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+ Review of EHA 2019

Amsterdam, Netherlands

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"This year's EHA congress showcased the very best research, innovations, and late-breaking data from across the haematology field."

Spencer Gore, CEO

+ ARTICLES

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Aims and Scope

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EMJ allows healthcare professionals to stay abreast of key advances and opinions across Europe.

EMJ aims to support healthcare professionals in continuously developing their knowledge, effectiveness, and productivity. The editorial policy is designed to encourage discussion among this peer group.

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EMJ Hematol.

EMJ Oncology 6.1 2018

This provides a comprehensive summary of the 5 days during which oncology professionals came together to lead the transformation of oncology research into everyday practice.

VIEW ALL JOURNALS ←

Welcome

A very warm welcome to *EMJ Hematology 7.1*! The whole team here at European Medical Journal is very proud to present the latest edition of this journal which features our independent review of this year's European Hematology Association (EHA) congress as well as an impressive array of peer-reviewed articles.

This year's EHA congress showcased the very best research, innovations, and late-breaking data from across the haematology field. It was a true privilege to attend this world-class event, and to be able to report on all the goings-on for those who attended and would like a refresher, or for those who were unable to attend. Read all about some of the top abstract presentations from the speakers themselves in our Abstract Reviews, stay up-to-date with our news updates in the Congress Review Stories, and learn all about the experiences, careers, and future goals of some of the key opinion leaders in haematology with our Interview section. All this, and much more will tell you all you need to know about this year's spectacular EHA congress.

Our peer-reviewed articles in this year's journal are second to none. Paubelle and Thomas discuss the current understanding of thalassaemia and the progress being made by researchers in ineffective erythropoiesis control, metal chelation, and gene therapy – all exciting prospects that could improve care and patient outcomes in the future. Chronic myeloid leukaemia is the subject of Grudeva-Popova et al.'s review, more specifically in relation to pregnancy and fertility for patients, understanding of which has remained elusive despite the huge strides that have been made in the improvement of prognosis and patient management in recent years. Biomarkers associated with neonatal sepsis are discussed by Gandhi and Kondekar, among many more topics that we believe will be of great value to any haematologist.

I would like to thank all of the contributors and the EMJ team who have worked hard to produce what I believe to be our best haematology journal yet! I am already excited to see what new developments will be announced at next year's congress, but for now, I hope you will be as inspired as I was by all of the content herein.

Spencer Gore

Chief Executive Officer, European Medical Group

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Foreword

Dear Colleagues,

It is with enthusiasm that I welcome you to the 2019 edition of *EMJ Hematology*, bringing together some fantastic highlights and advancements from the haematological field. Inside you will find a collection of brilliant peer-reviewed articles and highlights from this year's European Hematology Association (EHA) Congress in Amsterdam, Netherlands, including the latest breaking news in the field, interviews with members from the various committees, and a selection of abstract summaries written by the presenters themselves.

β-thalassaemia is a genetic condition characterised by a lack of β-chain synthesis in haemoglobin molecules, leading to anaemia that effects whole organ systems and that is associated with significant patient morbidity and mortality. In an informative review by Paubelle and Thomas, β-thalassaemia is given a thorough examination, particularly in regard to the exciting therapeutic advancements that are being made for the treatment of this severe pathology.

Neonatal sepsis is another disease that is a blight on human healthcare and that requires more attention from experts in our field. Diagnostic challenges often lead to it being misdiagnosed and inappropriately treated, leading to extended hospitalisation. Gandhi and Kondekar address this problem in a review aimed at evaluating the different parameters and biomarkers used for diagnosis of the disease, providing an aid to our colleagues in the clinic. In another piece, Yacoub et al. contribute a retrospective review of the role of abdominal imaging for cytopenia evaluation. It is important that our field constantly assess, adapt, and adopt techniques that we use for the diagnosis and treatment of different haematological diseases, making studies like these all the more important.

Additional to these peer-reviewed articles, a feature on umbilical cord blood donation is included within, discussing the merits of cord blood banking through the perspectives of both the research and charity sectors. Particular mention is given to the work that the Anthony Nolan charity is doing, perfectly complementing the content elsewhere in the journal by driving home the importance of the work that is being done across the field.

This is a varied *EMJ Hematology* edition and one that I'm sure you will all enjoy delving into.

Best wishes,

Emanuele Angelucci

Istituto di Ricovero e Cura a Carattere Scientifico, Italy

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Assessment of cardiac function prior to start of treatment is recommended. *Renal impairment:* Dose adjustment is not required for patients with mild (creatinine clearance [CrCL] 60 mL/min to 89 mL/min by Cockcroft Gault equation [C-G]) or moderate (CrCL 30 mL/min to 59 mL/min) renal impairment. There is no experience in patients with severe renal impairment (CrCL 15 mL/min to 29 mL/min) or end-stage renal disease. It should only be used in patients with severe renal impairment if the benefits outweigh the risks. *Hepatic impairment:* Dose adjustment is not required for patients with a bilirubin level less than or equal to 50 µmol/L. There is no experience in patients with hepatic impairment resulting in a bilirubin level greater than 50 µmol/L. 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AML: acute myeloid leukaemia
AML-MRC: AML with myelodysplasia-related changes
t-AML: therapy-related AML

1. Tolcher AW, Mayer LD. Future Oncol 2018; 14(13): 1317-32.
2. Lancet JE *et al.* J Clin Oncol 2018; 36(26): 2684-92.

Date of preparation: September 2018
EURW-INTVYX-0026

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Congress Review

Review of the European Hematology Association (EHA) Congress

Location: RAI Amsterdam at Europaplein 24, 1078 GZ, Amsterdam, Netherlands

Date: 13th – 16th June 2019

Citation: EMJ Hematol. 2019;7[1]:12-25.

The Netherlands have a long history of producing inspiring minds across a range of disciplines, where particular mention must be given to the quality of scientists it has gifted to the world. From Felix Andries Vening Meinesz inventing a precise measurement for gravity at sea in the early 20th century, to more recent, Nobel-prize winning advancements made by Sir Andre Geim involving graphene in 2010, the Netherlands have undoubtedly cemented their place in history as a hot-bed of inquiry and innovation. Perhaps it is fitting in this regard that the 24th European Hematology Association (EHA) Annual Congress was held in the picturesque streets of Amsterdam, bringing together the pioneers of the haematology field for 4 spirited days of discussion, debate, and optimism for the future.

EHA President Pieter Sonnevel welcomed the 12,614 haematology professionals to the Dutch capital, the largest number of attendees recorded with an increase of more than 1,000 since last year's congress. Whilst acknowledging the worth of all haematological inquiry, he highlighted two topics in particular that the scientific community, and indeed the whole team at EMJ, are becoming increasingly aware of: immunotherapy and haemoglobinopathies. Regarding the former, chimeric antigen receptor T (CAR T) cells were centre stage at this year's congress, included as a topic-in-focus session through which promising results were presented. The development of novel therapeutics is inevitably linked to the targets they can be used for, and sickle cell disease represented the second topic-in-focus session. Both these fields are marked by striking developments and progress.

Importantly, 82 countries outside of Europe were represented at the event, highlighting the far-reaching interest that comes from students, researchers, and clinicians with an interest in haematological disease. Over the course of the congress, more than 200 sessions were held detailing the results of the most recent advances across 11 key areas. These included transfusion medicine,

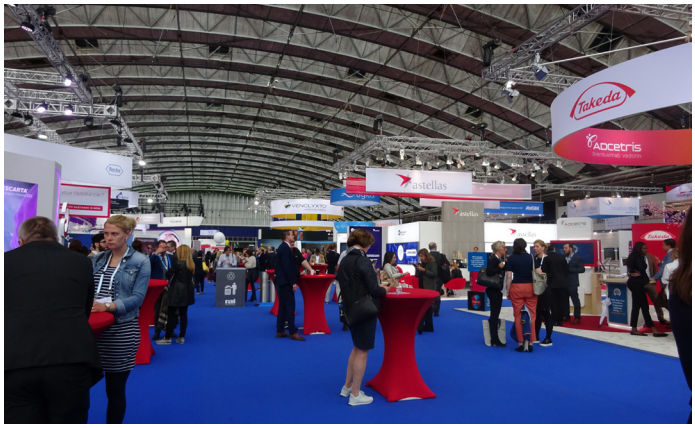
paediatric haematology, myeloid malignancies, benign haematology, and laboratory diagnosis. Undoubtedly a number of these developments will change the standard of care for patients.

A novel fixed-duration targeted therapy has been developed for chronic lymphocytic leukaemia, addressing a clear clinical need that has long been apparent.

Additional to these sessions, a large number of informative abstract presentations were given, of which we have included our hand-picked selection as part of this year's review. In the following pages, you will read about the new development of an autologous dendritic cell vaccination for preventing multiple myeloma progression; a novel, targeted means of tackling rare blastic plasmocytoid dendritic cell neoplasm; and reports from a Phase II study detailing haploidentical and HLA-matched transplant recipients whom received post-transplant cyclophosphamide.

