on real-world data, which showcased that CAR T-cell therapy can be delivered safely to patients deemed unfit for ASCT, and showed no difference in the incidence of CAR T-cell related toxicity or intensive care admission rates between ASCT-fit and ASCT-unfit patient cohorts.

Bispecific Antibodies

Gribben also discussed bispecific antibodies, spotlighting clinical trial data in relapsed/refractory DLBCL. They stated that responses have been impressive and durable when used as monotherapy. Further to this, bispecific antibodies can be effective in CAR T-cell failure. This is of importance, as it signifies that the mechanism by which tumours do not respond to CAR T-cell therapy is not due to intrinsic resistance to T-cell mediated killing.

TARGETED THERAPIES

Gilles Salles, Lymphoma Service Chief, Steven Greenberg Chair, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, USA, delivered a presentation on the progress and challenges associated with targeted therapies for MCL, FL, and DLBCL, with a focus on Bruton's tyrosine kinase inhibitors.

Bruton's Tyrosine Kinase Inhibitors

Salles explored the impact of ibrutinib, a Bruton's tyrosine kinase inhibitor (BTKi) on outcomes for relapsed/refractory MCL. Pooled analysis of clinical trial data showed that ibrutinib monotherapy resulted in improved patient outcomes and survival. Salles also discussed findings from SHINE, a Phase III randomised controlled trial comparing ibrutinib plus standard of care to standard of care plus placebo in the USA. The results showed improved median progression-free survival of 80.6 months versus 52.9 months, respectively. However, no difference was seen in OS between the two arms. Additionally, whilst more deaths due to disease progression occurred in the placebo arm, more deaths due to treatment-emergent adverse events, and more deaths during post-treatment follow-up that were not caused by disease progression, occurred in the ibrutinib arm. This was not felt to be sufficient to be a confirmatory trial of ibrutinib single agent.

Salles further discussed a European trial that evaluated the superiority of ibrutinib compared to the standard three cycles of R-CHOP and rituximab-dexamethasone, cytarabine, and cisplatin (R-DHAP) regimens followed by ASCT. The TRIANGLE trial used three arms: a control arm where patients received three cycles of R-CHP/R-DHAP and an ASCT; an experimental arm where patients received three cycles of R-CHOP+ibrutinib/R-DHAP, ASCT, and 2 years of ibrutinib maintenance; and another experimental arm where patients received three cycles of R-CHOP+ibrutinib/R-DHAP and 2 years of ibrutinib maintenance (no ASCT). Rituximab maintenance was added following national guidelines in all three trial arms. The results showed that ibrutinib had superiority over the control arm, and that there was no difference in outcome in patients treated with R-CHOP and R-DHAP plus ibrutinib in the presence or absence of ASCT (both experimental arms). Further work is required to clarify if the experimental arm without ASCT is superior to the control arm. The results of TRIANGLE have recently been implemented into the National Comprehensive Cancer Network (NCCN) guidelines for MCL.

Salles also discussed data from clinical trials investigating the use of BTKis as single agents, and in combination with other therapies in FL and MCL.

CHALLENGES AND FUTURE DIRECTIONS

During the presentation, Salles discussed the potential role for protein degraders, explaining that this novel class of therapeutics is being investigated for lymphoma treatment, and could have potential use in scenarios where resistance to other targeted therapies occurs, such as resistance to covalent BTKis.

Whilst this is an interesting area of research, and early results are becoming available, there is still further work to be done in this field.

Looking toward the future, Gribben discussed the successes of chemoimmunotherapy, CAR T-cell therapy, and the promise of bispecific antibodies as monotherapy. Bispecific antibodies are now being investigated for their potential role in combination therapy. Gribben stated: "We are in an era where we have seen immunotherapy markedly improve the outcome for our patients with lymphoma, and we're looking to see how we can improve it further." They commented on the potential for adding immunotherapies to targeted therapies to hopefully improve outcomes even further. Salles highlighted the potential for combination therapy and possibility for progression to chemotherapy-free regimens in the appropriate circumstances.

Regarding future challenges, Salles discussed that due to dysregulation of multiple oncogenic pathways, ensuring treatment is directed against the right target for the right lymphoma entity will remain an ongoing challenge. Additionally, the opportunities for therapeutic development will pose a challenge in a crowded market.

Despite the successes achieved thus far, Gribben commented that the future challenges will involve how to approach immune-mediated treatment for T-cell lymphomas. Salles discussed the ongoing need for translational research and collaboration between academia and industry, alongside examination of longer-term follow-up data.

"We are in an era where we have seen immunotherapy markedly improve the outcome for our patients with lymphoma."

Untangling Systemic Mastocytosis: An Update on Challenges in the Diagnosis and Treatment of Myeloid Neoplasms with Systemic Mastocytosis

This symposium took place as part of the European Hematology Association (EHA) Congress held in Frankfurt, Germany, 8th–11th June 2023

Speakers: Deepti Radia,[1] Andreas Reiter,[2] Julien Rossignol,[3] Eric Solary[4]

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2. Department of Hematology and Oncology, University Hospital Mannheim, Heidelberg University, Germany
3. Centre de référence de mastocytoses (CEREMAST), Hôpital Necker-Enfants Malades, Paris, France
4. Gustave Roussy Cancer Center and Paris-Saclay University, Villejuif, France

Disclosure: Radia has served on advisory boards and participated in training for Blueprint Medicines and Novartis; and has served on steering committees for Blueprint Medicines and Cogent Biosciences. Reiter has received research grants and honoraria from, provided consultancy to, and served on advisory boards for AbbVie, AOP Health, Blueprint Medicines, Bristol-Myers Squibb, GlaxoSmithKline (GSK), Incyte, and Novartis. Rossignol has served on an advisory board for Blueprint Medicines; and has received research grants from Blueprint Medicines, Bristol-Myers Squibb, and Novartis. Solary has provided consultancy to Granite Bio; received research grants from Amgen Foundation and Servier; and has been involved in meetings and training for Blueprint Medicines and Novartis.

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Keywords: Associated haematologic neoplasm (AHN), chronic myelomonocytic leukaemia (CMML), KIT D816V mutation, myeloid neoplasm, serum tryptase, systemic mastocytosis with an associated haematologic neoplasm (SM-AHN).

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Meeting Summary

This symposium was held on the first day of the 2023 European Hematology Association (EHA) Congress, held in Frankfurt, Germany. The main objective of the symposium was to gather experts from the field to raise awareness of the challenges in diagnosing and treating systemic mastocytosis (SM) with an associated haematologic neoplasm (AHN). Presentations focused on optimising the diagnosis of the SM component and recognising the different types of myeloid AHN. The expert panel considered the clinical management of SM-AHN, and how and when to prioritise the various disease components.

The overarching message from the symposium was that diagnosis of SM-AHN is challenging, and SM is often missed in patients with a myeloid neoplasm, such as chronic myelomonocytic leukaemia (CMML), myelodysplastic/myeloproliferative neoplasm (MDS/MPN), myelodysplastic syndrome (MDS), and myeloproliferative neoplasm (MPN), as well as AHN being missed in patients with SM. Identification of a SM-AHN through serum tryptase and/or molecular testing for *KIT*^{D816V} mutation in peripheral blood in a patient with a previous diagnosis of a myeloid neoplasm allows potentially efficacious targeted treatment with *KIT* inhibitors, such as midostaurin and avapritinib. Although SM-AHN is associated with a poor prognosis, a correct diagnosis and detailed understanding of an individual's disease can help to guide optimal treatment decisions, including when to prioritise SM treatment over AHN treatment, and vice versa.

Introduction

Julien Rossignol, Andreas Reiter, and Deepti Radia

Julien Rossignol, Haematologist at Centre de référence de mastocytoses (CEREMAST), a national reference centre for mastocytosis at the Hôpital Necker Enfants Malade, Paris, France, described mastocytosis as a group of rare myeloid neoplasms characterised by the accumulation of atypical, *KIT*^{D816V}-mutated (mostly clonal) mast cells, including cutaneous mastocytosis, SM, and mast cell sarcoma. Up to 10% of all cases of SM can be classified as advanced SM,[1,2] a category that includes SM-AHN, aggressive systemic mastocytosis, and mast cell leukaemia.[3-5] The prognosis for advanced SM is poor, with a median survival of 24–42 months,[6] mainly due to the abnormal infiltration of mast cells into various organs resulting in severe and debilitating symptoms, and life-threatening organ damage.[5,7]

Approximately two in three patients with advanced SM also have an AHN of myeloid origin.[7] Andreas Reiter, Professor at the Centre of Excellence for Mastocytosis, University Hospital Mannheim, Heidelberg University, Germany, mentioned that approximately 5–10% of patients with CMML, approximately 2–5% patients with MDS/MPN, and approximately 2–3% of patients with MPN or acute myeloid leukaemia (AML) may carry the *KIT*^{D816V} mutation (Reiter, personal communication based on the German Registry on Disorders of Eosinophils and Mast Cells, unpublished data). Moreover, it is one of the most frequent molecular abnormalities in the diagnostic work-up of eosinophilia.[8] Based on a retrospective study, the majority of patients (91%) with *KIT*^{D816V}-mutated chronic myeloid neoplasms, such as CMML, MDS/MPN, MDS, or MPN, had concurrent SM, which has been shown to be missed in nearly one-third of cases.[9]

Deepti Radia, Consultant Haematologist at Guy's and St Thomas' Hospitals NHS Foundation Trust, London, UK, explained that SM-AHN has a complex, heterogenous clinical presentation, involving the SM variant, SM burden, AHN subtype, and AHN risk profile.[3,10,11] This can make accurate diagnosis of advanced SM challenging, yet it is extremely important because of the substantial impact it has on patient management decisions.[2]

Which Myeloid Neoplasms Occur in Patients with Systemic Mastocytosis with an Associated Haematologic Neoplasm?

Julien Rossignol

The vast majority of SM-AHN are associated with myeloid neoplasms rather than lymphoid neoplasms, such as lymphoma or multiple myeloma.[3,5] Rossignol explained that this may be because of the clonal architecture of SM-AHN associated with additional mutations in myeloid neoplasms, particularly MDS, MPN, and MDS/MPN. This is suggested by several studies, which found that mutations associated with AHN affect genes such as *TET2*, *SRSF2,* and *ASXL1*, and that *KIT*^{D816V}, which is frequently associated with SM, is a sub-clonal mutation, occurring later in the hierarchy of differentiation.[5,9,12] Rossignol mentioned that in the French national registry, CMML is the most frequent AHN associated with SM, followed by other MDS/MPN, MPN, and MDS. The SM component is frequently advanced, especially in patients with MDS/MPN (Rossignol, personal communication based on the French national registry, unpublished data).

Optimising Diagnosis and Subtyping in Systemic Mastocytosis with an Associated Haematologic Neoplasm

Andreas Reiter, Eric Solary, and Julien Rossignol

Reiter highlighted that approximately 20% of cases of SM may initially be missed in patients with chronic myeloid neoplasms, leading to delayed diagnosis and treatment for patients.[13] Reiter explained that SM should be suspected in patients presenting with anaphylaxis, flushes, fatigue, typical skin lesions, or symptoms in bones or the gastrointestinal tract. Reiter highlighted that routine tryptase testing in blood (or tryptase staining in bone marrow biopsy) and high-sensitivity *KIT*^{D816V} variant allele fraction testing in peripheral blood can help to screen for hidden SM in myeloid neoplasms. Eric Solary, Professor of Haematology at the Gustave Roussy Cancer Center and Paris-Saclay University, Villejuif, France, recommended that AHN should be suspected in patients diagnosed with SM when there is evidence of monocytosis, eosinophilia, splenomegaly, elevated lactate dehydrogenase, high *KIT*^{V617F} variant allele fraction in peripheral blood, or additional somatic mutations.

The 2022 World Health Organization (WHO) and International Consensus Classification (ICC) criteria for the diagnosis of SM are very similar.[4,14] For SM diagnosis, a patient needs to meet one major and one minor, or three minor criteria. The major criterion for diagnosis of SM is the presence of "multifocal dense infiltrates of mast cells (≥15 mast cells in aggregates) in bone marrow biopsies and/or in sections of other extracutaneous organ(s) component of SM."[4,14] However, Rossignol stressed that bone marrow biopsy is not routinely performed in all countries, and where it is performed, it may be challenging for an inexperienced pathologist to recognise mast cells in bone marrow biopsy if not using appropriate mast cell biomarkers, such as tryptase and cluster of differentiation 117 (CD117). Rossignol suggested that these issues may contribute to the underdiagnosis of the SM component of SM-AHN.

One of the four minor criteria for the diagnosis of SM is the detection of a "KIT-activating KIT point mutation in codon 816 or in other critical regions of KIT in bone marrow or another extracutaneous organ."[4,14] Rossignol explained that next-generation sequencing has a low sensitivity for detecting *KIT* mutations, because of the low *KIT*^{D816} variant allele fraction in the peripheral blood of many patients, and they recommended the use of a high-sensitivity assay, such as droplet digital PCR, for this purpose.[15,16]

Another minor diagnostic criterion for SM is the detection of "baseline serum tryptase concentration >20 ng/mL."[4,14] Rossignol pointed out that tryptase is not routinely assessed in patients diagnosed with myeloid neoplasms (especially those with CMML), and suggested that this test should be more commonly performed to screen for SM in this population, in order to alert the clinician to the possibility of concurrent SM disease.