The variety in the types of session held at EHA were evident upon our arrival, including: education sessions, in which basic principles and mechanisms, translational research, and clinical aspects of specific topics were divided between three speakers and presented; clinical debates, in which controversial topics were broached and discussed; meet the expert sessions, in which the audience were given a valuable opportunity to ask questions directly to leaders in the haematological field; and YoungEHA sessions, in which scientists and clinicians in the early stage of their careers were able to discuss and address topics of interest.

The findings from a number of momentous studies were presented at this year's event. The first results from the CASSIOPEIA trial, aimed at determining whether daratumumab addition to stem-cell transplantation can improve responses in multiple myeloma patients, were made public, potentially having profound implications for how this disease will be treated in the future. A novel fixed-duration targeted therapy has been developed for chronic lymphocytic leukaemia, addressing a clear clinical need that has long been apparent. And additionally, we may have witnessed the discovery of the first disease-modifying drug for the treatment of patients with myelodysplastic syndromes, an achievement that holds unprecedented value in the improvement of lives. We highlight these stories and more in our review of EHA.



We may have witnessed the discovery of the first disease-modifying drug for the treatment of patients with myelodysplastic syndromes.

As one of the largest gatherings of haematologists in the world, EHA requires intricate planning and organisation within and outstanding committees involved with its running. We had the pleasure of interviewing representatives of three of these bodies. Shai Izraeli, treasurer of the Executive Board, enlightened us with an overview of how the Congress is organised, whilst Marek Mraz and Barbara Bain provide insight as to how the YoungEHA and Online Case Units, respectively, contribute to the EHA overall mission. Collectively, these interviews highlight the EHA as a sterling example of a congress that allows the fostering of innovation through an emphasis on sharing ideas and educating others, surely a positive sign of the direction the haematology field is moving as a whole.

EHA 2019 was an event that evidently inspired individuals across a range of disciplines, all with the common interest of improving the lives of those living with any haematic pathology. This inspiration has us already looking forward to the 25th Annual Congress being held in Frankfurt, Germany, but until then we hope you enjoy the following review of this year's congress, including highlights we're sure will get your blood pumping.

EHA 2019 REVIEWED →

Imetelstat: The First Disease-Modifying Drug for Myelodysplastic Syndromes?

EVEN though patients with low risk myelodysplastic syndromes (MDS) rarely progress to acute myeloid leukaemia, they do have to endure chronic and debilitating anaemia that does not respond adequately to therapy. Their response to erythropoietic stimulating agents (ESA) may be transient or inconsistent, resulting in the need for regular red blood cell transfusions. Imetelstat, a first-in-class telomerase inhibitor, has now been shown in a recent study to be a potential therapeutic for those with MDS. The results were presented in a press release at this year's EHA Congress.

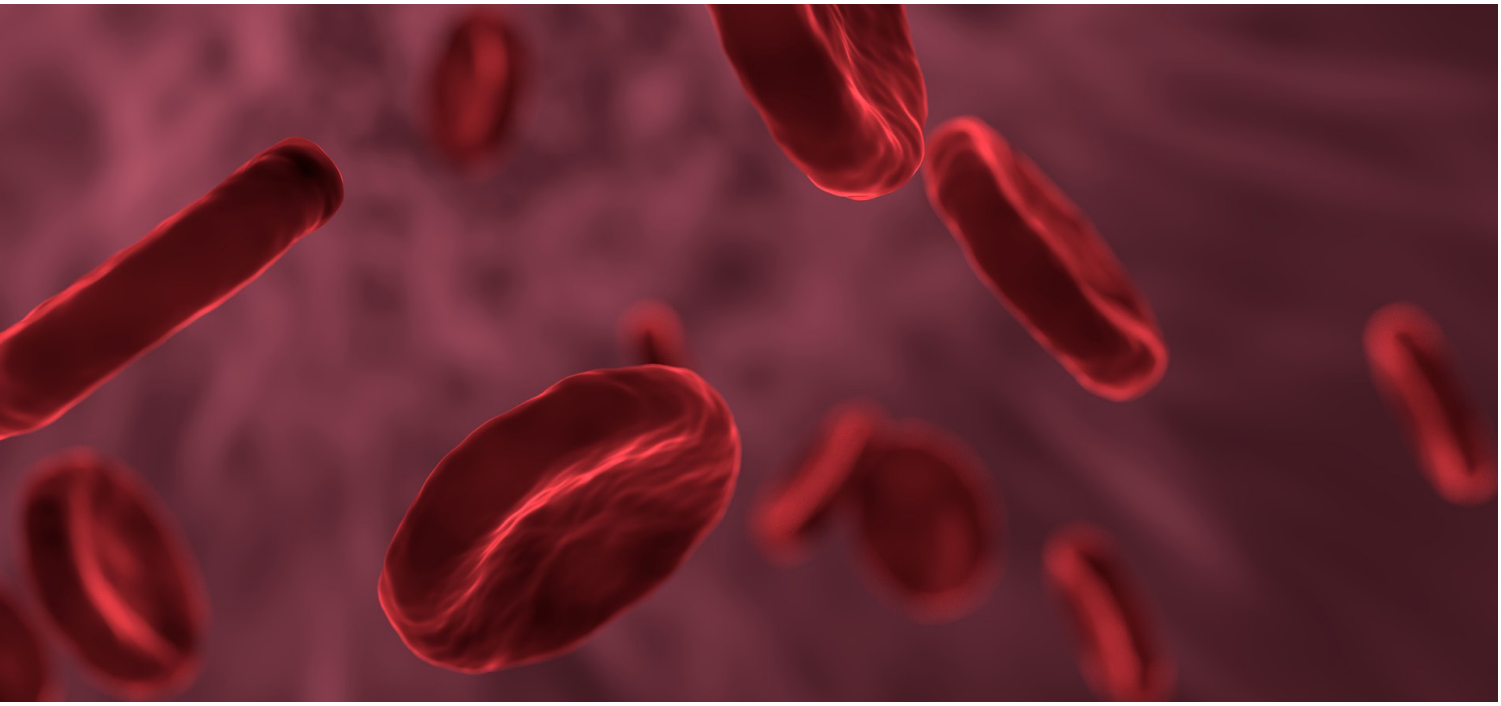
All of the 38 subjects involved in the study were lower risk (non del5q) patients who had a high transfusion requirement (median 8 red blood cell units transfused/8 weeks) and were resistant to ESA. Participants had a mean age of 71.5 years (46–83) and received 7.5 mg/kg Imetelstat for a median of 9 cycles.

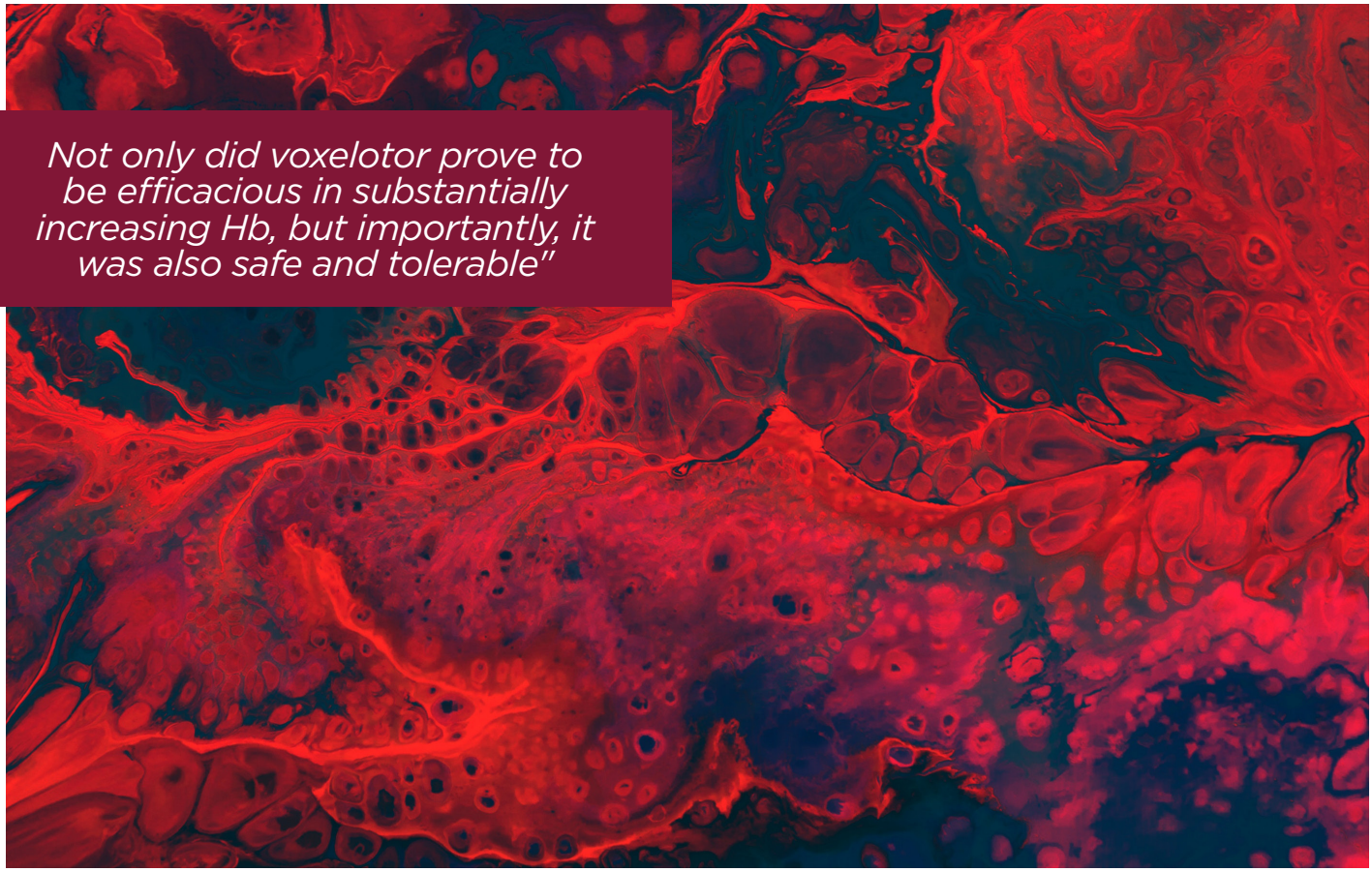
Imetelstat provides an alternate therapeutic path for a disease that currently has limited options for avoiding transfusions.

Transfusion independence was achieved in 16 (42%) of participants, and had a median actuarial duration of 86 weeks (8.0–140.9). Of those 16 participants, 12 (75%) had a high rise in ≥3 g/dL haemoglobin compared to the pre-treatment level. Despite this substantial improvement in transfusion need, reversible neutropenia and thrombocytopenia were seen in around 60% of patients.

Shorter overall survival in lower risk MDS patients is associated with higher telomerase activity and shorter telomeres. Imetelstat has already shown clinical activity in myeloid malignancies by targeting cells with short telomere length and active telomerase.

Imetelstat provides an alternate therapeutic path for a disease that currently has limited options for avoiding transfusions. The data show that Imetelstat produces meaningful and durable transfusion independence in MDS patients that would otherwise heavily require red blood cell transfusions, being the first disease modifying treatment for MDS. A continuation of this study is planned; a Phase III study comparing Imeltestat and placebo is due to commence later this year.





Not only did voxelotor prove to be efficacious in substantially increasing Hb, but importantly, it was also safe and tolerable"

New HOPE for Patients with Sickle Cell Disease

SICKLE cell disease (SCD) is caused by a genetic mutation in red blood cells and causes recurrent pain episodes named 'crises' (vaso-occlusions). This chronic disease affects millions of people worldwide yet no disease modifying treatment has been shown to work effectively in reducing the organ damage, chronic anaemia, and risk of stroke that is associated with SCD. However, results from the late-stage Hemoglobin Oxygen Affinity Modulation to Inhibit HbS PolymErization (HOPE) study (presented at the Presidential Symposium) suggest that voxelotor may be the therapeutic intervention that SCD patients have been hoping for.

The randomised, placebo-controlled, Phase III trial involved 274 patients with confirmed SCD aged 12–65 years of age. The patients were randomised to receive 1,500 mg voxelotor, 900 mg voxelotor, or placebo orally, once a day for 24 weeks.

Rationale behind voxelotor is to increase haemoglobin (Hb) affinity for oxygen, inhibiting Hb polymerisation and red blood cell sickling, which is the underlying molecular mechanism of SCD. An improvement of at least 1 g/dL in Hb can potentially result in improved clinical complications and mortality. In the patients who received voxelotor 1,500 mg, 59.5% achieved an increase in Hb of 1 g/dL, and an increase in Hb was seen in >80%.

Furthermore, fewer vaso-occlusions were observed and anaemia improvement was seen irrespective of baseline anaemia severity. Reduced amount of haemolysis (destruction of red blood cells) was also noted with voxelotor treatment. Not only did voxelotor prove to be efficacious in substantially increasing Hb, but importantly, it was also safe and tolerable.

These promising results will be put to the U.S. Food and Drug Administration (FDA) later this year as part of the New Drug Application that will be submitted by the drugs sponsor, Global Blood Therapeutics, Inc.

Successful Birth is the Most Common Outcome for Pregnant Chronic Myeloid Leukaemia Patients

WIDE-SPREAD adoption of tyrosine kinase inhibitors (TKI) for the treatment of chronic myeloid leukaemia (CML) has transformed patient expectations and outcomes, often resulting in a normal lifespan. Family planning has become a major consideration for female CML patients, spurring forward a recent study of which results were presented at this year's EHA Congress held in Amsterdam, the Netherlands.

In the study, pregnancy and conception outcomes were described for an international cohort of 234 CML patients from the European Leukemia Net registry, dating back to 2014, focussing specifically on factors such as characteristics of patients at diagnosis and pregnancy onset, and characteristics of children at follow-up.

These results attest that not only is it possible to experience normal childbirth as a CML patient, but this is in fact the most common outcome.

Encouragingly, the majority of pregnancies ended successfully in labour (77%). This was achieved across a variety of treatment options being applied across each patient in the study, including imatinib, nilotinib, and interferon. in 71% of cases, the child was conceived whilst TKI therapy was ongoing and ceased following pregnancy confirmation. At disease onset, pregnancies were discovered in 21% of cases. Major or deep molecular response (M/DMR) was 44% in patients of known molecular status. Importantly, born children were not afflicted with severe or life-threatening conditions, and congenital abnormality rate was 1.7%.

These results attest that not only is it possible to experience normal childbirth as a CML patient, but this is in fact the most common outcome. Despite limited data, the association between TKI use and no discernible side-effect on a patient's child provides further validation for the continuation of these treatment regimens for CML patients. Additionally, the results in terms of conception and pregnancy may be useful for the future development of targeted molecular therapeutics considering the variety of disease status.

New Fixed-Duration Targeted Therapy for Chronic Lymphocytic Leukaemia

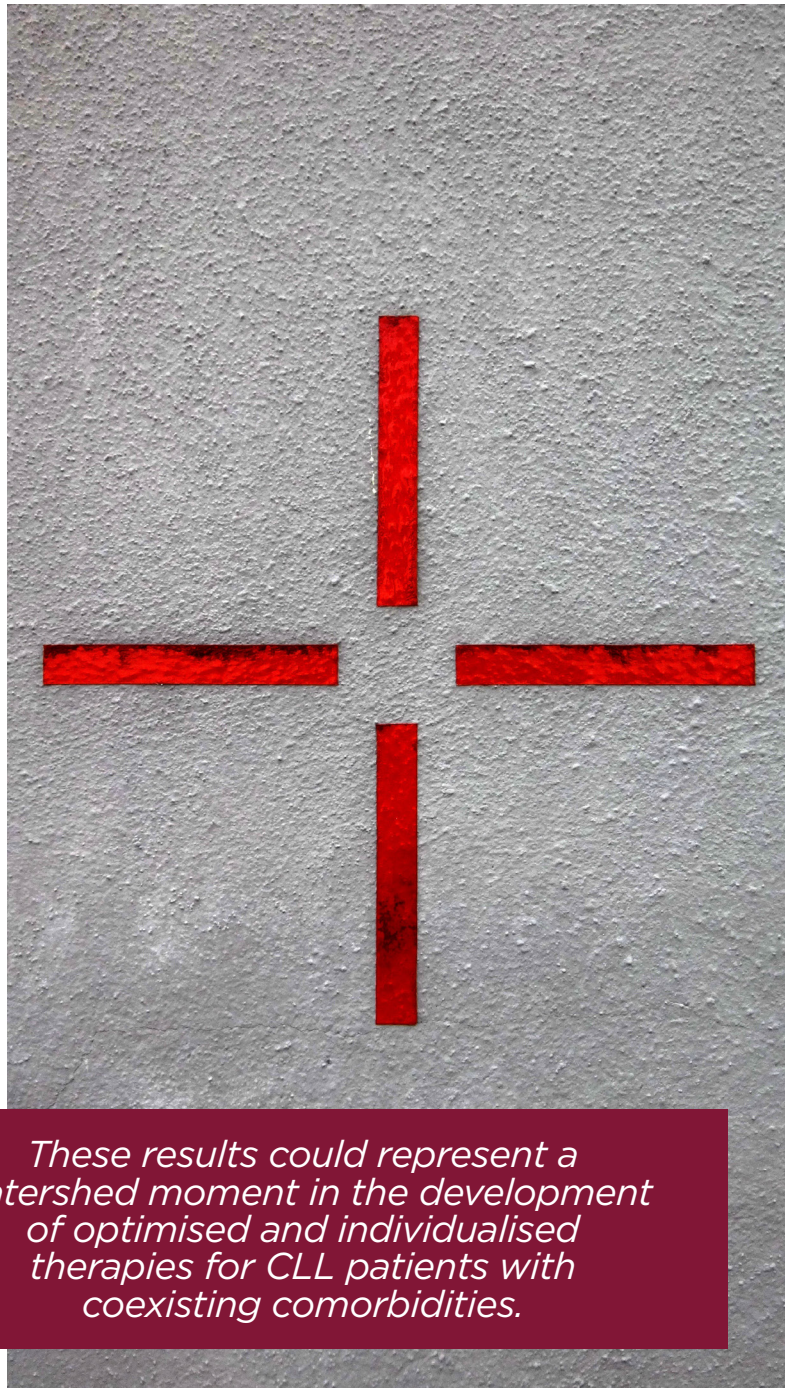
A NOVEL chemotherapy-free, fixed-duration treatment has been granted Breakthrough Therapy Designation by the U.S. Food and Drug Administration (FDA), and was approved for the treatment of previously untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma patients on the 15th May 2019. The study was presented at this year's EHA Congress in Amsterdam, the Netherlands, and promoted in a press release.