SM-AHN should be further classified according to AHN type.[3,4,14] The AHNs most frequently associated with SM are MDS/MPNs, particularly CMML.[9]

The 2022 WHO and ICC definitions of CMML are similar, incorporating blood monocytes at ≥500 cells/μL and ≥10% of white blood cells; clonality markers; and ('or' in the ICC definition) cell dysplasia. In addition, the ICC definition requires an abnormal immunophenotype consistent with CMML.[4,14] CMML-1 presents with <5% blast cells in peripheral blood and <10% in bone marrow, and CMML-2 with 5–19% blasts in peripheral blood and 10–19% in bone marrow.[4]

Solary described the typical CMML patient as a male of approximately 70 years of age, in whom monocytosis is revealed through a routine blood test. If subsequent tests reveal cell dysplasia, clonality, or an abnormal partition of monocyte subsets, then that patient should be diagnosed with CMML.[4] Overall, CMML is a severe disease with median survival of approximately 29 months.[17]

Clinical Updates in Treatment of Systemic Mastocytosis with an Associated Haematologic Neoplasm

Andreas Reiter and Eric Solary

Systemic Mastocytosis Component

Prior to the development of novel tyrosine kinase inhibitors, targeting KIT D816V, such as multikinase inhibitor midostaurin and selective inhibitor avapritinib, treatment for patients with advanced SM was based on the off-label use of the purine analogue, cladribine.[18] Despite remaining an off-label therapy, Reiter explained that cladribine is still a relevant treatment option for some patients.[18]

An analysis of registry data found that cladribine treatment in patients with advanced SM was associated with a median overall survival of 1.9 years at first-line (n=48) and 1.2 years at second-line (n=31), and risk stratification made little difference to these outcomes.[18]

In contrast, an open-label clinical trial found that midostaurin treatment of patients (N=116) with advanced SM was associated with a median overall survival of 2.4 years (28.7 months) and a median progression-free survival of 1.2 years (14.1 months). Moreover, for the first time, reductions in all measures of mast cell burden were observed, including bone marrow mast-cell burden, serum tryptase levels, and spleen volume. Midostaurin improved most symptoms except for nausea and vomiting, which were the most common non-haematologic adverse events (AE; experienced by 79% and 66% of patients, respectively).[19] Reiter noted that most patients achieved partial responses on midostaurin. Based on these data, midostaurin was approved in 2017 as a first tyrosine kinase inhibitor for the treatment of patients with advanced SM.[20]

In the absence of randomised trials in this rare disease setting, a retrospective comparative analysis of data from the German Registry on Disorders of Eosinophils and Mast Cells (GREM) for patients with advanced SM treated with midostaurin (n=63) and cladribine (n=23) showed that midostaurin was associated with a significantly improved median overall survival versus cladribine (4.2 years versus 1.9 years, respectively; p=0.033), and a significantly higher probability of leukaemia-free survival (2.7 years versus 1.3 years, respectively; p=0.044) on the basis of a propensity score-weighted analysis.[21]

In 2022, a second tyrosine kinase inhibitor, avapritinib, was approved for treatment of patients with advanced SM after at least one systemic therapy.[22] The safety and efficacy of avapritinib in patients with advanced SM was assessed in two open-label studies: EXPLORER[7] and PATHFINDER.[23] A post hoc analysis was conducted on the pooled sub-population of patients from these two studies who were initiated on 200 mg daily of avapritinib, and who had received ≥1 prior therapy (N=31).[24] With a median duration of follow-up of 17.7 months, the overall response rate among patients with advanced SM was 71%, and in patients with SM-AHN, the most challenging subtype, the overall response rate was 77% (n=22). Reiter noted that for the first time, complete remission (3%) and complete remission with partial haematologic recovery (16%) was observed in patients with advanced SM. Mutations in *SRSF2*, *ASXL1,* and/or *RUNX1* are associated with poor prognosis in advanced SM, but they had no apparent effect on avapritinib efficacy, with an overall response rate of 64% in patients with ≥1 mutation in *SRSF2*, *ASXL1,* and/or *RUNX1*;

and 78% in patients without. Avapritinib also reduced all measures of mast cell burden: 89% of patients had ≥50% reduction from baseline in bone-marrow mast cell infiltrates (60% had total clearance of mast cell aggregates); 89% had ≥50% reduction from baseline in serum tryptase; 66% had ≥50% reduction from baseline in *KIT*^{D816V} variant allele fraction (21% to below the limit of detection); and 70% had ≥35% reduction from baseline in spleen volume. In terms of the AHN components of disease, avapritinib appeared to reduce eosinophil counts in all patients with baseline eosinophilia; and to normalise peripheral monocytes in almost all patients with baseline monocytosis.[24]

The most common AEs shown to occur with avapritinib 200 mg in advanced SM were periorbital oedema (38%), thrombocytopenia (37%), peripheral oedema (33%), and anaemia (22%).[25] Among 193 patients enrolled in avapritinib studies for advanced SM (all doses), 12% experienced serious AEs during treatment.[25] Among patients on 200 mg avapritinib (n=126), only 7% experienced an AE leading to permanent discontinuation, and 79% reduced the dose of avapritinib after a median of 6 weeks of treatment. Serious AEs of intracranial haemorrhage have been reported in patients with advanced SM receiving avapritinib, and therefore avapritinib is not recommended in patients with platelet counts <50×10^9 /L. Platelet counts should be regularly monitored during treatment, and low platelets can be managed by temporarily interrupting avapritinib and modifying the dose. Platelet support, including thrombopoietin agonists, may be considered in some cases (see avapritinib summary of product characteristics for further details).[25]

There are no randomised trials that compared avapritinib with alternative therapies in advanced SM, because the disease is so rare. Therefore, Reiter et al.[26] compared clinical trial data for avapritinib (n=176) with real-world data from a multicentre, observational, retrospective chart review of patients who received systemic treatment for advanced SM (best available therapy cohort [including midostaurin and cladribine]; n=141). The study found that among patients with ≥1 prior line of therapy, those treated with avapritinib 200 mg had a 63% lower risk of death compared with those treated with best available therapy (p=0.006).[26]

Associated Haematologic Neoplasm Component

Given the clinical and biological heterogeneity of CMML, Solary explained that the current treatment approach ranges from 'watch and wait' with active monitoring, through erythropoiesis-stimulating drugs to treat anaemia, to more aggressive therapy in patients with proliferative disease and poor risk factors, including the use of cytoreductive drugs (e.g., hydroxyurea), hypomethylating agents (HMA; e.g., azacitidine and decitabine), or allogeneic haematopoietic cell transplantation (alloHCT), depending on the patients' age and comorbidities.[27]

Regarding alloHCT, Solary shared that a large retrospective cohort study found that performing alloHCT before a patient progresses from CMML to acute AML can decrease the life expectancy in lower-risk patients (N=1,114; hazard ratio [HR]: 3.19; p<0.001), but it can be beneficial and may be considered in high-risk patients with CMML.[28] Solary also presented data from two studies illustrating that HMA therapy does not impact the genetic component of disease in CMML. The first study showed that although an HMA can generate a complete clinical response, with correction of cytopenia, decrease in spleen volume, and reduction of monocytosis, it does not decrease the size of the mutated clone or prevent somatic evolution (N=17), and this can eventually lead to relapse.[29] The second study showed that while treatment with decitabine significantly reduced the risk of progression to AML compared with hydroxyurea treatment (HR: 0.62), it increased the risk of death without progression/transformation (HR: 1.55; N=170). Therefore, HMA treatment did not improve event-free survival when compared to hydroxyurea in this population (HR: 0.83).[30]

Solary described CMML as a disease of ageing with a proliferative component, few residual wild-type stem cells, and alteration of the bone marrow niche. Solary stressed that the current treatment approaches do little to reduce the diseased cell count, and that dedicated treatments need to be developed for specific subsets of CMML. Solary posited that it might be prudent to approach treatment with an aim to slow disease progression and improve quality of life, rather than eradicating the clonal cells.

In general, there is a strong need for new therapeutic strategies in CMML, including optimising the use of epigenetic regulators (epidrugs), such as HMAs and combinations; developing new treatments for cytopenia (e.g., ligand traps for activins and growth differentiation factor 11, and eltrombopag for thrombocytopenia); and targeting granulocyte macrophage colony stimulating factor signalling, rat sarcoma virus (RAS) signalling, or other pathways and targets, such as the cytokines released by mature CMML monocytes and the cells of the niche.[31]

Challenges in Treatment Decision-Making for Systemic Mastocytosis with an Associated Haematologic Neoplasm

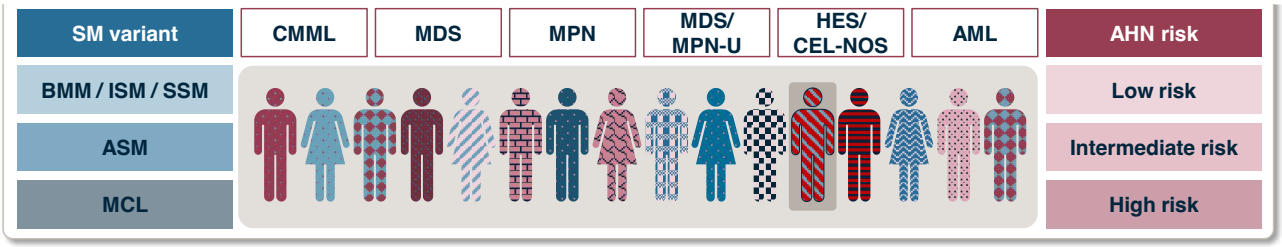
Deepti Radia

The complex, heterogenous clinical presentation of SM-AHM can make accurate diagnosis challenging (Figure 1). Radia explained that there are numerous variables that inform decisions on treatment strategy, such as the SM component subtype and symptom burden; the AHN component subtype, including mutations and lineage; the presence of organ involvement, comorbidity and age; and AHN risk category.[3,4,32]

Radia shared their approach to guiding treatment pathways in SM-AHN, explaining that they are more likely to prioritise treatment of the SM component if it is associated with a high symptom burden, C-finding attributed to SM, high tryptase level, and high *KIT* mutation burden; and more likely to prioritise treatment of the AHN component if it is associated with monocytosis or eosinophilia, low *KIT* mutation burden, and altered bone marrow morphology with significant additional high-risk mutations (Figure 2).[32]

The remaining challenges and questions that need to be addressed for optimal treatment of SM-AHN were summarised by Radia as: what are the best approaches to risk stratification for individual patients; should we routinely use mutational profiles to guide treatment and monitor responses in all patients with SM; how and when should combination or sequential treatment be offered; and what is the place of alloHCT as a curative option?

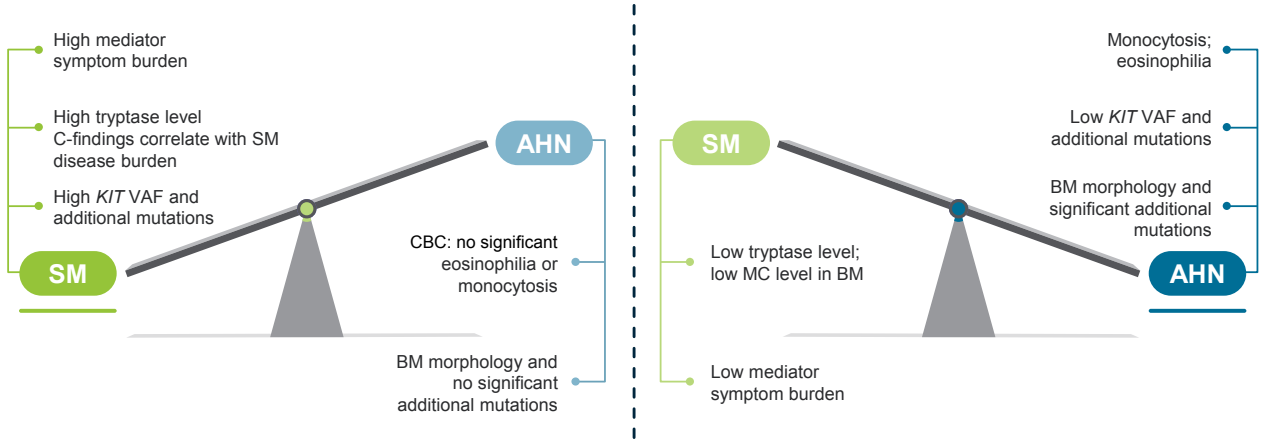
Figure 1: Clinical presentation of systemic mastocytosis with associated haematologic neoplasm varies, and involves both systemic mastocytosis variant and burden, and associated haematologic neoplasm subtype and risk profile.[3,10,11,13]



Reproduced with permission from Blueprint Medicines.[3,10,11,13]

AHN: associated haematologic neoplasm; AML: acute myeloid leukaemia; ASM: aggressive systemic mastocytosis; BMM: bone marrow mastocytosis; CEL-NOS: chronic eosinophilic leukaemia, not otherwise specified; CMML: chronic myelomonocytic leukaemia; HES: hyper-eosinophilic syndrome; ISM: indolent systemic mastocytosis; MCL: mast cell leukaemia; MDS: myelodysplastic syndrome; MPN: myeloproliferative neoplasm; MPN-U: myeloproliferative neoplasm-unclassified; SM: systemic mastocytosis; SSM: smouldering systemic mastocytosis.

Figure 2: An approach to guiding treatment priorities in systemic mastocytosis with associated haematologic neoplasm.[32]



Reproduced with permission from Radia.[32]

AHN: associated haematologic neoplasm; BM: bone marrow; CBC: complete blood count; MC: mast cell; SM: systemic mastocytosis; VAF: variable allele frequency.

Key Summary Points

- Myeloid neoplasms, such as CMML, MDS/MPN, MPN, and MDS, are most often found in association with SM (SM-AHN).
- The diagnosis of SM-AHN is frequently delayed: SM is missed in patients with myeloid neoplasm, or AHN is missed in patients with SM.
- Routine testing for serum tryptase and quantitative *KIT*^{D816V} analysis in peripheral blood using a high-sensitivity assay can help to screen for SM in patients with myeloid neoplasms, especially CMML.
- Identification of a SM-AHN in a patient with a previous diagnosis of a myeloid neoplasm allows potentially efficacious targeted treatment with midostaurin and avapritinib.
- Treatment decisions in SM-AHN depend on patient symptoms, mast cell burden, presence of C-findings, *KIT*^{D816V} lineage involvement, AHN burden, and additional somatic mutations.
- There is a risk of progression of AHN, e.g., secondary AML, with the need to monitor the clonal evolution during treatment.
- Sequential targeted therapy can be beneficial in the management of SM-AHN.

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Abstract Reviews

Sharing current research in haematology from the cutting-edge abstracts shared at the 28th Congress of the European Hematology Assication (EHA) 2023.

RAS-ERK Pathway Genes Mutations in the Lesions from Various Tumour Loci in Multiple Myeloma

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Keywords: Bone marrow, ctDNA, RAS-ERK cascade genes, multiple myeloma, plasmacytoma.

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BACKGROUND AND AIMS

Despite the fact that activating mutations in RAS-ERK cascade genes are quite often detected in multiple myeloma (MM), the literature data on their prognostic value are contradictory.[1,2] The tumour substrate should not only be analysed in the bone marrow and plasmacytoma, but also in the plasma circulating tumour DNA (ctDNA) for the heterogeneity of MM to be effectively analysed.[3,4] The aim was to study the mutational status of *KRAS*, *NRAS*, and *BRAF* genes in the tumour substrate from different loci in MM.

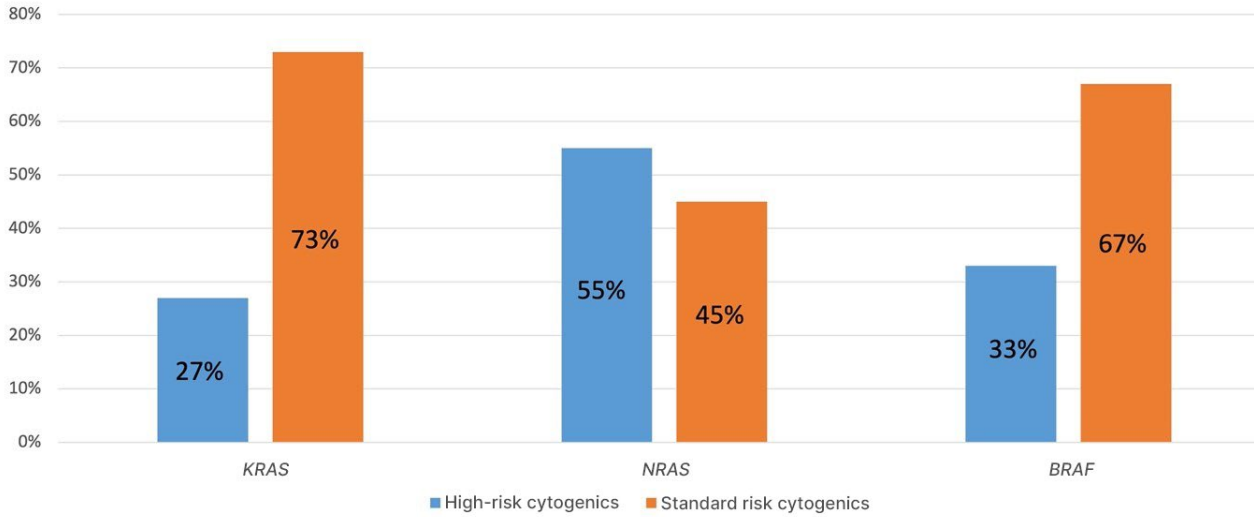
MATERIALS AND METHODS

The single-centre study from October 2021–January 2023 included 70 patients with symptomatic MM (29 male, 41 female) aged 35–84 years (median: 58 years). Plasmocytomas were detected in 66% of the patients with MM according to CT data. They were detected in the bone of 40 patients and extramedullary in six. A fluorescence in situ hybridization (FISH) study of CD138+ cells was performed using DNA probes to detect translocations of 14q32/IgH, 8q24/MYC; deletions of 17p13/TP53, 13q14, 1p32; amplification of 1q21; and multiple trisomies (MetaSystems, Altlussheim, Germany). Upon detection of t(4;14) translocation, t(14;16) translocation, del17p13, and amplification of 1q21, the patient was assigned to a high cytogenetic risk group. DNA was isolated from samples of various localisation: CD138+ bone marrow cells (n=60), ctDNA (n=19), bone plasmacytoma (n=9), and extramedullary plasmacytoma (n=6). The mutational status of *KRAS*, *NRAS*, and *BRAF* genes was studied in the tumour substrate from different loci. *KRAS* and *NRAS* gene mutations were identified by Sanger sequencing on the Nanophor 05 genetic analyser (Institute for Analytical Instrumentation Russian Academy of Science, Saint Petersburg, Russia), and by next-generation sequencing on the MiSeq System genetic analyser (Illumina, San Diego, California, USA). The *BRAF* V600E mutation was determined by real-time allele-specific PCR with the device CFX96 Touch (Bio-Rad Laboratories Inc., Hercules, California, USA).