An unmet clinical need previously existed in which standard of care for CLL patients was one of only two therapeutic approaches: i) fixed-duration chemoimmunotherapy, or ii) continuous or indefinite targeted therapy. The CLL14 study was designed by a German group incorporating two pharmacological compounds for the purpose of developing a fixed-duration targeted therapy. These were:

1. Venetoclax: an apoptosis-inducing drug that acts through inhibition of oncogenic protein BCL2, commonly overexpressed in CLL.
2. Obinutuzumab: an anti-CD20 monoclonal antibody that targets malignant lymphocytes.

This combined therapy was compared against a standard chemoimmunotherapy regimen of chlorambucil plus obinutuzumab in CLL patients who had received no prior treatment and presented with co-existing comorbidities.

Venetoclax plus obinutuzumab showed significantly improved primary endpoints and progression free survival in the cohort, with 88% of patients being free of disease progression following 2 years from treatment initiation (this was compared against 64% for the standard-of-care chemoimmunotherapy regimen). This treatment also exhibited 76% confirmation for minimal residual disease negativity 3 months after the treatment had ceased.



These results could represent a watershed moment in the development of optimised and individualised therapies for CLL patients with coexisting comorbidities.

A good safety profile was confirmed for elderly patients, and superior outcomes were evident in regard to overall response rate, complete response rate, and minimal residual disease negative response: this was more than double the 35% negativity rate shown in the chemoimmunotherapy-treated patients. These benefits were shown across multiple common subgroups, including those in which patients harboured *TP53* mutations.

These results could represent a watershed moment in the development of optimised and individualised therapies for CLL patients with coexisting comorbidities.

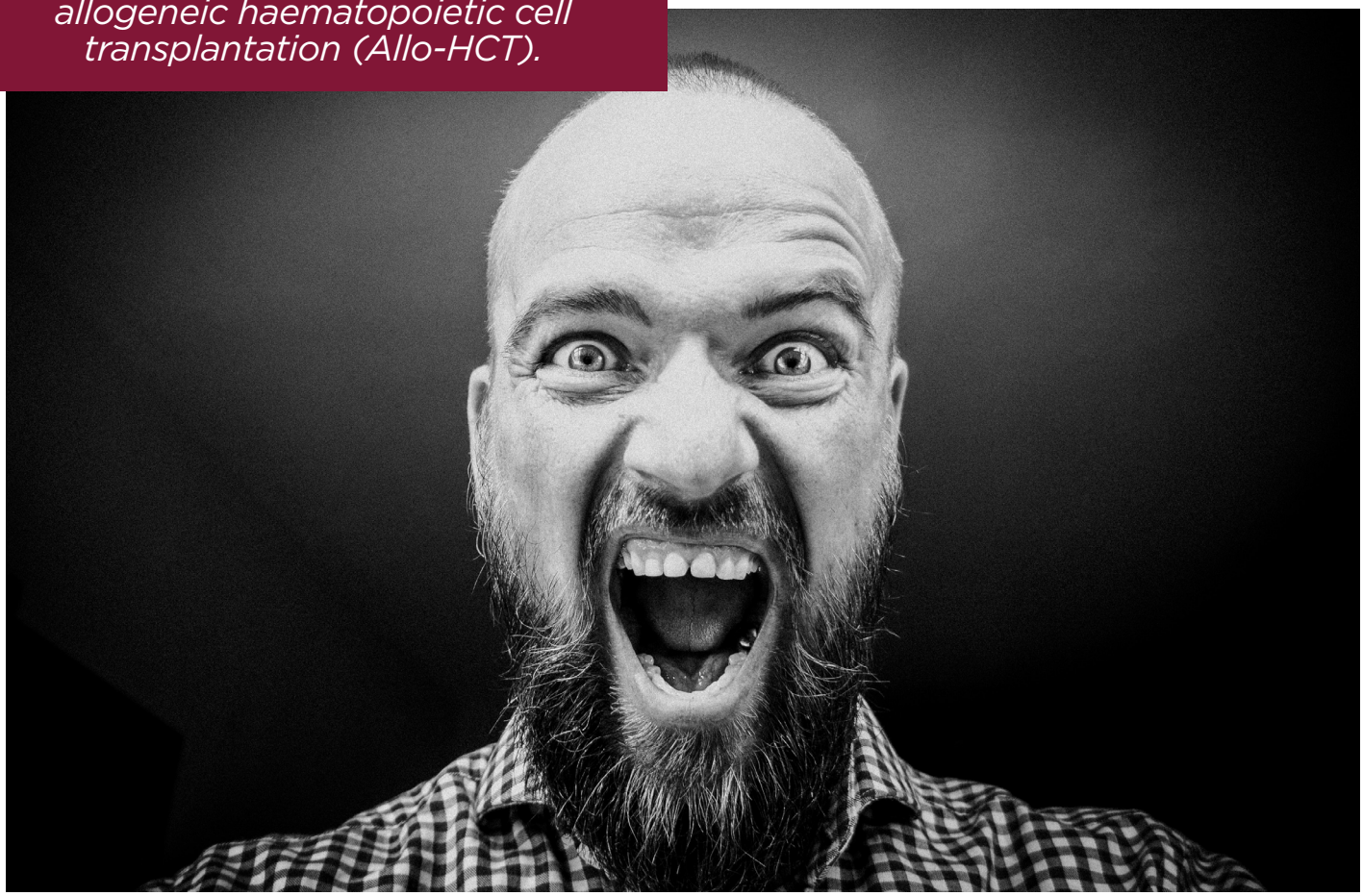
Astonishing Results from Acute Myeloid Leukaemia Preparative Therapy Trial

HUGE steps forward have been made in the understanding of pre-transplant preparative therapy and its impact on acute myeloid leukaemia (AML) patients in remission following allogeneic haematopoietic cell transplantation (Allo-HCT). The results of a randomised, Phase III clinical trial were presented at the EHA congress and reported in a EHA press release, shedding light on the impact of two different methods of pre-transplant preparative therapy on patient outcomes.

Huge steps forward have been made in the understanding of pre-transplant preparative therapy and its impact on acute myeloid leukaemia (AML) patients in remission following allogeneic haematopoietic cell transplantation (Allo-HCT).

The BTN CTN 0901 trial, performed between 2011 and 2014 by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), enrolled 188 patients who were in remission from AML. The patients had been randomised to receive either high-intensity myeloablative (MAC) or reduced intensity conditioning (RIC). The aim of the study was to determine whether these types of preparative therapy reduces relapse rates and/or improves survival following a transplant if given before a stem cell transplant to patients in conventional remission but with genomic evidence of residual disease. To do this, the blood samples of the patients were assessed using ultra-deep next-generation sequencing.

The results demonstrated that, in patients with genomic variants pre-transplant (adjusting for disease risk and donor group), RIC was associated with increased relapse (hazard ratio [HR]: 5.98 [3.19–11.26], p<0.001), decreased disease-free survival (HR: 2.80 [1.76–4.44], p<0.001), and decreased overall survival (HR: 2.16 [1.30–3.60], p=0.003) compared with MAC. This clearly demonstrated the inferiority of RIC in comparison to MAC in AML patients with genomic evidence of residual disease when in clinical remission.



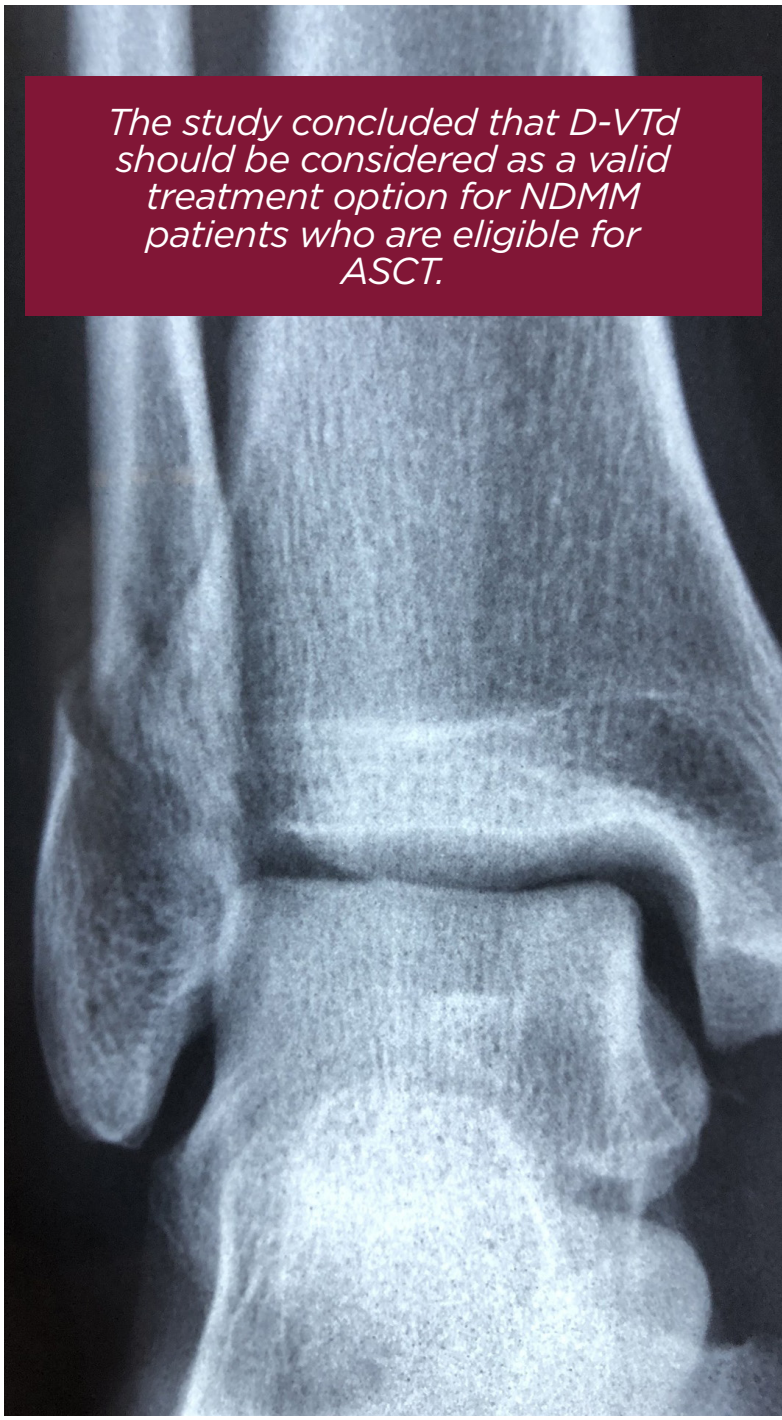
Results from Part 1 of CASSIOPEIA: Addition of Daratumumab to the Standard Treatment for Multiple Myeloma

STANDARD treatment for newly diagnosed multiple myeloma (NDMM) patients who are transplant-eligible in Europe usually consists of a multidrug and autologous stem-cell transplantation (ASCT) regimen. The results from the first part of a recent trial (CASSIOPEIA), investigating whether the addition of daratumumab to this treatment plan improved stringent complete response (sCR) rate in patients with NDMM, were presented in a press release and abstract on the 14th June at EHA 2019.

Spread across 111 sites, this two-part, randomised, Phase III CASSIOPEIA trial recruited 1,085 patients between September 2015 and August 2017. Participants were split and randomly assigned to either the standard treatment (bortezomib, thalidomide, and dexamethasone [VTd] plus ASCT; n=542) or standard treatment plus daratumumab (D-VTd; n=543). During the pre-treatment phase, VTd or D-VTd was administered in four 'induction' cycles over 28 days. Post-ASCT, patients then received further doses of their assigned treatment in two 'consolidation' cycles over 28 days.

After the consolidation phase, sCR was achieved in 157 (29%) of the D-VTd patients versus 110 (20%) of the VTd patients (odds ratio: 1.60, 95% confidence interval: 1.21–2.12, p=0.001). Complete response or better was achieved in 211 (39%) of patients in the D-VTd group versus 141 (26%) in the VTd group. Furthermore, 346 (64%) patients in the D-VTd group versus 236 (44%) in the VTd group achieved minimal residual disease-negativity (10–5, assessed by multiparametric flow cytometry; both p<0.0001). Neutropenia (28% versus 15%), lymphopenia (17% versus 10%), and stomatitis (13% versus 16%) were the most common Grade 3 or 4 adverse events, and only 46 deaths in the study were observed (14 versus 32, 95% confidence interval: 0.23–0.80).

Results from this first part of the study showed a 53% reduction in the risk of progression or death during D-VTd treatment and consistently improved post-consolidation responses, including sCR, minimal residual disease, and complete response. Including the data and the fact that addition of daratumumab was well tolerated, the study concluded that D-VTd should be considered as a valid treatment option for NDMM patients who are eligible for ASCT.



The study concluded that D-VTd should be considered as a valid treatment option for NDMM patients who are eligible for ASCT.

NADK Gene New Target for Treating T-Cell Acute Lymphoblastic Leukaemia

NADK could be a new therapeutic target in the treating aggressive cancer T-cell acute lymphoblastic leukaemia (T-ALL). The research presented at the EHA congress in Amsterdam on the 15th June 2019 studied the *NOTCH1* gene. Results showed a better survival rate in T-ALL mice who underwent NADK gene target therapy.

T-ALL is fatal in 15% of children patients and 50% of adult patients. A new therapeutic approach is being called for as treatment options have not undergone significant change in decades. The majority of T-ALL cases are propelled by mutations in *NOTCH1*, or relevant genes, which switch on genetic programmes that result in T-ALL cells multiplying at a fast rate. The researchers used a CRISPR-Cas9-based method to screen around 20,000 genes in the human genome and found >50 genes that were required for *NOTCH1*-driven T-ALL cells to survive.

The *NADK* gene was a potential therapeutic target that showed great promise. The gene's product, NADP, has the ability to protect cells from reactive oxygen species that can be damaging. *NOTCH1*-driven T-ALL cells were found to create large quantities of damaging oxygen compounds. *NOTCH1* delivers a signal that activates *NADK* in order to protect the cells from these compounds. The cells multiply rapidly. *NADK* subdued T-ALL cells from growth and, in turn, prolonged survival prospects of mice who had T-ALL. There were no noticeable side-effects.

The researchers' findings suggest that NADK inhibitors have the potential to improve T-ALL treatment ability while removing some side-effects for the patients.

The researchers' findings suggest that *NADK* inhibitors have the potential to improve T-ALL treatment ability while removing some side-effects for the patients. While these results are promising in the search for a new treatment option for T-ALL, further research would be needed to see whether similar results were found in human patients. The team outline development plans for new inhibitors to test individually and in combination with the standard chemotherapy.

Hu5F9 and Rituximab Combination Could Treat Drug-Resistant Non-Hodgkin's Lymphoma

RITUXIMAB combined with Hu5F9 has been found to be a potential treatment option for drug-resistant non-Hodgkin's lymphoma. The study, presented at EHA in Amsterdam on the 15th June 2019, found that rituximab could place signals on lymphoma cells for them to be eaten by the body's immune system. The results were promising, and the treatment was found to have excellent long-term safety.