RESULTS

KRAS gene mutations were detected in 16% of patients (11/70), of which less than one-third (27%) had high-risk cytogenetic abnormalities.

Figure 1: Cytogenetic abnormalities in patients with multiple myeloma with *KRAS*, *NRAS*, or *BRAF* gene mutations.



NRAS gene mutations were detected in another 16% of patients, while more than half (55%) were assigned to a high cytogenetic risk group. *BRAF* gene mutations were found in 9% of patients (6/70), one-third of whom had high-risk aberrations (Figure 1). Paired tumour samples (plasma ctDNA and CD138+ bone marrow cells) were analysed in 15 patients with MM. In 11 patients, mutations in any of the three genes were found in the bone marrow, while in five patients (45%) similar mutations were also detected in a paired sample of tumour ctDNA isolated from plasma. No cases with *KRAS*, *NRAS*, or *BRAF* gene mutation detected in the plasma and the absence of the corresponding mutation in the bone marrow were found. The mutational status of the three genes was analysed in 15 plasmacytoma samples (nine bone, six extramedullary). It turned out that only *KRAS* gene mutations (7% of cases) were detected in the samples of bone plasmacytomas, and only *NRAS* gene mutations (50% of cases) were detected in the samples of extramedullary plasmacytomas.

CONCLUSION

There was a trend towards higher frequency of high-risk cytogenetic aberrations in patients with *NRAS* gene mutations compared to patients with *KRAS* gene mutations (55% versus 27%). It was also determined that the *NRAS* gene was mutated in 50% of extramedullary plasmacytomas samples. In 45% of the cases with *KRAS*, *NRAS*, or *BRAF* gene mutation detected in the bone marrow substrate, similar mutations were also detected in the tumour ctDNA isolated from plasma. ●

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UBA1 Non-M41 Variants Are More Aggressive than *UBA1* M41 Variants in Their Haematological Manifestations

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Keywords: Auto-inflammation, DNA damage repair, leukaemia, myelodysplastic syndrome (MDS), nuclear localisation, somatic variants, *UBA1*, ubiquitin-proteasome pathway, VEXAS, X-linked.

Citation: EMJ Hematol. 2023;11[1]:37-38. DOI/10.33590/emjhematol/10308258. https://doi.org/10.33590/emjhematol/10308258.

BACKGROUND AND AIMS

In 2020, three somatic mutations in the X-linked gene *UBA1*, coding for an essential ubiquitin activating enzyme, were reported to cause VEXAS syndrome, a novel haemato-inflammatory disease that manifests with both cytopenias and autoinflammation.[1] The mutations alter the start codon (M41) of the cytoplasmic isoform of *UBA1*, resulting in the cytoplasmic-only loss of function of *UBA1*. Approximately 50% of patients with VEXAS develop myelodysplastic syndrome (MDS), but interestingly progression to acute myeloid leukaemia (AML) is extremely rare. The speculated protective mechanisms of *UBA1* mutations from malignant transformation intrigued the authors to retrospectively analyse the whole genome data from more than 4,000 patients diagnosed with various haematological malignancies (HM), which revealed 16 putative somatic non-M41 *UBA1* variants.[2] Most of the novel mutations surrounded either adenosine triphosphate-contacting, ubiquitin-contacting, or interdomain-interacting residues, which are considered to affect both the nuclear and cytoplasmic isoforms of *UBA1*. Surprisingly, secondary AML progression was not rare in patients harbouring the novel non-M41 *UBA1* variants. Literature indicates involvement of *UBA1* in DNA damage repair,[3] which suggested mutations impairing *UBA1* nuclear isoform may be more malignant than M41 variants.

MATERIALS AND METHODS

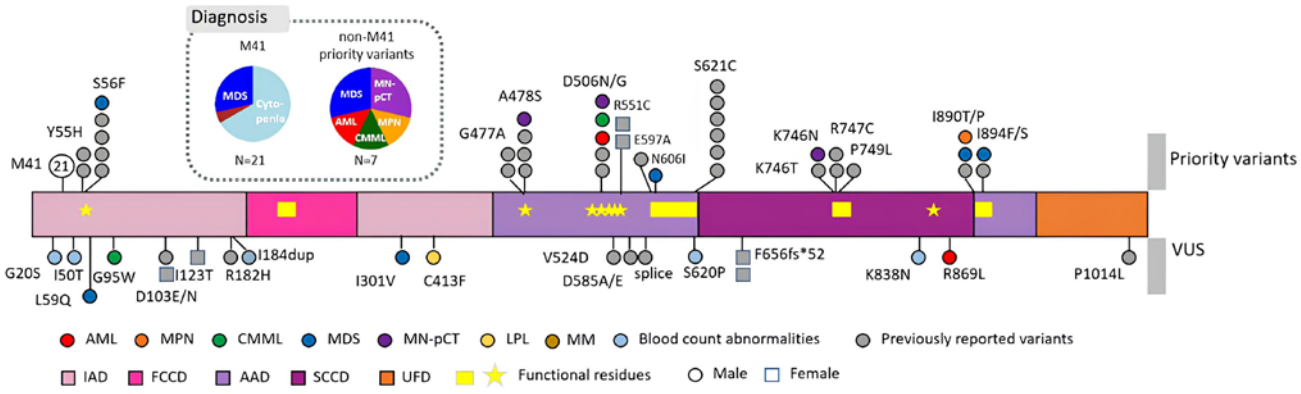
To further understand this difference, Munich Leukemia Laboratory (MLL), Germany, introduced the entire coding sequence of *UBA1* in the gene panel for 9,771 samples sent for diagnostic testing. The somatic state of the variants were assigned based on the variant allele frequency as previously described,[2] and the variants were further classified into priority variants, if they had been previously detected in symptomatic patients[2,4,5] and surrounded the functional residues.[6] All other variants were classified as variants of uncertain significance (VUS).

RESULTS

In this new screen, the authors detected 28 *UBA1* variants in 42 patients (Figure 1). M41 variants were detected in 21 patients, non-M41 priority variants in seven patients, and non-M41 VUS in 15 patients (nine males; six females), including five patients with multiple mutations. All priority variants were detected in male patients.

Concerning diagnosis, M41 variants were detected only in patients diagnosed with MDS (N=6) or with suspected MDS (N=14), with one multiple myeloma exception. In contrast, the priority variants were again detected in patients diagnosed with more aggressive HMs (two MDS; one chronic myelomonocytic leukaemia; one myeloproliferative neoplasm; one AML; and two myeloid neoplasms post cytotoxic therapy), three of whom showed more than 10% blasts. The non-M41 VUS also received diverse diagnoses. The patients carrying the M41 variants infrequently carried co-mutations (29%) or cytogenetic aberrations (5%),

Figure 1: Detected *UBA1* variants and associated diagnoses.



Loci of variants are shown as circles on the genes, with their diagnoses colour coded. Loci of previously reported variants are shown in grey to denote recurrence. Known functional regions are highlighted by yellow within the gene. Females are denoted by squares.

AAD: active adenylation domains; AML: acute myeloid leukaemia; CMML: chronic myelomonocytic leukaemia; FCCD: first catalytic cysteine half-domain; IAD: inactive adenylation domains; LPL: lymphoplasmacytic lymphoma; MDS: myelodysplastic syndrome; MM: multiple myeloma; MN-pCT: myeloid neoplasm post cytotoxic therapy; MPN: myeloproliferative neoplasm; SCCD: second catalytic cysteine half-domain; UFD: ubiquitin fold domain; VUS: variants of uncertain significance.

whereas the male non-M41 variants often harboured co-mutations (67%) and cytogenetic aberrations (33%).

Presence of inflammatory symptoms was not required to be included in the screening, but records of inflammatory symptoms were communicated for nine out of 21 patients harbouring M41 variants. Two out of 7 patients carrying priority variants had cutaneous vasculitis, and one patient carrying a VUS (L59Q) was suspected to have sweet syndrome.

CONCLUSION

In summary, the ongoing large-scale screen of non-M41 variants in patients suspected of HMs continues to detect both recurrent and novel non-M41 variants. The patients harbouring non-M41 variants are rare but may be more malignant, and functional validation would contribute to clarifying the role of UBA1 in haematology and its prognostic significance.

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Introducing the Concept of Patient Blood Management and Haemovigilance in Government Sector Hospitals of Sindh, Pakistan

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Keywords: Cross match to transfusion ratio, haemovigilance, patient blood management, restrictive transfusion strategy.

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BACKGROUND AND AIMS

Patient blood management encompasses all aspects of the transfusion decision-making process, beginning with the initial patient evaluation and continuing through clinical management.[1] It involves the timely, multidisciplinary application of evidence-based medical and surgical concepts, aimed at diagnosing and appropriately treating anaemia, along with minimising surgical and iatrogenic blood losses and managing coagulopathic bleeding, as well as supporting the patient while appropriate treatment is initiated.[1]

Haemovigilance is the set of surveillance procedures covering the entire blood transfusion chain, from the donation and processing of blood and its components, through to their provision and transfusion to patients, including their follow-up.[2]

The restrictive transfusion threshold uses a lower haemoglobin concentration as a threshold for transfusion (most commonly 7–8 g/dL), and the liberal transfusion threshold uses a higher haemoglobin concentration as a threshold for transfusion (most commonly 9–10 g/dL).[3]

MATERIALS AND METHODS

In this retrospective analysis, the authors aimed to critique and study their own performance since the establishment of the Regional Blood Centre (RBC) Karachi (2020–2022), Pakistan, and its associated hospital-based blood banks (currently three).

The authors calculated parameters, including cross match to transfusion ratio and transfusion index; introduced the concept of maximum surgical blood ordering schedule; assessed the cold chain maintenance through data loggers and transportation containers; reported transfusion reactions; and overviewed the overall haemovigiliance concept over 3 years' time.

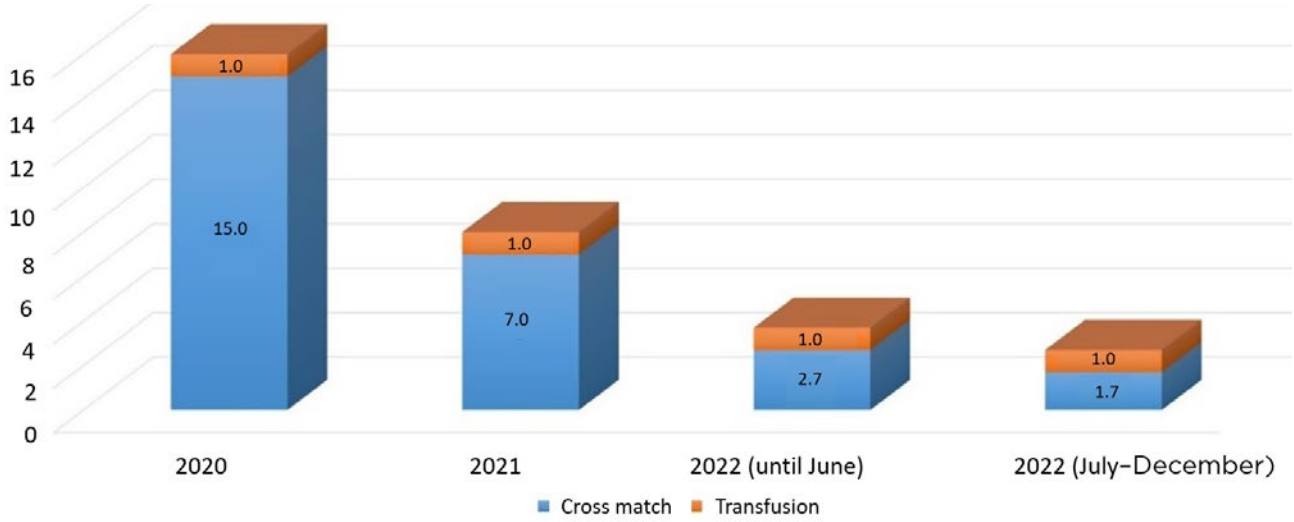
RESULTS

When the authors started their blood banking in government sector hospitals of Karachi, whole blood was being issued to the patients. From the first day, RBC Karachi worked on blood products and did not issue a single whole blood to any patient. Initially, the cross match to transfusion ratio was 15:1, but with time and management, at the end of third year, they achieved the ratio of 1.5–1.7:1 for different hospitals (Figure 1). Transfusion index was also calculated to be 0.2 at the start of 2020 and was reported to be 0.8 at the end of 2022.

CONCLUSION

Initially, for 1.5 years, the authors were not able to get a single transfusion reaction reported;

Figure 1: Graphical representation of cross match to transfusion ratio of red blood cells and its associated blood banks.



however, after several awareness and training sessions, and continuing medical education, they started getting transfusion reactions reporting around 2–3 times fortnightly. Initially, wastage was higher than utilisation; however, with hard work and communication, the authors were able to reduce the wastage and suggested the idea of a restrictive transfusion strategy, so that the right blood component is given to the right patient at the right time. It was a tough journey as there are, unfortunately, no haematologic units in the government sector hospitals, and dealing with doctors along with patients was not easy.

The authors' aim is to provide the best transfusion services to those who cannot afford it and their journey is still ongoing.

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Abstract Highlights

Classical Hodgkin lymphoma, acute promyelocytic leukaemia, post-transplant relapse, massive transfusion, and many more essential topics in haematology were explored in several unique and insightful abstracts presented at the European Hematology Association (EHA) 2023 Congress.

Citation: EMJ Hematol. 2023;11[1]:41-47.
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https://doi.org/10.33590/emjhematol/10305989.

Is There a Correlation Between Progression-Free and Overall Survival in Classical Hodgkin Lymphoma?

PROGRESSION-FREE survival (PFS) is often a primary endpoint in clinical trials as a measurement of treatment efficacy. Another of these treatment efficacy measures is overall survival (OS). Despite this, the relationship between PFS and OS is unknown.

Researchers from the German Hodgkin Study Group evaluated whether there is a correlation between PFS and OS following first-line treatment for patients with classical Hodgkin lymphoma (HL). The team analysed data obtained during and after polychemotherapy from 10,605 patients with classical HL, who were enrolled across nine Phase III randomised German Hodgkin Study Group first-line clinical trials between January 1993–August 2018. PFS and OS were defined as time from randomisation until progression, relapse, or death, and time from randomisation until death, respectively.

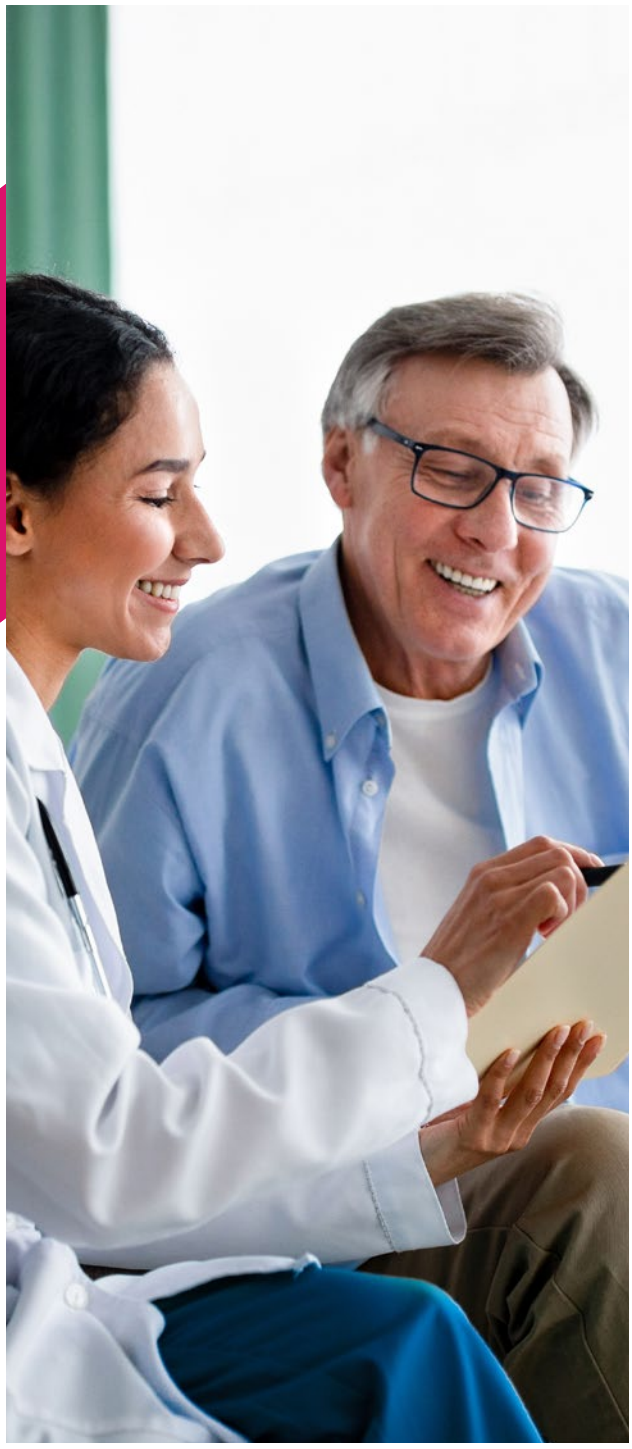
Records of ≥1 PFS and ≥1 OS event occurred for 1,682 and 1,064 patients, respectively. A significant and high correlation was seen at the trial level for treatment effects on PFS and OS (Pearson correlation coefficient [Pearson r]: 0.72; r^2=0.54; p<0.001). Application of a multiple regression model to account for differing effectiveness of experimental treatments and historical progress over trial generation yielded an r^2 of 0.93. In addition to this, analysis at the patient level also showed a high correlation between PFS and OS.

For the clinical trials, the researchers found that the average Pearson r was 0.74 (range: 0.61–0.85), with p<0.001 for each trial. All bar two trials showed high correlation, with Pearson r values of >0.70. Furthermore, Pearson r was higher in more advanced stages of HL. At the patient level, a high correlation was noted between the effects of risk factors on PFS and OS (Pearson r: 0.74–0.85; each p<0.001 using Wei–Lin–Weissfeld method to apply marginal Cox PH models for multiple endpoints) and PFS and OS directly (Pearson r: 0.72–0.83; each p<0.001 using copula models), were also identified.

> **"Analysis at the patient level also showed a high correlation between PFS and OS."**

The researchers concluded that PFS can predict treatment effects on OS in advance of reliable OS evaluation, as there is a high correlation between PFS and OS, as well as treatment effects and prognostic effects of risk factors on PFS and OS in first-line clinical trials in classical HL. ●

Factors Associated with Long-Term Survival in a Patient Cohort with Acute Promyelocytic Leukaemia



"The HARMONY registry includes 1,868 patients with APL diagnosed between 2007–2020."

Acute promyelocytic leukaemia (APL) is currently curable in 75–90% of patients using targeted agents, such all-trans retinoic acid (ATRA) and arsenic trioxide (ATO), or ATRA combined with chemotherapy (ATRA+idarubicin, AIDA-based). The HARMONY registry enabled the merging of APL patient populations from both clinical trials and real-world settings, aiming to address unresolved aspects in the management of the disease. The HARMONY registry includes 1,868 patients with APL diagnosed between 2007–2020.

At the EHA Congress 2023, held in Frankfurt, Germany, Maria Teresa Vosso, Tor Vergata University of Rome, Italy, presented data from the HARMONY registry, which analysed factors associated with long-term survival in patients with APL.

Vosso and colleagues analysed patients (n=674) who underwent treatment and met the data quality requirements. Of these, 320 patients were treated with ATRA-ATO (median age: 48.5 years; range: 16–87; 47.8% female), while the remaining 354 were treated with AIDA (median age: 47.0 years; range: 17–82; 51.1% female). The data were harmonised and transformed using an Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM), and ultimately registered in the HARMONY Big Data platform.

The results revealed that patients treated with the ATRA-ATO regimen had a 92% overall survival rate at the 10-year mark, whereas those treated with the AIDA regimen had an 85% survival rate. The survival advantage was consistent across various risk groups, as determined by the Sanz risk-score. Additionally, age emerged as a crucial factor, with younger patients exhibiting better outcomes.

Based on a large international patient cohort, these findings affirm the significant survival benefit of the ATRA-ATO chemotherapy-free regimen for patients with APL, irrespective of their risk profile. ●

Chimeric Antigen Receptor T Cell Therapy for Post-Transplant Relapse

RESULTS from a retrospective study assessing outcomes following chimeric antigen receptor (CAR) T cell therapy, tisagenlecleucel (Tisa-cel), for post-haematopoietic stem cell transplant (HSCT) relapse in young patients (≤25 years) with CD19 positive acute lymphoblastic leukaemia (ALL), were presented at the EHA Congress 2023.

Data from 145 consecutive patients at 27 centres across seven European countries, who received Tisa-cel as treatment for post-HSCT relapse between 1st September 2018–1st January 2022, were evaluated. Median patient age was 9 years (range: 1–25 years). Of the 145 patients, 71 (57%) had <5% leukaemic blasts in their bone marrow upon lymphodepleting chemotherapy, 53 (43%) had >5% leukaemic blasts, and data was missing for 21 patients. Post-HSCT relapse occurred in ≤6 months for 38 patients (30%) and >6 months in 87 patients (70%). Those who relapsed at >6 months were deemed late relapsed patients, and those who relapsed within 6 months were deemed early relapsed.

The study found that 2-year event-free survival (EFS) and 2-year overall survival (OS) was 44.3% (±4.8%) and 64.0% (±4.7%), respectively. At Day 28, 135 of the total 145 patients were in remission; of these, the 2-year relapse-free survival was 46.1% (±5.1%); the 2-year non-relapse mortality was 1.6% (±1.1%); and the 2-year probability of persistent B cell aplasia was 46.3% (±6.7%).

For early relapsed patients, 2-year EFS was 19.5% (±8.3%) compared to 53.0% (±6.3%) for late relapsed patients (p=0.001). The 2-year OS was 35.9% (±9.2%) and 78.2% (±5.3%) for early and late relapsed patients, respectively (p<0.001). Alongside improved 2-year EFS and 2-year OS, 2-year relapse-free survival was also higher in late relapsed patients, at 51.9% (±6.6%) compared to 24.0% (±10.0%) for early relapsed patients (p=0.020).

"Alongside improved 2-year EFS and 2-year OS, 2-year relapse-free survival was also higher in late relapsed patients."

The 2-year cumulative incidence of relapse after Tisa-cel was lower in late relapsed patients than early relapsed patients at 42.8% compared to 70.4% (p=0.006). The 2-year persistent B cell aplasia was higher in late relapsed patients than early relapsed patients (55.5% and 13.7%, respectively), which could be suggestive of CAR-T cell sub-potency in patients who experience early relapse. Cytokine release syndrome occurred in 79 patients (63%), and immune effector cell-associated neurotoxicity syndrome occurred in 13 patients (11%).

The authors concluded that late relapsed patients treated with a single Tisa-cel infusion and no further consolidation have an excellent prognosis, and that T cell effector function may be sub-potent, resulting in early CAR-T cell loss in early relapsed patients. ●

Sex Differences in Patients with Sickle Cell Disease

SICKLE cell disease (SCD) is a disorder with a range of clinical manifestations. This variability is determined by several factors, including biological sex. The King's College Hospital, London, UK, patient record system was therefore used to examine a cohort of homozygous patients with SCD (HbSS) and heterozygous patients with SCD (HbSC). The effects of sex on a range of laboratory measurements and clinical parameters were investigated, with the aim of extending understanding of sex differences in SCD outcomes.

A total of 802 individuals with HbSS (median age: 35.1 years; 54% female) and 267 with HbSC (median age: 45 years; 64% female) were included in the study. Analysis of variance was used to test the association between sex and clinical laboratory measurements.

Data suggested male sex was associated with increased haemoglobin, absolute reticulocyte count, and haematocrit in individuals with HbSS and HbSC. Males with HbSS also had increased inflammatory markers compared to females, with elevated eosinophils (p=0.00043), monocytes (p=3.9E-08), and C-reactive protein (p=4.4E-06). Liver function test and estimated glomerular filtration rate were increased in males with HbSS, but not HbSC.

For patients receiving hydroxyurea therapy, unpaired T-tests were utilised to compare responses based on sex. The increase in foetal haemoglobin, total haemoglobin, and mean corpuscular volume during hydroxyurea treatment was significantly higher in females than males (p=0.00098, p=0.046, p=0.012, respectively).

Further analysis showed that males also had a higher incidence of all adverse cerebrovascular outcomes, and males with HbSS demonstrated an increase in the number of hospitalisations per year (p=0.04) compared to females. However, survival analysis of nearly 900 patients showed that sex had no effect on survival in individuals with HbSS and HbSC (p=0.77), with median survival of 62 and 80 years, respectively.

Overall, males with HbSS had worse disease outcomes across almost all SCD aspects when compared to females. However, males did have higher haemoglobin, usually associated with a milder phenotype, and a difference in survival was not identified. Increased understanding of how sex affects the pathophysiology of SCD will ultimately lead to improved clinical management, and thus warrants further investigation.

"The effects of sex on a range of laboratory measurements and clinical parameters were investigated."

Has a Definition for Massive Transfusion Been Found?

RESEARCH into the definition of massive transfusion (MT), which indicates there is significant heterogeneity in the current definitions used in randomised controlled trials (RCT), was presented at EHA 2023. Currently, there is no standardised definition in use, making it difficult to compare efficacy and safety data across studies on patients who are critically bleeding.

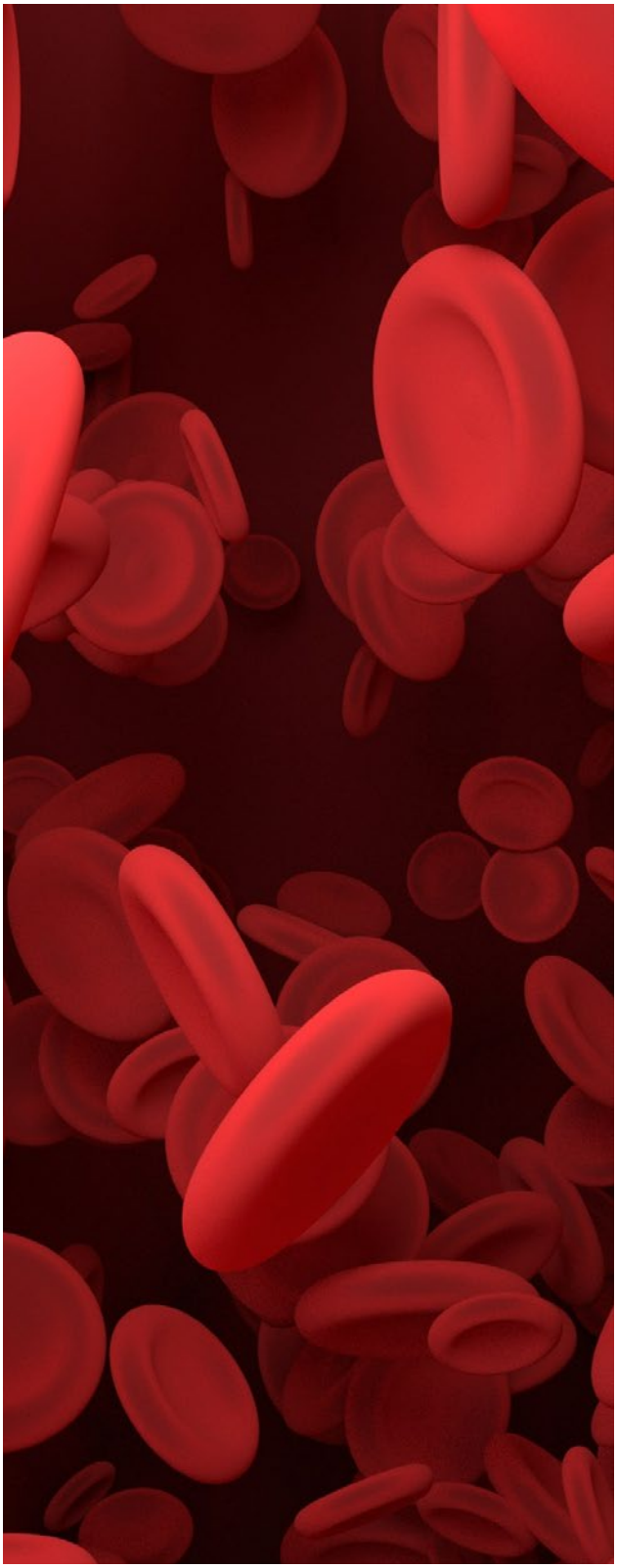
Victor Lin, Monash University, Melbourne, Australia, and colleagues, performed a scoping review of MT-related RCTs to evaluate currently used definitions. They searched for RCTs on numerous databases from inception until 11th August 2022. There was no language restriction, and trials could be ongoing.

In the initial search, a total of 8,460 distinct references were found. The inclusion criteria included being an RCT; having a specific definition of MT; and including adult patients with an acquired bleeding disorder who had received, or were to receive, an MT in a clinical setting. Content other than RCTs was excluded. Of the identified references, only 30 studies met the criteria.

The researchers noted a lack of uniformity in the definitions of MT, with 15 distinct definitions being used in RCTs across four different specialities. These included trauma and obstetrics/gynaecology, as well as orthopaedic and cardiothoracic surgery.

Most definitions were based on the number of red blood cell (RBC) units or whole blood administered within a certain time interval, while none included other blood products, such as plasma, and others did not specify the interval time. However, the researchers discovered that the most common definition was ≥10 RBC units in 24 hours, which appeared in 33% of the RCTs. This was preferred in trauma, featuring in 60% of RCTs, while obstetrics/gynaecology RCTs favoured >5 RBC units. In more recent studies, the trend was to use shorter timeframes.

With these findings, the researchers believe that a standardised definition of MT can be developed; one that will balance the strengths and weaknesses of previous definitions, and can be applied consistently in future RCTs.



"There is no standardised definition in use, making it difficult to compare efficacy and safety data."