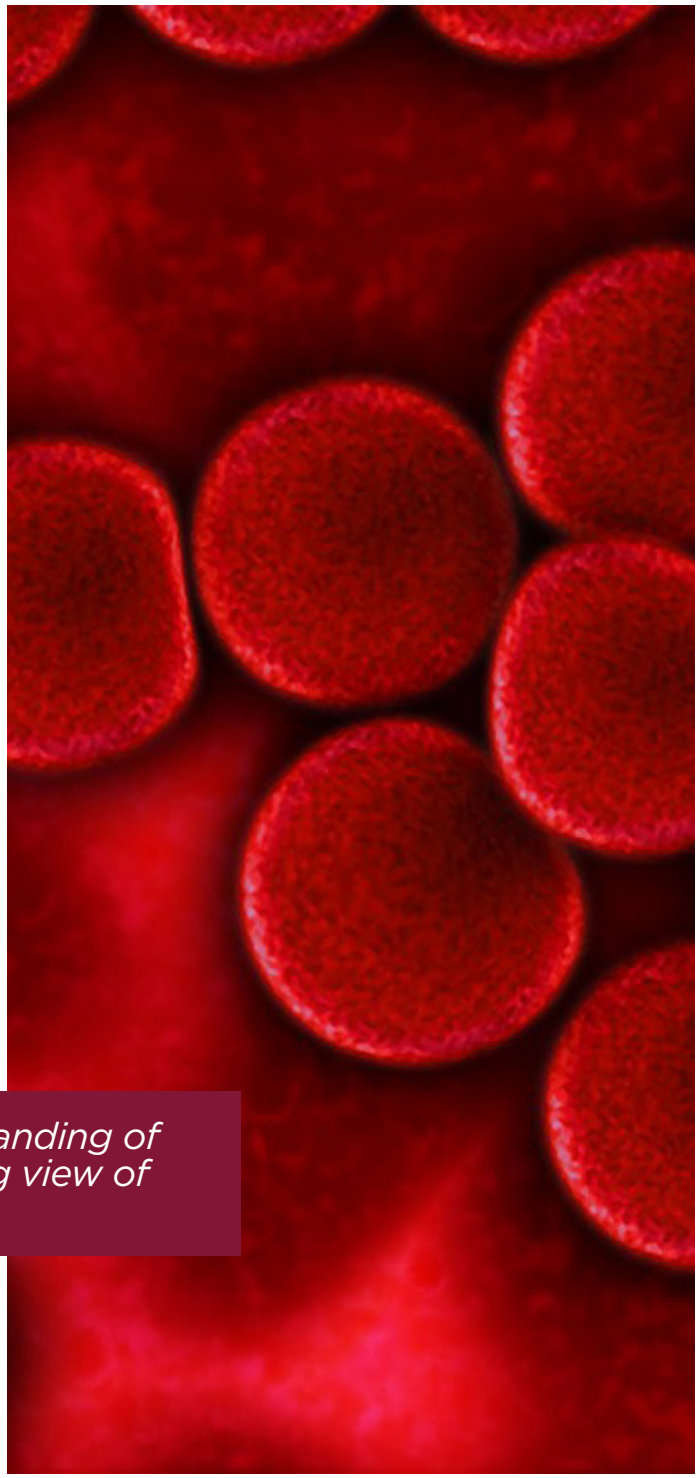
Many patients with non-Hodgkin's lymphoma have a highly effective response to chemotherapy. First-line chemotherapy has the ability to cure most patients of aggressive lymphomas, such as diffuse large B-cell lymphoma (DLBCL), and it can induce remission in the majority of patients with indolent lymphomas, including follicular lymphoma (FL). When refraction or drug resistance occurs, the prognosis quickly becomes poor. A satisfactory safety profile and an ability to overcome drug resistance is key for all novel agents.

CD47 is one of the body's defences against phagocytosis: the process of cell's engulfing foreign or host bodies. The antibody Hu5F9 targets CD47, which lymphoma cells will often use to save themselves from getting eaten. Blocking CD47 removes the signal for not being eaten and the immune system is able to eat the lymphoma cells. This approach is most successful when it is combined with rituximab as it places the signal to be eaten on the lymphoma cells. Most normal cells can then avoid the effects.

This research improves our understanding of the effect and provides a promising view of the durability of responses.

The combination of Hu5F9 and rituximab has been demonstrated as successful in working against drug-resistant lymphoma. However, the cases were of a limited number and the resilience of the effects are unknown.

This research improves our understanding of the effect and provides a promising view of the durability of responses. Long-term safety can be considered to be excellent as the majority of the side-effects are present in the first cycle. There is the need for further research that can build on this study and compare this option to alternatives. As there is excellent long-term safety, the therapy usage potential is great as it can be used in most patients. To improve efficacy, additional agents can be added and are likely to be safe.



Phase III Study of Venetoclax Shows Improvement Over Placebo for Multiple Myeloma

AS THE second most common haematological cancer, multiple myeloma carries an enormous burden for healthcare professionals and patients around the world. In spite of major advances in previous decades, the disease remains incurable and new therapeutic options are sorely needed. Now, as revealed in a press release from the 2019 EHA congress dated 15th June, results from the Bellini trial have shown an improvement for the drug venetoclax over placebo, when both are used in combination with bortezomib and dexamethasone for multiple myeloma.

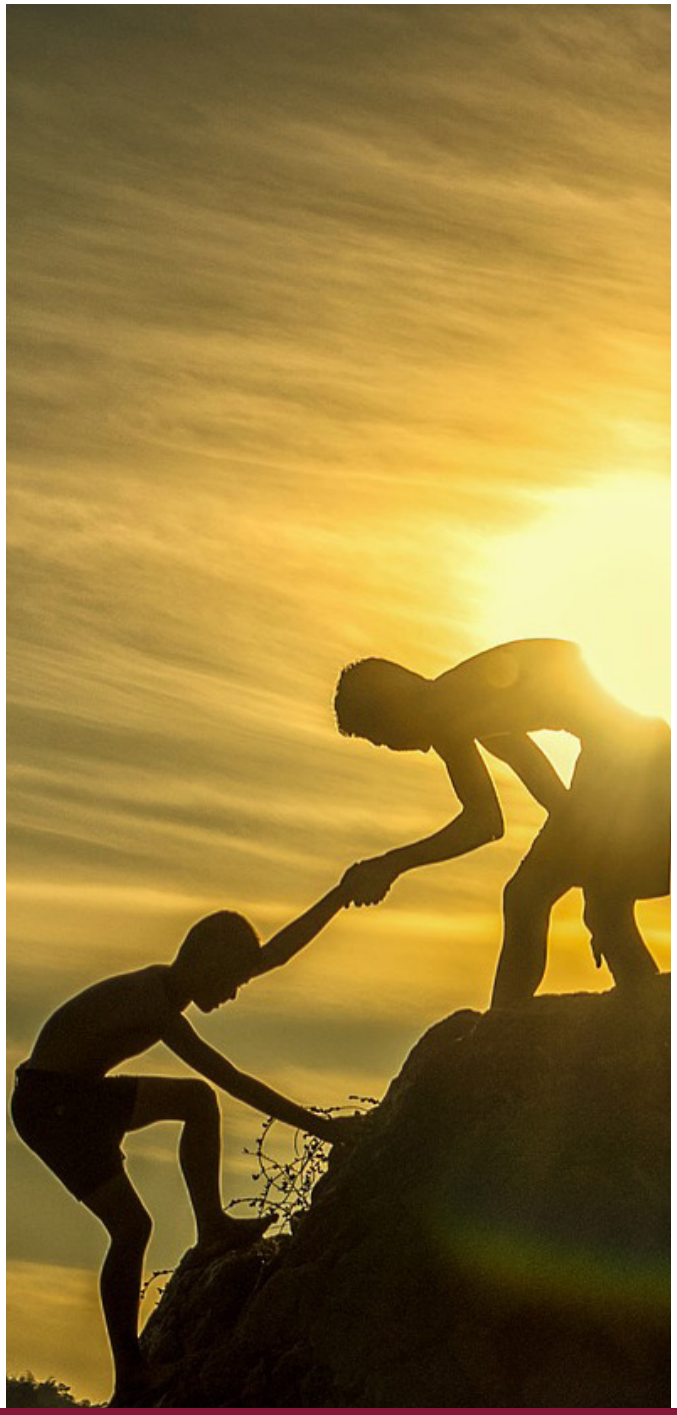
Many cancers feature alterations of apoptotic pathways, allowing cancer cells to survive and multiply. Venetoclax is a small molecule inhibitor of bcl2, a family of anti and pro-apoptotic proteins that is known to enhance cell survival in some cancers. Following preclinical work that suggested venetoclax could induce apoptosis in myeloma cells, with successful Phase I and II trials showing the drug's efficacy in combination with dexamethasone or bortezomib, the Phase III, randomised, placebo-controlled trial Bellini was developed by researchers at the Mayo Clinic, Rochester, Minnesota, USA. This trial enrolled 291 patients with relapsed myeloma, randomising them 2:1 to receive either venetoclax or placebo in combination with dexamethasone or bortezomib.

An increased overall response rate was seen in the drug group compared to placebo (82% versus 68%; p<0.01), as well as very good partial response or better (59% versus 36%; p<0.01). A great increase in progression free survival was also noted in this group (22.4 versus 11.5 months; hazard ratio: 0.630; p=0.01). However, the venetoclax group saw a decrease in overall survival (hazard ratio: 2.027; 95% confidence interval: 1.042–3.945) at interim analysis, with most additional deaths attributed to infections and or progressive disease, notably during the first 6 months of the trial. Patients with high risk cytogenetics, later disease stage, without translocations (11;14), or with low levels of bcl2 proteins experienced a lower benefit from this treatment.

Further studies are required to clarify these results, but researchers are hopeful that venetoclax will soon become a useful treatment option in the haematologists armamentarium for use against multiple myeloma.

Further studies are required to clarify these results, but researchers are hopeful that venetoclax will soon become a useful treatment option in the haematologists armamentarium for use against multiple myeloma.