Luspatercept in Patients with Non-Transfusion-Dependent β-Thalassaemia

UNTREATED anaemia in patients with non-transfusion-dependent β-thalassaemia (NTDT) can cause serious clinical complications. At the moment, there is no approved treatment for NTDT-associated anaemia; however, research has suggested that luspatercept could durably increase haemoglobin (Hb) levels and decrease transfusion burden in patients with NTDT. A study, presented at EHA 2023, looked into long-term efficacy data from patients in the BEYOND trial receiving luspatercept.

Participants were included in the study if they had NTDT or HbE/β-thalassaemia, defined as 0–5 red blood cells units transfused in the 24 weeks before randomisation, and Hb ≤10 g/dL. They were randomised to receive either placebo, or luspatercept 1.0–1.25 mg/kg subcutaneously for a duration of ≥48 weeks. Those receiving placebo were assessed up to discontinuation or crossover to luspatercept, while those receiving luspatercept were assessed on treatment. The team assessed mean change in Hb up to Week 144, in continuous 12-week intervals, as well as incidence of red blood cell transfusion events and units transfused. A mean change in Hb from baseline of ≥1 g/dL was defined as erythroid response.

Mean Hb change from baseline was 1.28 g/dL in Weeks 1–12, and 1.48 g/dL in Weeks 13–24 in the luspatercept arm. This increase was maintained in those remaining on study across all time points. The team noted nominally significant Hb level improvements from baseline up to Week 96 compared to placebo. In those taking luspatercept, mean change in liver iron content at Week 48 was 0.24 mg/g dry weight.

Furthermore, the team noted an increase in the proportion of patients with an erythroid response during any 12-week interval from 91.7% at the primary data cut-off date, to 93.8% at the current data cut-off date. There was also an increase in luspatercept arm responders, with ≥1 12-week rolling response from 35.2% to 61.1% between the cut-off dates, as well as an increase in mean total duration of erythroid response in patients with ≥1 12-week rolling responders from 611.1 to 873.1 days.

"The team noted a smaller proportion of transfusions in those receiving luspatercept compared to placebo."

The team noted a smaller proportion of transfusions in those receiving luspatercept compared to placebo (10.4% versus 32.7%), and lower mean number of units transfused and transfusion events in the luspatercept group compared to placebo. In those receiving luspatercept, mean number of units and events remained stable in Weeks 97–144.

The team concluded that in patients with NDT receiving long-term luspatercept, Hb levels were sustained and significantly improved, and erythroid response duration improved with an additional year of luspatercept. Cumulative incidence of transfusions stayed low and relatively stable throughout. ●

Interviews

EMJ is delighted to introduce Cynthia Dunbar and Janis Abkowitz, thought leaders in haematology who delve into their illustrious careers and ground-breaking research, providing insight into the American Society of Hematology (ASH).

Cynthia Dunbar

Secretary, American Society of Hematology (ASH); Chief, Translational Stem Cell Biology Branch, and Head, Molecular Hematopoiesis Section, National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, USA; Member, National Academy of Medicine (NAM), USA; Fellow, American Association for the Advancement of Science (AAAS), USA

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Q1 What inspired you to first pursue a career in medicine, to later specialise in haematology, and then more specifically find topics like stem cell biology and haematopoiesis?

I first got interested in a career in medicine because I found science courses really interesting at school, and I was good at them. In high school, I had a close friend with Hodgkin's lymphoma, and that was my first exposure to blood diseases and blood cancer. Nobody in my family worked in the medical field, but they were perfectly happy for me to go into medicine. Surprisingly, I had more friends develop Hodgkin's lymphoma and saw the different outcomes between my friend who died of it in the late 70s, when effective treatments were just starting to be developed, and then the early 80s, when it had moved forwards because of research.

When I reached medical school, I was still interested in blood cancers and had some great professors in haematology. After internal medicine training in Boston, Massachusetts, USA, where I cared for many patients with sickle cell anaemia, I interviewed for a clinical oncology training programme at the National Institutes of Health (NIH), and Arthur Nienhuis, the Head of the Haematology Branch at that time was impressed that I was interested in the molecular basis of blood diseases and actually knew about haemoglobin switching. He invited me to come and work in his laboratory for several years, before doing clinical training to see if I had an interest and aptitude for laboratory research, which was really accelerating in haematology at that time due to introduction of new molecular biology tools, such as PCR. He was a great mentor and very supportive.

The laboratory focused a lot on haemoglobinopathies, sickle cell, and thalassaemia, but Nienhuis was also at the forefront of first trying to develop gene therapies for those disorders. Most people in the laboratory were working on haemoglobin gene regulation, early haemoglobin gene transfer viral vectors, and drugs to induce foetal haemoglobin production. However, before the genome was

fully sequenced and gene expression control elements such as enhancers were not yet understood, it turned out trying to modulate gene expression to treat haemoglobinopathies via gene therapies was premature. I happened to get involved in a project to do with autocrine production of cytokines by stem cells in leukaemia, which turned out to be serendipitous since the project was more feasible. Even though I originally came to the laboratory to work on haemoglobinopathies, being open to an alternative project particularly good for a physician with some knowledge of leukaemia ended up being extremely productive and beneficial for my career progression. Taking advantage of opportunities and being open to changing plans was an important lesson!

Q2 How is the American Society of Hematology (ASH) positively impacting the treatment landscape of blood related diseases for patients and healthcare professionals?

I got involved in ASH as a young faculty member, when Ken Kaushansky, the new Editor-in-Chief of *Blood* asked me to join his team as an Associate Editor. There were hardly any female editors involved with major journals at that time, and I am sure that had something to do with Ken seeking me out. Being a part of ASH and this journal has been a highlight of my career. I got to know doctors and scientists who were interested in haematology from all over the world. I think the reason many of us were drawn to haematology is because the laboratory work is so directly connected to clinical treatments and outcomes. It is important to try to maintain this close connection, but maintaining it is becoming more challenging due to pressures imposed by the health care system, at least in the USA. ASH and *Blood* have the ability to foster interaction between scientists and clinicians, educating healthcare professionals on current basic and translational research, and scientists on gaps in effective clinical care.

I think one of the most active areas of progress in haematology more generally and a major focus at ASH has definitely been in sickle cell disease; there have been so many new treatment modalities and drugs in the pipeline and receiving regulatory approval over the last 4–5 years. On top of this, there have been major advances in curative options such as allogeneic transplantation, with modalities to allow safer and more efficacious alternative donor transplants and to prevent graft-versus-host disease and rejection. ASH has made a major new commitment to funding patient and community education and engagement, a real-world data registry, and a clinical trials network to speed up the pipeline from research to direct positive impact on patients.

Q3 You have been involved in several aspects of front-running research on molecular technologies and novel therapies. Which of these areas shows the most promise, and are there any gaps in research that you feel require greater attention?

For non-malignant but very serious disorders, particularly gene and cell therapies, I think the challenge has always been breaching the 'valley of death' between academic investigation/ biotechnology start-ups initiating early translational or Phase I pilot trials, and uptake by larger pharmaceutical companies that are generally necessary to be able to actually move to regulatory approval. This process can take so long that by the time a therapy is available to patients, a better approach is already supplanting it in the research pipeline, requiring its own prolonged development process. Costs are astronomical, with no predictable outcome for the initial smaller companies. Gene therapies for hematopoietic stem cell disorders, such as sickle cell disease or immunodeficiencies, are a good example. Almost 30 years elapsed between initial clinical trials using early viral vectors showing minimal gene transfer to engrafting haematopoietic stem cells until recent trials with

"The challenge has always been breaching the 'valley of death' between academic investigation/ biotechnology start-ups."

modern lentiviral vectors expressing anti-sickling globins showed clear clinical efficacy and likely cures. However, longer follow-up and larger trials have now uncovered a real risk of insertional mutagenesis turning on a cancer gene and causing leukaemia.

In the meantime, the newer gene editing approaches based on clustered regularly interspaced palindromic repeats have exploded over the past decade, reaching patients with incredible speed. In sickle cell disease, gene editing to destroy a locus in the genome that normally shuts off foetal haemoglobin production, rather than actually correcting the sickle mutation, has already been shown to be effective in patients, albeit with much shorter follow-up than in patients treated with lentiviral gene addition. Both approaches are likely to receive regulatory approval in the near future, but how patients and their doctors will choose between the therapies and how medical systems will pay is very unclear.

Then we have newer, and what seem to be more elegant gene editing approaches, which actually correct a mutation, such as in sickle cell disease, via swapping in a new piece of DNA via homologous recombination, or chemically changing a mutation via base editing. Pressure to get these approaches into patients is intense; however, there much less animal and pre-clinical data, and the homology-directed repair approach to sickle cell disease resulted in a halt to the first clinical trial and discontinuation of the programme by the biotech company after the first treated patient showed haematopoietic stem cell toxicity from the procedure.

Q4 What are the most significant changes you have observed in haematology over the course of your career?

One of the biggest changes has been the scale and rapidity with which you can generate data. For instance, there has been an incredible acceleration in the past 5–10 years in being able to look at all expressed genes and/or the epigenetic landscape at an individual cell level in up to hundreds of thousands of individual cells via technologies, such as RNA sequencing and assay for transposase-accessible chromatin using sequencing. Instead of having to come up with a hypothesis focusing on one or a few genes of interest and testing only that candidate gene, these approaches allow an unbiased approach to discovery. In addition, these new approaches can overcome the issue of cellular heterogeneity in tissue, such as the bone marrow, where differences in gene expression in cells at many different stages of differentiation are obscured when looking at the tissue in bulk, instead of at a single cell level.

There are many different approaches to analyse and visualise this data, and there are really elegant ways to use these new and amazing tools. But the biggest challenge is finding or training researchers to work on these projects that bridge the knowledge of the underlying biology together with ability to analyse large datasets. For instance, computer scientists and bioinformaticists often do not understand haematopoietic stem cell functions or leukaemia dynamics, and biologists or haematologists cannot fully grasp the analytic approaches being applied, leading to a ‘failure to communicate’

that can result in being led astray. PhD students and research-oriented MDs must become comfortable with coding and data analytics early in their career to 'grow up' in this new scientific ecosystem to bridge these gaps.

Q5 What advice would you give to a young and aspiring research-oriented clinician looking to establish themselves?

Trying to get meaningful research as well as clinical exposures early, even before medical school and certainly before residency and fellowship training, to determine what pathways to pursue. Medical schools and residencies need different tracks emphasising clinical practice versus research, it is becoming impossible to learn about everything involved in these enterprises in depth in one curriculum or training programme. In addition, students need to learn more about health policy, finance, research, funding, ethics, and access to care. We all need to understand how our healthcare system works (or does not work), so that we can effectively advocate for our patients or critical research. Anyone pursuing a clinical or laboratory research career must become facile in statistics, programming, and data analytics.

It is also important to think proactively about integrating milestones in your training and career stages with your personal life. At least in the USA, physicians and scientists are older and older when they finish clinical or research training and become an independent investigator or faculty member. This is due to starting elementary school later, and often having multiple gap years between high school and college and medical or graduate school, or during each phase, as well as the increased expectations for multiple high impact publications to land an academic job. If one is also starting a family while still an underpaid trainee whose schedule is not under personal control, it can be extremely difficult and leads to many leaving the academic/research pipeline. I was very fortunate to start my own laboratory at the age of 32, so was my 'own boss' and began having children soon thereafter; but becoming independent this early is almost unheard of at present. I would recommend that, if you are interested in pursuing science, to know all the options, and to try and acquire needed skills throughout your education and training, perhaps rather than taking multiple long 'gaps' outside education and clinical training to gain those experiences. Not to mention encouraging our society, at least in the USA, to provide better childcare options and more financial support during scientific and medical education, so that some of the pressures involved in an academic research career are less intense. ●

"The biggest challenge is finding or training researchers to work on these projects that bridge the knowledge of the underlying biology together with ability to analyse large datasets."

Janis Abkowitz

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Q1 What led you to pursue a career in haematology, sparking your interest in stem cells, erythropoiesis, and other disorders which you are involved with?

For me, the first question is why did I go into medicine? In college I majored in biochemical sciences but hated the lab-based project that I was assigned. I was quite active politically, and I had an interest in both anthropology and in social justice. And so, being discouraged by the laboratory, and loving sociology and anthropology, medicine just seemed like the right place.

I spent a year travelling in developing countries between college and medical school as a Sheldon Traveling Fellow. When I came back, I was much more focused on the social aspects of medicine, but also continued to love the logic of mathematics. Haematology was a great match. Unlike other disciplines at the time, you could readily access blood cells; it wasn't like the liver, or the brain, where you couldn't look at primary material. You could ask clinically-important, physiologically-based questions in the laboratory, and you could apply logic and rigor to patient care decisions.

All of this was further inspired by a mentor who taught our second year class in medical school, Steve Robinson. He was a thoughtful individual, who also was both an excellent clinician and a lab-based investigator. I think we all have these role models, or inspiring individuals, who lead us down our path.

Q2 You served as President of the American Society of Hematology (ASH) in 2013. Where does this rank for you in your list of personal achievements, and how is the organisation 'helping haematologists conquer blood diseases worldwide'?

ASH is actually the best-run organisation I've ever touched, and it's quite inspiring. The best position in ASH is being on council, for the reason that you have 12 colleagues from different areas that you wouldn't normally know. Everyone works wonderfully together and ASH staff are spectacular at gathering all the information you need to make thoughtful decisions. You rapidly go from talking about something like the ethics of stem cell investigation, to how to highlight more basic science, to pay for performance, and how Medicare payments in the United States impact healthcare decision-making. It's just really fun.

My earlier contribution to ASH was leading the education programme. At that point, stem cells were becoming a hot topic, something that my own research had diverted in part towards. I suggested that there be a scientific committee on stem cells, and that was embraced. I led this committee for its first 3 years. The friends that you make through ASH commitments are longstanding, like college roommates or colleagues that you work with on your medicine residency or internship. They are people that you'll see over your career, infrequently, but you know them well, and trust interactions because you've worked closely together.

ASH deals with all sorts of issues, and as a leader, you deal with issues that you know all

about, and others that you don't know about at all. One example of an issue I didn't know about was how to construct a new building and finance it. I think the most exciting, unique issue that I dealt with was the inappropriateness of testing for sickle cell trait as a prerequisite for participation in college athletics. Interacting with the National Collegiate Athletic Association (NCAA) was a novel experience. I also interacted frequently with the European Hematology Association (EHA).

After you finish your President year, you are ignored; you are not even informed of the outcomes from your last meeting. It's very different than EHA, for example, that keeps an 'Immediate Past President' to guide incoming officers. However, this assures a very vibrant organisation, even though it's quite unsettling for someone who spent several intense years as an ASH leader. I've done occassional things for ASH since my presidency, the most recent with the President of EHA, Elizabeth McIntyre. We were co-leads of the Translational Research Training in Haematology (TRTH) program, an intense training opportunity for beginning faculty members or group leaders, along with very late postdoctoral fellows. The programme involves 20 scholars, 10 from Europe, and 10 from the USA. We spent time together, focused translational, laboratory-based research career development, with 14 other mentors, faculty members like the two of us. The intent is that the scholars will be successfully launched as haematology investigators, and that they also will collaborate with each other throughout their careers. We were the leaders during the COVID-19 pandemic, and so the 1-year programme became a 2-year programme, and then a 2-and-a-half-year programme by the time we conducted our final in-person meeting, as a result of COVID outbreak delays.

Q3 Looking back at your career and reflecting on your time in the field, where do you feel you gained the most valuable experience? Could you tell us about the Frederick Sheldon Traveling Fellowship you were granted by Harvard University?