Benefits of Acalabrutinib for Chronic Lymphocytic Leukaemia Reach New Heights in the ASCEND Study



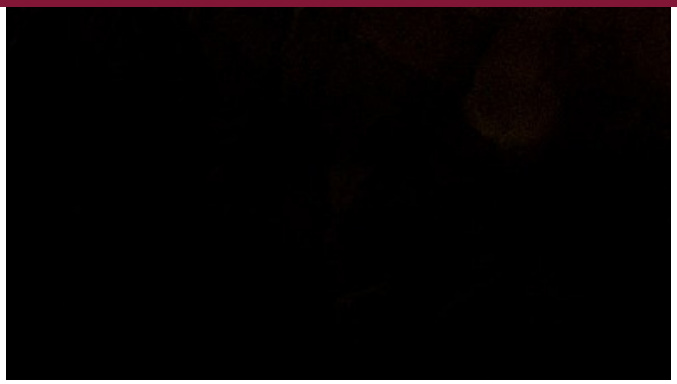
CHRONIC lymphocytic leukaemia (CLL) is the most common form of adult leukaemia and is rarely curable. The inhibition of Bruton's Tyrosine Kinase (BTK) is a well-known therapeutic approach for this cancer. Now, as revealed in a press release at the 2019 EHA congress on 15 June, the Phase III ASCEND trial has shown positive effects of the BTK inhibitor acalabrutinib.

Previous studies have shown acalabrutinib to be a highly selective BTK inhibitor, with a demonstrated activity and improved tolerability in patients with CLL. In the ASCEND study, 310 patients with relapsed/refractory CLL were randomised 1:1 to receive either acalabrutinib monotherapy 100 mg orally twice daily, or rituximab with idelalisib (IdR) or bendamustine (BR), which are commonly used CLL regimens.

The results of this study showed that the acalabrutinib monotherapy significantly improved progression-free survival compared to idR/BR, as well as a more tolerable safety profile. The risk of disease progression or death saw a huge decline (69% after 16.1 months). Similarly, at 12 months, 88% of patients on the monotherapy showed no disease progression, versus 68% in the combination arm.

"These significant results from the ASCEND trial, the first randomised controlled trial examining acalabrutinib, could have a large impact on current practice, showing the drug to be a well-tolerated, highly effective BTK inhibitor that could soon become a common treatment for CLL."

Treatments for CLL are currently limited and there is a great need for more effective and better tolerated therapies. These significant results from the ASCEND trial, the first randomised controlled trial examining acalabrutinib, could have a large impact on current practice, showing the drug to be a well-tolerated, highly effective BTK inhibitor that could soon become a common treatment for CLL.



Congress Interviews

Find out more about about the EHA Congress through our interviews with members of the various committees required to help run it.

Featuring: Professor Shai Izraeli, Doctor Marek Mraz, and Professor Barbara Bain.

Professor Shai Izraeli

Treasurer of EHA Executive Board and Director of the Division of Pediatric Hematology and Oncology, Schneider Children's Medical Center, Petah Tikva, Israel

Q1

You are the treasurer of the executive committee for the European Hematology Association (EHA). How do you prioritise and delegate the funding which is provided to the EHA and use it in the most effective way possible?

The board and the committees of the EHA are working on an investment plan for the next 3 years. Our two major goals are to support education and research of haematology in Europe and beyond. The process ensures the incorporation of diverse ideas generated by many members of EHA committees.

Q2

How do you find time to juggle your responsibilities with the EHA and your roles outside the association, most notably as the Director of the Pediatric Hematology Oncology Division in Schneider Children's Medical Center of Israel.

This is indeed challenging but there is a saying: if you want something to get done, give it to a busy person. I am fortunate to have fantastic assistance both in my main activity as the head of a very large clinical paediatric haematology oncology department and the activity in the EHA. One can do quite a bit in 24 hours each day.

Q3 As an Executive Board Member, you can directly influence how the EHA operates. How important is communication between the different committees towards fulfilling the association's main objectives and ensuring the best congress possible?

Communications are critical indeed. Committee chairs are often invited to board meetings and many chairs are board members. In addition, we established two committees: the education and research committees that oversee most of the other committees in the two most important fields in the EHA – promoting education and research towards better clinical care of patients with haematological disorders. In addition, we are in direct contact with the Scientific Working Groups – which are groups organised by the European haematology community usually around a disease topic (such as myeloma and chronic lymphocytic leukaemia). Finally, we interact with the national haematology associations. All these communications ensure that EHA is a true representative of haematology in Europe.

"This is the field that pushes the envelope. Problems and unmet needs of patients are taken to the laboratory where new discoveries are made that are quickly translated to the clinic and change patients' lives."

Q4 Education is clearly a key focus of the EHA. Can you explain how the association decides on and assimilates the content that is provided across the various platforms on your website (e.g., Master Class and Hematology Curriculum)?

The education committee is one of the most active committees in the EHA. In addition to the web content EHA conduct training that focusses on young haematologists and haematologist scientists. This focus on 'YoungEHA' includes a course on Translational Research Training in Hematology (TRTH), a joint initiative with the American Society of Hematology (ASH), and Clinical Research Training in Hematology (CRTH). The goal of both programmes is to train the future basic and clinical researchers in haematology.

Q5 Your professional career spans three decades, the majority of which has been spent in research institutes in either Israel or North America. Are there striking differences or similarities that you can comment on regarding the outlook and emphasis you have experienced in these institutes?

Basically, I was in two types of institutions: I was trained in the NIH National Cancer Institute USA. This is a unique place, in that it is the only one in the world that is devoted to both basic translational and clinical research. There is no emergency room in the NIH. It is highly selective, admitting and treating only patients who enrol on specific clinical research protocols. The budget is almost unlimited, and one does not have to apply for grants. Hence the NIH is the place for ground-breaking research.

In Israel I have been working in public academic hospitals; most recently, I head up the Division of Pediatric Oncology in Schneider Children's Medical Center: a major referral centre for children with cancer and serious haematology disorders. We do not select patients, we serve everyone. We combine superb clinical care with advanced diagnostics and research. We do not have the financial means of the NIH. Moreover, in the last 19 years, since returning from the NIH to Israel, I had to compete on research grant funding and have been lucky to be successful.

Q6 What are some of the most significant haematological or technological developments to have occurred during your professional career and how have they influenced your day-to-day work?

Amazingly, since I have started my career as a medical student, the outcome of childhood leukaemia has been transformed from an incurable disease to a cure of close to 90% of children with acute lymphoblastic leukaemia (ALL) and at least 70% of children with acute myeloid leukaemia. Now it is reasonable to set the goal to cure every child with cancer with less toxic, targeted, scientific-based therapies.

The most significant leap in the last few years has been the genomic revolution that enables us to administer more precise, personally adjusted medicine for treatment of both malignant and non-malignant disorders. The developments in fields such as genomic editing could lead to cure of many of the serious haematological disorders.

Q7 In your current lab, you are combining advanced genomics technologies with functional preclinical models to investigate haematological malignancies. Can you describe some of the difficulties you are experiencing in translating molecular findings into clinically relevant outcomes? How can this be improved?

Cancer is a complex disease driven by genomic instability and incredible versatility: one closes the door and it enters through the window. Ten years ago, we discovered a subtype of ALL characterised by acquired mutations activating the JAK–STAT pathway. We first discovered it in children with Down's syndrome and ALL. Later it has been discovered that this leukaemia characterises between 5–10% of children and adults without Down's syndrome and is associated with a poor prognosis. A trial with target therapy with ruxolitinib, a JAK inhibitor, is ongoing now in many hospitals of the Children Oncology Group (COG).

However, genomic analysis of diagnosis and relapse of these JAK driven leukaemia that we published a year ago demonstrate that JAK signalling at diagnosis is often replaced by RAS signalling at relapse. This observation is concerning. It illuminates a potential resistance mechanism to treatment with JAK inhibitors. Additional research is needed to study the interaction between these two signalling pathways and the proper way to target these high-risk leukaemias.

Q8 Looking forward to future EHA congresses, are there research topics that you believe are evolving rapidly and that will be increasingly popular points of discussion?

Immunotherapy, gene editing and gene therapy, interaction between cancer cells, and the microenvironment.

Q9 Finally, are there any points of advice you can offer to young haematologists experiencing and/or contributing to a congress for the first time?

As a physician I focus on children; they may be only 20% of the population but they are 100% of the future. In the EHA, we invest in young people because they are the future of haematology with our programme 'YoungEHA' directed at young haematologists, young scientists who chose the field of haematology, and young physicians who also want to pursue a career in science. It is combined from training programmes CRTH for clinical research and TRTH for basic research (partnering with the ASH); from special grants for early career scientists and physician-scientists; and from special programmes in the EHA congress. These are composed not only from special sessions during the congress, but also from a special pre-congress scientific meeting of PhD and postdoctoral fellows.