The fellowship was certainly critical to my career decision-making. I spent time with physicians in the Congo, Papua New Guinea, Thailand, and India. It was unusual to travel then as a woman, and it predated all the travel resources we have now; I had to get information from other travelers en route. There were no travel books, no cell phones or phone connections, and mail was unreliable and took 6-8 weeks. This travel opened my eyes to an awful lot of social issues and international concerns that I hadn't thought about. I learned to understand different behaviors and adapt to different cultural norms without judgement, such as learning why a cassowary bird or banana leaf necklace is important in rural Papua New Guinea. We had no backup support and limited supplies, so physicians had to use anthropologic clues and physical examination to make a medical decisions. I didn't realise how much I was learning at the time, but this exposure to cultural diversity has been absolutely fundamental to how I think about care.

A nice thing about haematology is that patients rarely cause their haematologic problems; they just happen. You are not dealing with someone who smokes repetitively who then develops chronic pulmonary diseases. In haematology, there are causes and effects, but no fault.

Regarding my current practice, the University of Washington in Seattle is the only medical school for five states: Washington, Wyoming,

"I didn't realise how much I was learning at the time, but this exposure to cultural diversity has been absolutely fundamental to how I think about care."

Alaska, Montana, and Idaho. Thus, we care for patients across a quarter of the geographic area of the USA. However, it's nowhere near a quarter of the population of the USA. I think my prior experiences impact my current life, in terms of understanding people's priorities, and when, why, and how they access care.

Q4 What are the most significant changes you have observed in the field of blood disorders? Are there any innovative approaches you are particularly excited about on the horizon?

The explosion of genomics, other omics, and epigenetics is huge for blood diseases. In the clinical space, we are faced with important questions, from healthcare access and equity, to sequencing technology and producing personalised medications, to looking at cost efficacy and risk versus benefit, as well as exploring and developing new drugs and new approaches. Gene therapy, as an example, comes with many complexities. For example, in sickle cell disease this decision is challenging, as we have no good predictors of who's going to do badly until they're already starting to do badly. Gene therapy can have significant morbidities, and as a new method, can have unknown or unappreciated consequences, as well as a major positive impact.

Q5 The lab you lead at the University of Washington is investigating the interaction between haeme and globin during erythropoiesis. What are the key findings from this research to date?

I'm interested in how red cells grow and develop in the marrow, from early progenitors to mature fully-functional cells, and how this goes awry. In particular, my lab investigates ineffective erythropoiesis, that is when cells start to differentiate but die in the marrow, and never make it out. There are many diseases that are very different, or appear on the surface to be very different, but result in this common outcome. These include Diamond–Blackfan anaemia, which is an inherited problem; myelodysplastic syndrome, which is an acquired disorder; and deficiency of B12, a side effect from the use of extra medicines, like hydroxyurea, which is a treatment for sickle cell disease. They all have the same physiology downstream, whereby cells start to develop and then they die en route. My lab has shown that ineffective erythropoiesis develops when there is excessive haem inside differentiating red cells.

Over 95% of the protein content of a mature red cell is haemoglobin which is constructed by haem (a toxic chemical if free) combining with globin (a protein) in a precise fashion. The fundamental issue that we are looking at now in our lab is the molecular relationship of haem with globin as red cells mature.

Although it used to be very common, the unusual thing about what I do, and that not many people do now, is to be a practising doctor and a lab-based scientist. Now, people tend to focus their practice and do clinical trials or correlative research that connect. In my practice, I see patients with diverse blood disorders, including leukaemia, and I also teach medicine and hematology trainees. When you work in a lab, you learn how to be logical and rigorous in your approach to patient care; the two complement each other.

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Targeted Therapeutics in CLL and MCL

Applying Emerging BTK Inhibitor Therapy Data to Practice

This infographic was supported by an educational grant from Lilly.

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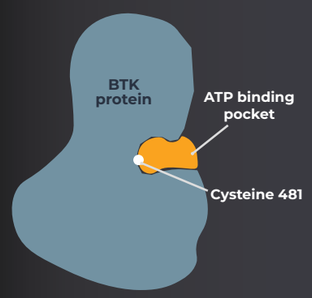
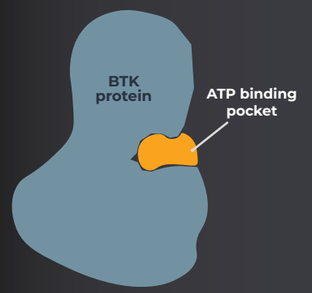
MoA for Approved BTK Inhibitors[1–3]

Covalent BTKi



Ibrutinib, acalabrutinib and zanubrutinib are covalent BTKi that bind to the ATP binding site to form an irreversible, covalent bond with C481.[3]

Non-covalent BTKi



Pirtobrutinib is a non-covalent BTKi that binds reversibly to the BTK protein in the ATP binding pocket. It does not depend on C481, and pirtobrutinib can bind to wild-type and C481^{mut} BTK.[1]

Drug Interactions

Avoid grapefruit juice

COVID-19 considerations: nirmatrelvir/ritonavir is a strong CYP3A4 inhibitor that interacts with all BTKi

Consider holding BTKi for duration of 5-day nirmatrelvir/ritonavir course

	Ibrutinib[4]	Acalabrutinib[5]	Zanubrutinib[6]	Pirtobrutinib[7]
CYP3A4 inhibitors (moderate)	**Decrease** to 280 mg once daily	**Decrease** to 100 mg once daily	**Decrease** to 80 mg twice daily	N/A
CYP3A4 inhibitors (strong)	**Avoid or hold** ibrutinib if CYP3A4i used ≤7 days Decrease to 140 mg or 70 mg once daily for concomitant use with voriconazole or posaconazole, depending on CYP3A4i dosing schedule	**Avoid or hold** acalabrutinib for ≥24 hours after last dose of CYP3A4i if used ≤7 days	**Decrease** to 80 mg once daily Interrupt dose as recommended for any AEs	**Avoid**; if unavoidable, decrease dose by 50 mg. After 5 half-lives of CYP3A4, resume at previous dose
CYP3A4 inducers	**Avoid**; may consider monitoring for reduced efficacy with moderate inducers	**Avoid**; if unavoidable, increase dose to 200 mg orally twice daily	**Avoid**; if moderate inducers unavoidable, increase dose to 320 mg twice daily	**Avoid**; if moderate inducers unavoidable, increase dose to 300 mg once daily if current dose is 200 mg once daily, or increase by 50 mg for other doses
Anticoagulants	⚠ Consider risk versus benefit and monitor for increased risk of bleeding ⚠			
Antiplatelets	⚠ Consider risk versus benefit and monitor for increased risk of bleeding ⚠			

New tablet formulation for acalabrutinib no longer has a restriction for gastric acid-reducing agents

Dose Modifications

STARTING DOSE → 1 → 2 → 3 → 4

Ibrutinib Dose Modifications[4]

Grade 2 cardiac failure, Grade 3/4 non-haematologic AEs, Grade 3/4 neutropenia with infection/fever, Grade 4 haematologic AEs

420 mg daily for CLL/SLL → 1st occurrence: ***INTERRUPT*** and reduce by 140 mg once AE resolves to Grade 1 → 2nd occurrence: ***INTERRUPT*** and reduce by 140 mg once AE resolves to Grade 1 → 3rd occurrence: ***DISCONTINUE***

Grade 3 cardiac arrhythmias

420 mg daily for CLL/SLL → 1st occurrence: ***INTERRUPT*** and reduce by 140 mg once AE resolves to Grade 1 → 2nd occurrence: ***DISCONTINUE***

Grade 3 cardiac failure or Grade 4 cardiac arrhythmias

420 mg daily for CLL/SLL → 1st occurrence: ***DISCONTINUE***

Acalabrutinib Dose Modifications[5]

For Grade ≥3 non-haematologic AEs, Grade 3 thrombocytopenia with bleeding, Grade 4 thrombocytopenia, or Grade 4 neutropenia lasting >7 days

100 mg BID → 1st occurrence: ***INTERRUPT*** and resume at current dose once AE resolves to Grade 1 → 2nd occurrence: ***INTERRUPT*** and resume at current dose once AE resolves to Grade 1 → 3rd occurrence: ***INTERRUPT*** and resume at 100 mg QD once AE resolves to Grade 1 → 4th occurrence: ***DISCONTINUE***

Grade 3 cardiac arrhythmias

Zanubrutinib Dose Modifications[6]

For Grade ≥3 non-haematologic AEs, Grade 3/4 febrile neutropenia, platelet count decreased to 25,000–50,000/mm³ with significant bleeding, neutrophil count decreased to <500/mm³ (lasting >10 consecutive days), platelet count decreased to <25,000/mm³ (lasting >10 consecutive days)

320 mg once daily or 160 mg BID → 1st occurrence: ***INTERRUPT*** and resume at current dose once AE resolves to Grade 1 → 2nd occurrence: ***INTERRUPT*** and resume at 160 mg QD (or 80 mg BID) once AE resolves to Grade 1 → 3rd occurrence: ***INTERRUPT*** and resume at 80 mg QD once AE resolves to Grade 1 → 4th occurrence: ***DISCONTINUE***

Grade 3 cardiac arrhythmias

Pirtobrutinib Dose Modifications[7]

For Grade 3/4 non-haematologic AEs, absolute neutrophil count <1–0.5x10⁹/L with fever and/or infection, absolute neutrophil count <0.5x10⁹/L lasting ≥7 days, platelet count <50–25x10⁹/L with bleeding, platelet count <25x10⁹/L

200 mg once daily → 1st occurrence: ***INTERRUPT*** and restart at the same dose once AE resolves to Grade 1 → 2nd occurrence: ***INTERRUPT*** and reduce to 100 mg daily once AE resolves to Grade 1 → 3rd occurrence: ***INTERRUPT*** and reduce to 50 mg daily once AE resolves to Grade 1 → 4th occurrence: ***DISCONTINUE***

No dose adjustments or discontinuations required for Grade 1/2 AEs*

Dosing and Administration

	Ibrutinib[4]	Acalabrutinib[5] NEW FORMULATION	Zanubrutinib[6]	Pirtobrutinib[7]
	Capsules: 70 mg, 140 mg Tablets: 140 mg, 280 mg, 420 mg	100 mg tablet formulation can be co-administered with gastric acid–reducing agents*	80 mg capsules	50 mg, 100 mg tablets
	420 mg once daily for adult patients	100 mg orally twice daily	160 mg twice daily or 320 mg once daily	200 mg once daily
	Capsules should be swallowed whole with water	Tablet should be swallowed whole with water, with or without food	Tablet should be swallowed whole with water, with or without food	Tablet should be swallowed whole with water, with or without food
	For missed doses: Take as soon as possible on same day and return to normal schedule on the next day	**For missed doses:** If dose is >3 hours past normal time, skip and resume at the next scheduled time	**For missed doses:** Take as soon as possible on same day and return to normal schedule on the next day	**For missed doses:** >12 hours past normal time: skip and resume at next scheduled time

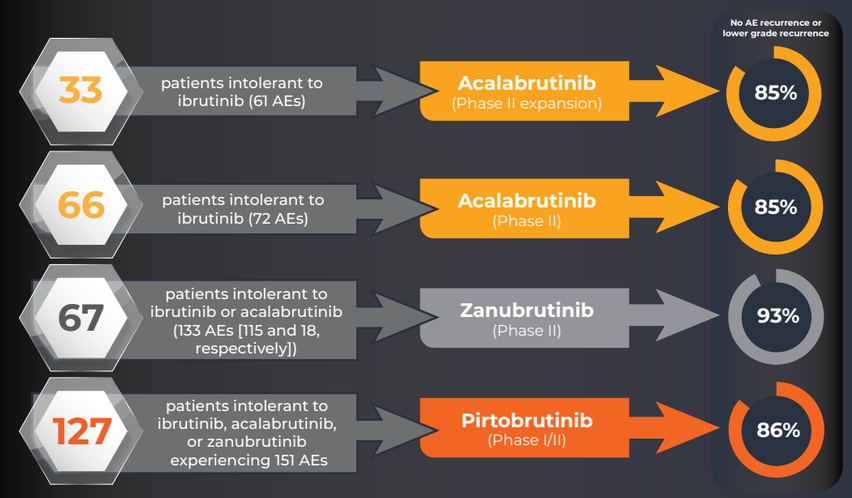
*Acalabrutinib exposures were comparable for tablet versus capsule formulations (AUC_{inf} 567.8 ng h/mL [36.9] versus 572.2 ng h/mL [38.2]; C_{max} 537.2 ng/mL [42.6] versus 535.7 ng/mL [58.4], respectively) and tablet can be co-administered with PPIs, food, or via NG tube without affecting the PKs or PDs.
†Non-covalent, reversible BTKi

Approximate Rates of Select AEs

	Ibrutininb[4,8,9]	Acalabrutinib[5,8]	Zanubrutinib[6,9]	Pirtobrutinib[7,10]
Atrial Fibrillation	Any Grade: 13-16% Grade ≥3: 3-4%	Any Grade: 9% Grade ≥3: 5%	Any Grade: 5% Grade ≥3: 2.5%	Any Grade: 2.8% Grade ≥3: 1.2%
Hypertension	Any Grade: 20-22% Grade ≥3: 9-14%	Any Grade: 9% Grade ≥3: 4%	Any Grade: 23% Grade ≥3: 15%	Any Grade: 9% Grade ≥3: 2%
Bruising or Bleeding	Any Grade: 41-51% Grade ≥3: 4-5%	Any Grade: 38% Grade ≥3: 4%	Any Grade: 42% Grade ≥3: 3%	Any Grade: 35% Grade ≥3: 0%
Infection	Any Grade: 73-81% Grade ≥3: 28-30%	Any Grade: 78% Grade ≥3: 31%	Any Grade: 71% Grade ≥3: 27%	Any Grade: NR Grade ≥3: 17%*
Cytopenias	Any Grade: 43% Anemia: 19% Neutropenia: 26% Thrombocytopenia: 14% Grade ≥3: 36%	Any Grade: 41% Anemia: 22% Neutropenia: 23% Thrombocytopenia: 16% Grade ≥3: 29%	Any Grade: NR Anemia: 15% Neutropenia: 39% Thrombocytopenia: 13% Grade ≥3: NR	Any Grade: NR Anemia: 7% Neutropenia: 13% Thrombocytopenia: NR Grade ≥3: NR
Arthralgia	Any Grade: 16-23% Grade ≥3: 1%	Any Grade: 16% Grade ≥3: 0%	Any Grade: 15% Grade ≥3: NR	Any Grade: 14% Grade ≥3: <1%

*Data only reported in PI.

Consider Switching BTKi due to AE Intolerance[11-14]



Abbreviations: AE: adverse events; AUC_{inf}: total drug exposure across time; BID: twice daily; BTK: Bruton tyrosine kinase; BTKi: Bruton tyrosine kinase inhibitor; CLL: chronic lymphocytic leukaemia; C_{max}: peak concentration; MCL: mantle cell lymphoma; MoA: mechanism of action; NG tube: nasogastric tube; PD: pharmacodynamic; P-gp: P-glycoprotein; PK: pharmacokinetic; PPI: proton pump inhibitors; QD: once daily; SLL: small lymphocytic lymphoma.

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Sickle Cell Disease

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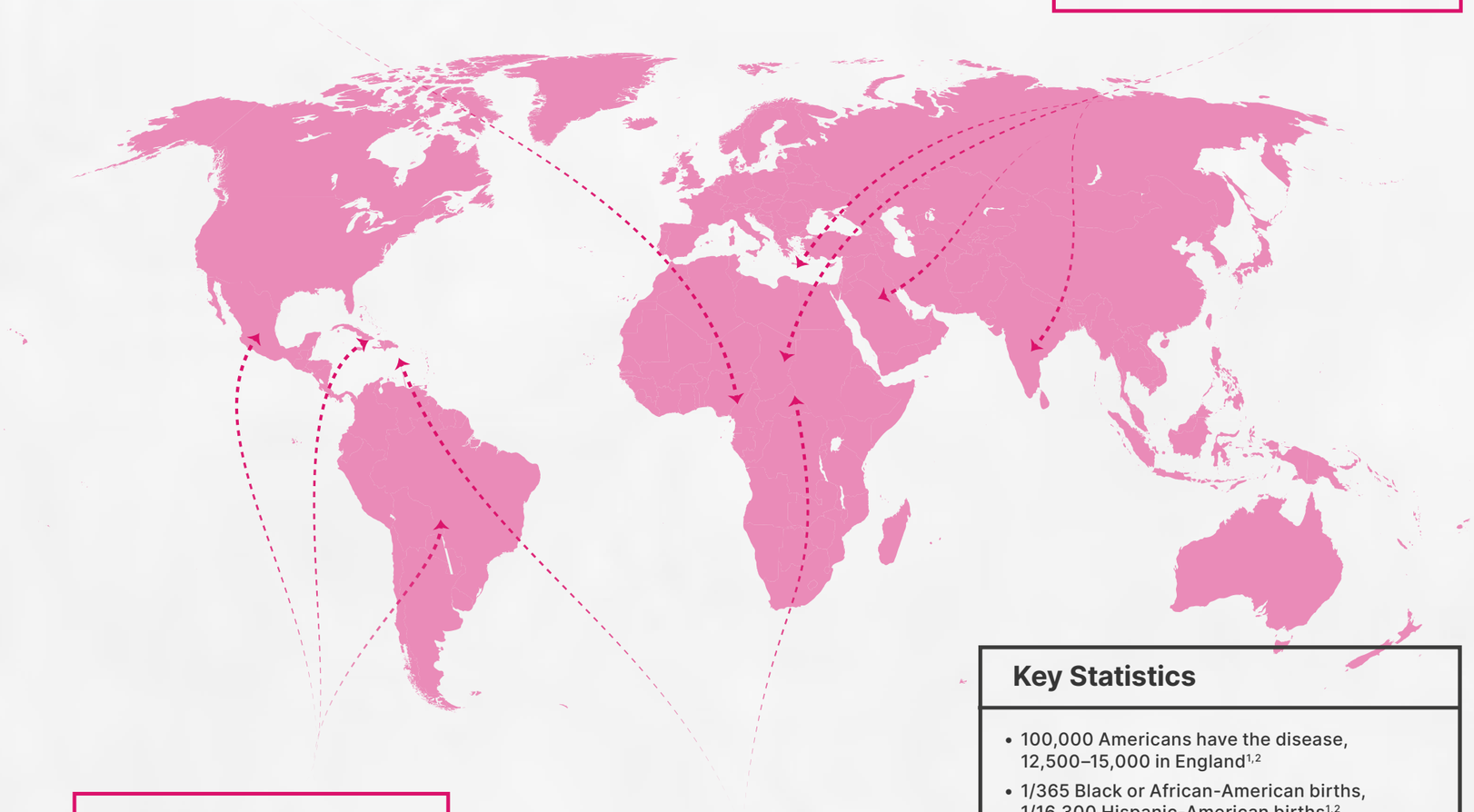
Infographic

Prevalence

In **Cameroon**, **Republic of Congo**, **Gabon**, **Ghana**, and **Nigeria** prevalence 20–30%, in some parts of **Uganda** 45%.[4]

Sickle trait has a protective effect against malaria; global distribution has emerged from positive selection for this gene mutation.[2]

Occurrence highest in **sub-Saharan Africa** and small pockets of the **Mediterranean**, the **Middle East**, and **India**.[5]



Caribbean, **South American**, and **Central American** populations more at risk.[1]

Prevalent in populations where malaria is endemic, particularly **African** and **African-Caribbean** origins.[2]

Key

SCD: sickle cell disease

Key Statistics

- 100,000 Americans have the disease, 12,500–15,000 in England[1,2]
- 1/365 Black or African-American births, 1/16,300 Hispanic-American births[1,2]
- 1/13 Black or African-American babies and 1/79 in the UK are born with sickle cell trait[1-3]
- Patients with SCD in the UK have median survival of 67 years, 58 years in the USA[6]
- 1/2,000 births in England[3]
- Global estimation 120 million affected by SCD, and 1,000 babies born with the disease each day in Africa alone[9]

Current Treatment

Lifelong management:

- Avoid sudden **changes in temperature** and **dehydration** to reduce clot risk.[7]
- **Hydroxycarbamide (hydroxyurea)**, **crizanlizumab**, **L-glutamine**, and **voxelotor** for pain crises, vaso-occlusive issues, sickling of blood cells, and complications.[7,8]
- **Long-term antibiotic**s like penicillin mitigate susceptibility to infection.[7]
- **Blood transfusions**; acute, red blood cell, and regular.[8]

Curative

- **Blood and marrow transplant**; only current curative option, usually conducted in children unresponsive to other treatment. **Cell replacement therapy** for production of healthy red blood cells, significant risks involved.[7]
- Gene therapy: **CRISPR-Cas9 editing** *BCL11A* in hematopoietic stem cells provides durable engraftment, high foetal haemoglobin expression, and elimination of vaso-occlusive episodes or a need for transfusion.[10]
- **Further experimental testing required**, providing generalisable results, before this option is made readily available.[10]

Unmet Needs

Access to quality treatment:
Worst affected areas of Africa see 50–90% of children with SCD die before the age of 5 years.[4,6] In the UK, 99% of children diagnosed survive to adulthood.[6]

Cost:
Financial burden is extremely high, a lifetime dependent on treatment ≈$1.7 million USD medical bills.[11]

Blood and marrow transplants succeed in 85% of children; this must be from a related donor with human leukocyte antigen matched.[8]

Adults:
interventions are focused on children, but millions of adults live with the disease globally, awaiting a cure and new treatment options made readily available.

Limitations:

1. Difficulty finding donor matches
2. 15% still unsuccessful
3. risk of graft versus host disease and immune rejection of transplant
4. procedural complications such as infections and seizures
5. 5% undergoing this procure die.[8]

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Steroid Toxicity in Immune Thrombocytopenia – A Series of Unfortunate Events: A Case Report

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Abstract

Immune thrombocytopenia (ITP) is a common bleeding disorder characterised by isolated thrombocytopenia, due to immune-mediated accelerated platelet destruction, usually without any specific or identifiable precipitating factor. ITP most commonly presents with bleeding associated with a low platelet count <100×10⁹/L. Corticosteroids are the first line of treatment in adults. However, steroid-induced complications are widespread in patients with ITP, and sometimes are more atrocious than the risk of bleeding associated with thrombocytopenia. The authors report the case of a 29-year-old male with ITP with recurrent episodes of epistaxis, who was treated with prednisolone for 8 weeks and developed acne, steroid-induced hyperglycaemia, and urinary tract infection with epididymitis and pyocele. A few weeks later, the patient developed blurring of vision, and was found to have central serous chorioretinopathy. They were treated adequately for each of these complications, and had complete resolution of symptoms following cessation of steroids. While acne and hyperglycaemia are common, urinary tract infections with epididymitis and central serous chorioretinopathy are infrequent complications following steroid administration. The complexity of adverse events and the challenges in diagnosing and treating these unique complications prompted the authors to report this case.

Key Points

1. This article summarises the occurrence of very unusual and rare steroid-related toxicity. It is a cautionary tale of modern medicine where the treatment-related adverse events are more atrocious than the primary disease.

2. This article highlights the importance of close monitoring of patients on steroids, which would help detect any steroid-related toxicity early in the course of occurrence.

3. Early intervention and timely treatment can revert the toxicities of steroid therapy, and prevent the advent of permanent organ damage. Further, this case also teaches that patients with immune thrombocytopenia may be considered for shorter duration of steroid therapy, and steroid sparing agents should be considered early, especially in those prone to develop therapy-related adverse events.

INTRODUCTION

The aetiology of immune thrombocytopenia (ITP) is a subject of an enigma, and the diagnosis is one of exclusion.[1] The standard recommendation is to initiate therapy in an adult with newly-diagnosed ITP with a platelet count <3×10^9/L, regardless of any bleeding manifestations.[2,3] Bleeding in ITP may range from mild petechial spots to severe intracranial bleeds.[4,5] The severity of bleeding rarely correlates with the severity of thrombocytopenia. Corticosteroids remain the most elementary group of drugs in the initial management of ITP, alongside intravenous immunoglobulin and anti-D immune globulin (in the Rhesus-positive blood group).[2] Systemic corticosteroids are administered at a high dose (prednisolone 1 mg/kg) for more extended periods in treating ITP, owing to the relapsing and remitting course of the disease.[6,7] This may lead to a multitude of adverse events.[8,9]

The authors report a case of a young male with newly-diagnosed ITP. The patient was started on corticosteroids and developed several steroid-related complications, including hyperglycaemia, acne, and urinary tract infection (UTI). They also complained of blurred vision, and were diagnosed with central serous chorioretinopathy (CSC). They were treated adequately for each of these complications, and recovered completely. While steroid-induced hyperglycaemia and acne are quite common, UTIs in males and pyocele are rare complications associated with steroid administration. CSC in patients with ITP following short-course steroids is singularly uncommon. This case report highlights the importance of close monitoring of patients on steroids, and the significance of timely intervention in treating therapy-related complications, and thereby preventing permanent end-organ damage and morbidity.

CASE REPORT

A 29-year-old male presented to the authors' outpatient department with a history of three episodes of acute onset epistaxis (World Health Organization [WHO] Bleeding Score: Grade 2)[10] over 1 week. The patient had no history of bleeding in the past; nor was there any history of bleeding among their siblings or family in the past. The patient was conscious and alert on examination, and their vitals were stable. There was no pallor, icterus, cyanosis, clubbing, or pedal oedema. The patient had left-sided scrotal swelling. There was no pain, redness, or tenderness over the swelling. The rest of their systemic examination was unremarkable. The complete blood count showed isolated thrombocytopenia viz haemoglobin 11.7 g/dL, total white blood cell (WBC) count 5×10^9/L, and platelet count 5×10^9/L with a differential WBC count of 60% neutrophils, 34% lymphocytes, and 6% monocytes. Peripheral smear examination showed microcytic to macrocytic red blood cells with moderate anisocytosis, adequate WBCs, and markedly reduced platelets. Other investigations included serum electrolytes, urea and creatinine, serum bilirubin and transaminases, HbA1c, serum lactate dehydrogenase, erythrocyte sedimentation rate, C-reactive protein, thyroid function test, serum antinuclear antibody, urine examination, and chest X-ray; all were normal. Screening for blood-borne viral diseases such as HIV, hepatitis C virus, and hepatitis B surface antigen were negative. Direct and indirect antiglobulin test was negative. The patient's baseline abdomen, pelvis, and scrotum ultrasonogram showed a left-sided hydrocele.

Since all the possible secondary causes of thrombocytopenia were ruled out, the patient was diagnosed with ITP and started on tablet prednisolone at a daily dose of 1 mg/kg. They were followed up weekly to monitor their

platelet count, and to look for any possible steroid-related complications. The patient developed hyperglycaemia within 1 week of starting steroids, and was treated with oral hypoglycaemic agents. An adequate glycaemic control was achieved with oral hypoglycaemic agents, without the requirement of insulin. Therefore, steroids were continued along with oral hypoglycaemic agents. The patient developed papules and comedones on their face and trunk over the next few days, i.e., within 1 week of starting steroids, and was treated for acne with adapalene and benzoyl peroxide ointment. Their acne improved significantly following topical therapy.

The patient had a partial haematological response to steroids with a rise in the platelet count to 70×10^9/L at the end of 4 weeks of steroid therapy. So, prednisolone was tapered. However, following the initiation of tapering of steroids at 4 weeks of therapy completion, there was a sudden drop in platelet count to 16×10^9/L, and the patient developed one episode of epistaxis (WHO Bleeding Score: Grade 2)[10]. Since the patient had a recurrence of bleeding along with a drop in platelet count at the time of steroid tapering, the prednisolone dose was increased again, and a very slow tapering of prednisolone dose was planned. Around 6 weeks of steroid therapy, the patient developed a burning micturition. A routine and microscopic examination of urine showed the presence of numerous red blood cells and pus cells, and urine culture sensitivity showed the growth of *Klebsiella* species (Table 1). The patient was started on oral antibiotics, anti-spasmodic agents, and supportive measures. They also complained of pain and swelling over the left scrotum. Clinical examination of the left scrotum showed inflamed skin over the left-sided hydrocele, and there was significant tenderness on palpation of the swelling. An urgent scrotum ultrasound was done, which revealed an oedematous left epididymis and increased echogenicity, with internal echoes of the left-sided scrotal swelling suggestive of left-sided epididymitis and pyocele. An urgent urology opinion was sought, and steroids were rapidly tapered and stopped. The patient's expressed prostatic secretion was sent for culture and sensitivity, and showed the growth of *Klebsiella* species (Table 1). The patient was treated with appropriate antibiotics as per the culture and sensitivity report for a total duration of 2 weeks. They were also treated with other supportive measures, such as analgesics, scrotal support, and anti-spasmodic agents. They had a spontaneous rupture of the pyocele with a spontaneous pus drainage, obviating the need for surgical intervention. They had remarkable symptomatic relief and complete resolution of epididymitis and pyocele. A repeat scrotum ultrasound done after 2 weeks of antibiotic therapy showed normal bilateral scrotum, epididymis, and normal bilateral testicles.

Following this, the patient was on a regular follow-up to monitor their platelet count and assess their wellbeing as steroids were stopped. Their platelet count was 70×10^9/L at 8 weeks of therapy completion. However, the patient complained of blurred vision in both eyes around this time. They were off steroids at this point. A detailed ophthalmologic evaluation revealed a best-corrected visual acuity (BCVA) of 20/40 and 20/20 in the right eye and left eye, respectively. The anterior segment examination of both eyes was unremarkable. Intraocular pressures of both eyes were also within normal limits. Fundus evaluation of the right eye showed a dull foveal reflex with subretinal fluid and multiple yellow-pigmented spots in the foveal region. In contrast, the left eye had a normal foveal reflex. Further evaluation with a spectral domain optical coherence tomography (OCT) confirmed the presence of subretinal fluid (SRF) in the fovea. It revealed pigment epithelial detachments with subretinal deposits in the right eye (Figure 1A, 1C, 1D), and a normal fovea of the left eye (Figure 1B). A diagnosis of steroid-induced CSC was made. The patient was advised close observation, and was kept on a regular follow-up. Repeat OCT done after 2 weeks showed a reduction in SRF and improved BCVA to 20/30 in the right eye. After a follow-up of 1 month, BCVA was restored to 20/20 in the right eye (Figure 1E) with a complete resolution of subretinal fluid, and the left eye continued to be normal (Figure 1F).

Further, on follow-up, the patient's platelet count was 40×10^9/L approximately, while not on any therapy, and they had no bleeding manifestations. Hence, no second-line treatment was started, and the platelet count was closely monitored. It was decided to initiate a second line of therapy should there be any decrease in platelet count to $<20\times10^9$/L, or any new onset bleeding manifestation.

Table 1: Urine and expressed prostatic secretion culture and sensitivity.

Antibiotic Subclass	Antibiotic	Sample: Urine Organism: *Klebsiella spp.* CC ≥10^5 CFU/mL	Sample: Expressed Prostatic Secretion Organism: *Klebsiella spp.*
Penicillins	Ampicillin	S	R
β-lactam/ β-lactamase inhibitors	Piperacillin-tazobactam	S	S
	Amoxycillin-clavulanate	S	S
	Ampicillin-sulbactam	S	S
	Piperacillin-tazobactam	S	S
Cephalosporins	Ceftriaxone	S	S
	Cefotaxime	S	S
	Cefepime	S	S
Aminoglycosides	Amikacin	S	S
	Gentamicin	S	S
	Tobramycin	S	S
Carbapenems	Meropenem	S	S
	Imipenem	S	S
	Doripenem	S	S
	Ertapenem	S	S
Nitrofurans	Nitrofurantoin	S	N/A
Folate pathway inhibitors	Co-trimoxazole	S	S

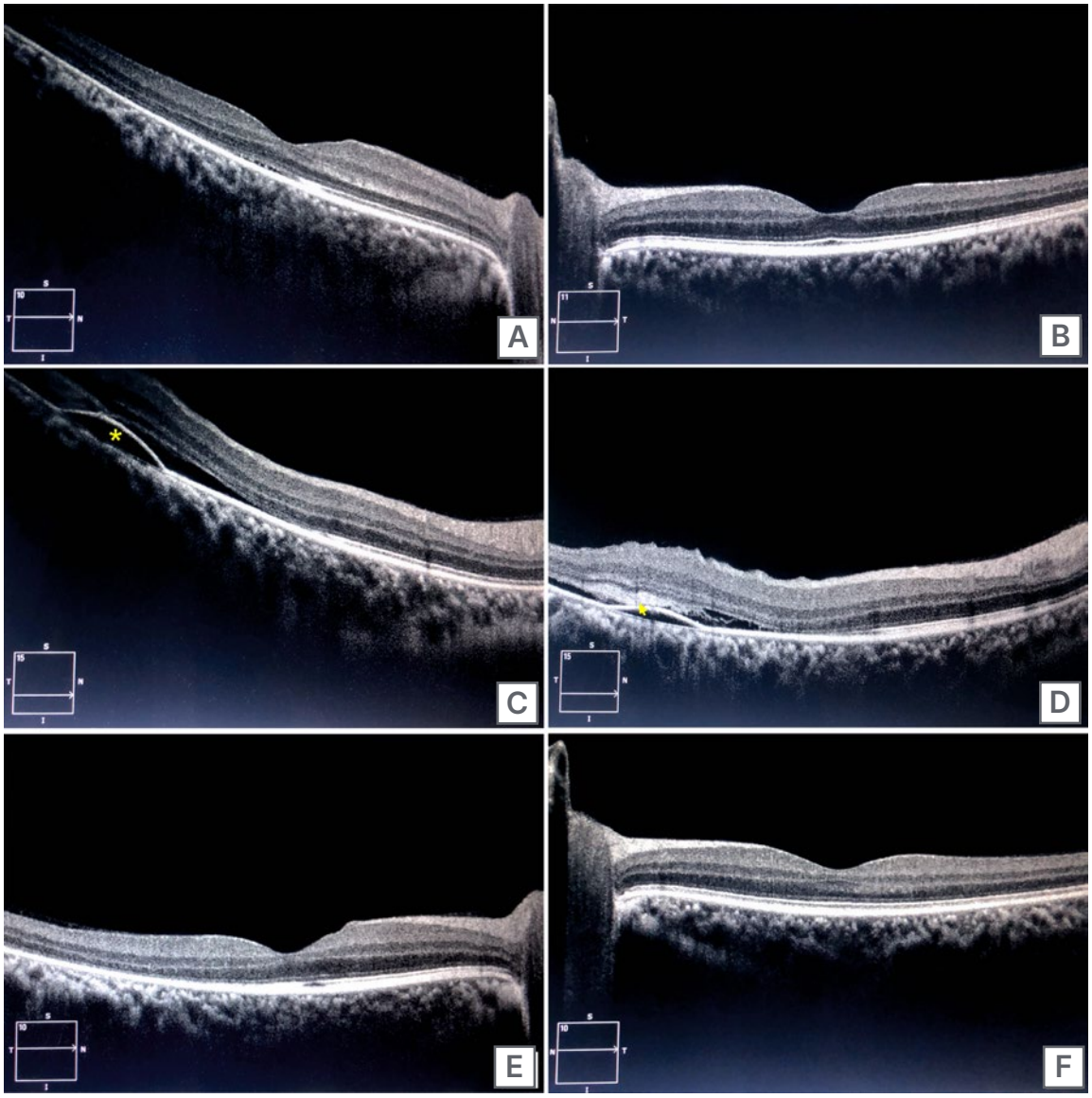
R - Resistant S-Sensitive

CC: colony count; CFU: colony forming unit; Klebsiella spp.: Klebsiella pneumoniae; N/A: not applicable.

DISCUSSION

ITP is a common bleeding disorder characterised by isolated thrombocytopenia without any specific or identifiable precipitating factor.[11] The decreased platelet count is usually secondary to immune-mediated accelerated platelet destruction and decreased platelet production.[12] ITP may occur without any apparent underlying cause (primary) or associated with other underlying diseases (secondary ITP). Secondary causes include infections (both

Figure 1: Optical coherence tomography images.



A) OCT of the right eye showing minimal subfoveal neurosensory detachment; **B)** OCT of the left eye showing a normal foveal contour with intact retinal layers; **C)** OCT of right eye with a section inferior to fovea demonstrating PED (yellow asterisk), neurosensory detachment with shallow SRF; **D)** OCT of right eye with another section inferior to fovea demonstrating PED, SRF, and subretinal hyperreflective material (yellow arrow); **E)** OCT of right eye after 1 month showing resolution of SRF and a normal foveal contour; **F)** Left eye continued to be normal after 1 month.

OCT: optical coherence tomography; PED: pigment epithelial detachment; SRF: subretinal fluid.

bacterial [*Helicobacter pylori*] and viral, including varicella zoster, hepatitis C virus, and HIV viral infections), autoimmune diseases, underlying lymphoproliferative disorders, drugs, etc.[11]

Bleeding in ITP is heterogenous, unpredictable, and most likely associated with many environmental and genetic risk factors.[13] The patient with ITP may be asymptomatic, or present with mild mucocutaneous or severe life-threatening bleeding.[4,13] The incidence of extreme life-threatening bleeding in ITP is fortunately low, approximately 9.6% and 20.2% in adults and children, respectively.[2] Though severe

bleeding is rare, it is the most critical clinical endpoint, and crucial indication to initiate therapy.

In addition to the bleeding manifestations, patients with ITP also present with fatigue, anaemia, and poor health-related quality of life. A final rationale for treating an asymptomatic patient with ITP upfront is to prevent chronic and relapsing disease.[2,14] The standard recommendation is to initiate therapy in an adult with newly-diagnosed ITP with a platelet count <3×10^9/L, regardless of the initial bleeding manifestations. The International Working Group (IWG) devised the ITP-specific bleeding assessment tool (ITP–BAT) to allow for uniformity of assessment of bleeding manifestations. However, the simplicity of application makes the WHO bleeding score[10] a more widely used bleeding assessment tool.

Corticosteroids remain the most elementary group of drugs in the initial management of ITP.[11,15] Intravenous immunoglobulin and anti-D immune globulin (in the Rhesus-positive blood group) are also recommended as first-line therapy.[3,11] Second- and third-line treatment options are generally reserved for those who fail first-line therapy. These therapeutic strategies include immunomodulators, such as rituximab, azathioprine, and dapsone, and thrombopoietin-stimulating agents like eltrombopag and romiplostim.[6,16]

Glucocorticoid treatment is the standard initial therapy in ITP because of its effectiveness in increasing the platelet count, low cost, and convenience. Approximately 60–80% of patients with ITP have an initial response to glucocorticoids, but only 30–50% of adults have a sustained response after it is discontinued.[7] For most patients, the platelet count response only lasts as long as the corticosteroids are continued. The duration of corticosteroid treatment is not standardised; it is often continued for 3–4 weeks, or until side effects become intolerable.[17] Long-term steroid administration is associated with a myriad of complications. While hyperglycaemia, acne, and infections are the more common complications, CSC is a relatively rare entity.[8]

Steroid-induced hyperglycaemia causes new-onset hyperglycaemia or worsening glucose control in patients with previously known diabetes,[18] with an incidence of 46% in patients with diabetes and 68% in patients with increases in glucose levels compared to baseline,[18-20] making it one of the commonest steroid-related toxicities. Furthermore, there may be acute complications such as a nonketotic hyperosmolar state or diabetic ketoacidosis. No evidence exists to establish therapeutic goals for patients with steroid-induced hyperglycaemia. According to the American Diabetes Association (ADA), glucose targets should be individualised according to specific factors, such as life expectancy, comorbidities, patient compliance, and risk of hypoglycaemia. In hospitalised patients, a target glucose range of 140–180 mg/dL is recommended for critically and non-critically ill patients. More stringent goals, such as 110–140 mg/dL, may be appropriate for selected patients if this goal can be achieved without hypoglycaemia. Oral hypoglycaemic agents might suit inpatients with stable and non-critical disease and mild hyperglycaemia.[18,21] In contrast, for those with significant hyperglycaemia and severe illness, insulin remains the treatment of choice. The authors' patient was treated with oral hypoglycaemic agents, and achieved optimal glycaemic control.

Acneiform lesions in steroid acne are usually seen on the chest, but may also be seen on the face, neck, back, and arms. In most cases, steroid acne resolves with the discontinuation of steroid therapy. However, in clinical scenarios where prolonged steroid administration is warranted, other modalities may be used, including topical preparations like salicylic acid and benzoyl peroxide; retinoids; and topical antibacterial or antifungal therapy, like doxycycline and ketoconazole.[22,23] The authors' patient was treated with retinoid (adapalene) and benzoyl peroxide, and improved significantly.

UTIs are among the most common ailments, affecting 150 million people worldwide yearly.[24] However, UTIs in young males are very unusual, and increase dramatically with age.[25] Urethritis and epididymitis are painful conditions caused by bacterial infections of the urethra and epididymis, respectively. Acute epididymitis is usually treated in the outpatient setting. Rarely, intravenous antibiotics are required for systemic symptoms, abscess formation, or Fournier's

gangrene. Epididymitis usually improves within 2–3 days of antibiotic treatment, but residual pain may persist for several weeks. In addition, supportive therapy in the form of analgesics, anti-inflammatories, and scrotal elevation is recommended for acute epididymitis.[26]

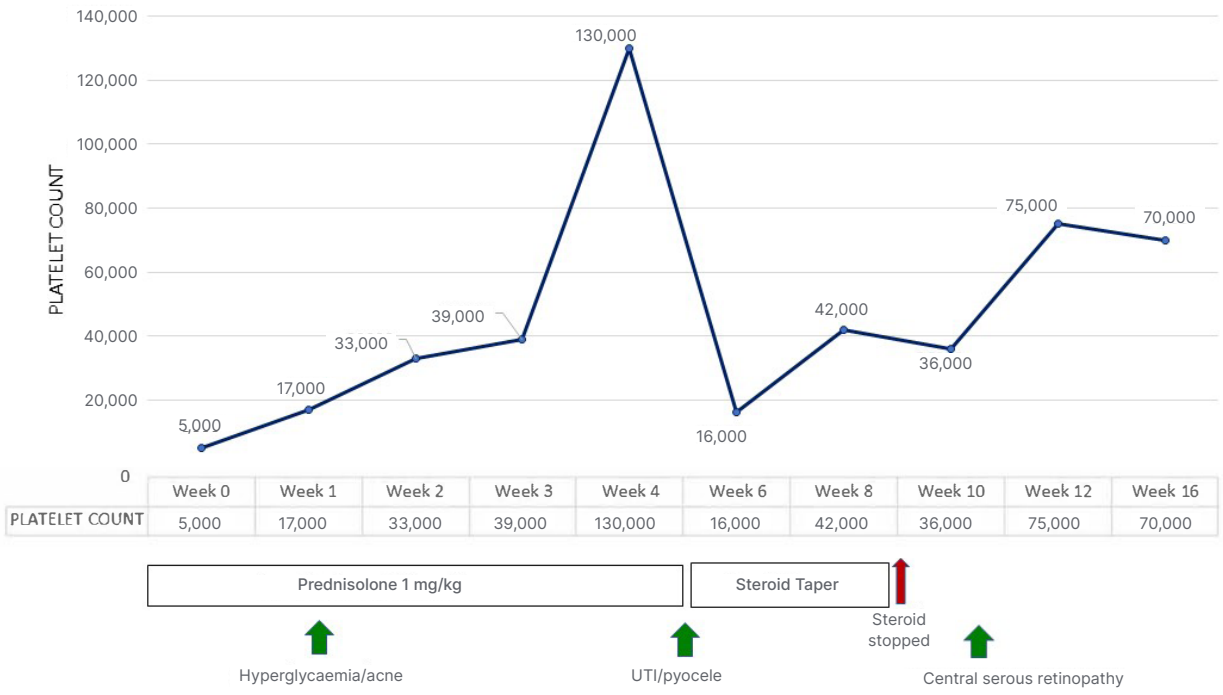
The authors' patient developed a complicated UTI with an infected hydrocele (pyocele), left-sided acute epididymitis, and urethritis. There was a spontaneous rupture of the pyocele. The patient was treated with oral antibiotics for 2 weeks and other supportive measures, and had a complete resolution of symptoms following treatment.

CSC is a chorioretinal disease that causes an idiopathic serous retinal detachment. It is associated with one or more areas of leakage from the choroid through a defect in the retinal pigment epithelium outer blood–retina barrier.[27] Most patients are ales who have decreased and distorted vision together with altered colour appreciation.[28] The exact mechanism of steroid-induced central serous retinopathy is not very well defined. The pathophysiology of CSC is multifactorial, which causes retinal pigment epithelial disturbances and circulatory changes in the choroid. Although the natural history of CSC shows a self-limiting course, patients are known to present with persistent, recurrent, or even bilateral CSC with distressful visual loss. OCT is the first line of investigation in CSC. The presence of SRF is characteristic of CSC. The resolution of SRF can be documented on serial OCT.[29] Corticosteroid use is the most critical identifiable external risk factor in patients with CSC.[30] The primary approach to treating CSC is conservative with observation, and requires cessation of steroid intake.

Burkhodari et al.[31] and Sandhya et al.[32] also demonstrated a similar occurrence of central serous retinopathy in ITP, but without complete vision recovery. There is no gold standard for the treatment of persistent CSC. The U.S. Food and Drug Administration (FDA) approves no therapeutic options. However, local modalities, both pharmacologic and photic, and systemic medical treatments are under ongoing investigation. They may hold promise for future patients diagnosed with CSC.[27,33,34]

The authors' patient rapidly recovered normal vision in both eyes within 1 month of stopping steroids. Other complications, including steroid-induced hyperglycaemia, acne, and UTIs, also

Figure 2: Graph depicting the temporal association of events.



resolved with treatment. Figure 2 depicts a graph representing the temporal association of events.

CONCLUSION

The authors conclude that patients on systemic steroids for ITP, or any other systemic illness, should be closely monitored for the development of any steroid-related adverse event. The occurrence of a chain of steroid-related complications in succession, including hyperglycaemia, acne, UTIs, pyocele, and the delayed onset of central serous retinopathy, even after cessation of steroid therapy, prompted the authors to report this case. This case emphasises the role of close follow-up and vigilant monitoring, which helped in the early detection of complications. This case also taught the authors as a team that considering a shorter duration of steroid therapy, early initiation of steroid-sparing second-line therapy, and a closer follow-up in cases of patients prone to steroid toxicity, together with timely intervention and optimal treatment, can prevent the occurrence of such series of adverse events in future. The authors hope to re-emphasise and create a more comprehensive awareness of the atrocities of steroid-related toxicity so that physicians may consider curtailing the dose and duration of steroid therapy, and prevent the advent of permanent organ damage.

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