I have chosen haematology because this is the clinical field with the closest link between the lab and clinic. I was fascinated from seeing the disease under the microscope. This is the field that pushes the envelope. Problems and unmet needs of patients are taken to the laboratory where new discoveries are made that are quickly translated to the clinic and change patients' lives.

Doctor Marek Mraz, MSc, MD, PhD

Assoc. Prof. of Oncology
CEITEC MU and University Hospital Brno, Czech Republic
Member of the Young EHA Committee

Q1 How does YoungEHA promote the involvement of PhD students and young haematologists in the EHA congress and other important events?

YoungEHA organised a so-called 'Young EHA tract' during the EHA Annual congress, which was a series of sessions recommended to young haematologists/scientists. This year, we had several sessions specifically designed to attract and educate young researchers and clinicians. We had a 1-day pre-congress meeting (YoungEHA Research Meeting, Thursday 13th June, 8:45–18:00) that covered numerous interesting topics of basic and translational research in haematology and alternated young speakers and keynote lectures by top senior experts. During the congress, the YoungEHA session (Friday 14th June, 14:30–15:30) covered the different sides of haematology, from discovering a novel drug target to performing clinical trials, and also the processes at regulatory agencies. The second 'YoungEHA session' (Sat 15th June, 14:14–17:15) focussed on the future of haematology, personalised therapy, and the use of genomics. YoungEHA also helps to promote the Translational Research Training in Hematology (TRTH) and Clinical Research Training in Hematology (CRTH) classes, and I very much recommend that scientists and haematologists apply for these in the future. Finally, on Saturday night we threw an EHA Grooves party, which was open for everybody but it is definitely a great opportunity to have a good time with young peers.

Q2 Personally, what are your roles and responsibilities as a member of the committee, prior to and during the congress?

We rotate our duties each year, and in principle this involves organisation of the sessions that I have described above and giving input to other EHA committees regarding topics such as early-career membership, harmonisation of access to education in different countries, and the identification of future challenges in haematology such as integration of truly personalised medicine via genomic approaches. My responsibility this year was to design together with other members the structure of the YoungEHA sessions and select potential speakers. We also all help to promote the EHA congress, and prepare materials for the EHA press office. This year, several new members are joining the YoungEHA committee, and I will be rotating-off next year.

Q3 YoungEHA focusses on inspiring young haematologists and ensuring they reach their full potential; what type of support and opportunities does YoungEHA provide to help young haematologists progress in the field?

The short answer here would be to visit our website: https://ehaweb.org/youngeha/. This will provide useful information regarding all the interesting options for young haematologists and trainees. We have put lot of energy into developing this site in a clear and engaging way. I can mention several opportunities that should not be missed: i) the EHA provides research grants for young scientists and clinicians; ii) the TRTH and CRTH special training and mentoring programs are something that I cannot recommend highly enough; and iii) the Master Class online training platform.

Q4 Do you think there are the same opportunities now as there were when you were studying for your PhD or just starting your career in the field? How have things changed?

I think nowadays the science is even more interconnected and thus also more competitive than ever. I left the Czech Republic very early in my career, and I was very lucky that my supervisor and head of the department supported this. I was also lucky when I wanted to return back to Europe after my post-doc in the USA, since I was to be one of the first to receive the EHA Non-Clinical Research grant, which helped me to start my own group. I am not sure that I would have been able to do this without this support. I highly recommend that young researchers use all the training and grant options provided by EHA... They are all well organised and administratively non-demanding.

Nowadays, the mobility options for basic scientists are nearly unlimited, but there are some remaining limitations regarding the transferability of education and clinical training for physician/physician-scientists between different countries, for example between Europe and North America. At least within Europe, this should be addressed in the coming years, including the uncertainty around Brexit. I very much encourage young people to use the opportunity to find a great supervisor and mentor, something that can be done in their home country, but also anywhere in the world.

Q5 You work with young scientists in your lab: Do you instil the same ethos of YoungEHA in your own style of supervision? If so, how?

I have met some great people to emulate. These include Thomas J. Kipps, who I worked with for several years at the University of California, San Diego; Greg S. Nowakowski and Clive S. Zent from the Mayo Clinic, Minnesota; and Sarka Pospisilova and Jiri Mayer from our University Hospital in Brno, Czech Republic. I guess my style is a mixture of what I learned from these great people. I am trying to push each of my students to their maximal individual potential and acknowledge that each person has some specific talents and weaknesses that can be harnessed and worked on. However, sometimes I joke that the only thing that I can ever really teach them is to be curious and use proper positive and negative controls in their experiments. I also think that persistence and focussed work pays off.

Q6 Congratulations on winning the ERC grant from European Commission in 2018 for your research into chronic lymphocytic leukaemia (CLL) and B-cell lymphoma! How does this compare to other achievements in your career?

This is extremely important for my lab, and for developing our ideas and research field. We are interested in understanding microenvironmental interactions in chronic lymphocytic leukaemia (CLL) with a special emphasis on the role of non-coding RNA. We have recently showed in several studies that it appears that microRNA are regulating the B cell receptor (BCR) signalling pathway, and that this is deregulated in CLL/lymphomas. This grant allows me to support the lab, and I am looking for enthusiastic post-docs to join this project. It was also followed by multiple invitations to give lectures at conferences and institutes. It is important for the lab, but the only real achievement is the publications and research that my group produce: that is where all our work and passion goes.

"I am trying to push each of my students to their maximal individual potential and acknowledge that each person has some specific talents and weaknesses that can be harnessed and worked on."

Q7 Last year, whilst under your supervision, one of your colleagues won a Discovery award. How do you motivate and support young scientists around you to achieve their best?

Gabriela Pavlasova is my PhD student and she published two papers that defined the regulation and molecular function of CD20 in CLL cells. It is paradoxical that anti-CD20 monoclonal antibodies such as rituximab have been used for over 20 years, but the function of CD20 remains unclear. She showed that CLL cells, in the

context of immune niches, induce CD20 to boost BCR signalling, and rituximab interferes with this by eliminating cells with the highest levels of CD20 and thus more active BCR signalling. These observations also have implications for therapy, since she described that BCR inhibitor ibrutinib leads to down-modulation of CD20 by interfering with CXCR4 signalling. Practically, this means that ibrutinib is probably not suitable to combine with rituximab, and the Discovery award provided by Novartis acknowledged her for these discoveries.

Gabriela is very hard working, but it also took me about a year to find a project that fits her talents and natural inclinations. Not everything was easy, and I had to put some more time into discussions with her at the beginning of the project. Nowadays however she is very independent and runs multiple projects. It is a serious responsibility of the supervisor to put students on the right path, and it sounds easier than it is sometimes.

Q7 Have you observed any areas of research that particularly interest the younger generation of haematologists, or that appear to be an evolving topic of inquiry?

There are so many interesting things, and some of them are obvious in that many people see them, but many things remain unasked because researchers are blinded by the shiny and obvious problems.

My personal impression is that noncoding RNA will be a very fruitful and fascinating area of research, and a lot of young scientists envision this too. There must be a good reason for having >95% of our genome coding RNA that are not translated to proteins....

Young clinicians often also want to take up the challenge of performing a fully personalised therapy in patients. How to do this in a timely fashion, involving the sequencing of gene panels/genomes within days and the quick analysis of big data to make therapeutic decisions is difficult. There is a real need to figure this out. Do we need to combine targeted agents in a fully personalised fashion, and have clinical trials in which each patient receives a unique 'drug cocktail'?

Q8 How has the field of haematology changed since you started your career in research, and what developments are you most excited about for the future?

Everything has changed in last 15 years: we have next-generation sequencing techniques for analysing all layers of regulation; we have genome editing technology such as CRISPR/Cas; we have many newly discovered non-coding RNA; and we have BCR inhibitors developed for B cell leukaemia and lymphomas. I feel privileged to work in a time when we are finally starting to understand some problems in depth, and also witness many new drugs being approved for the benefit of patients.

Q9 Finally, do you have any advice to young haematologists who are starting their careers in the field?

The mentoring from supervisors that you receive and determining the scientific area you wish to specialise in is vitally important and is likely to affect your personal life too. Select your mentors carefully. Be ready to fail many times with your experiments (or unfortunately sometimes with your patients), but if you use good positive and negative controls you will always learn something for the next time.

Professor Barbara Bain

Imperial College, London, UK
Member of the EHA Online Case Unit

Q1 What is your favourite part of attending events, such as the EHA congress?

I must confess that my favourite part is meeting people that I have worked with or known in various contexts, complementary to the scientific part of the meeting.

Q2 As a member of the EHA online case unit, what does your work comprise?

I am one of four case editors. Between us we edit all cases that are to be presented at EHA tutorials, to make sure that the science is up to date and clearly presented, and also that the English is correct and the meaning is clear. This requires tact and active collaboration with the authors. Later, we each review all the cases that have been presented at EHA tutorials in the previous year and then meet to discuss which cases should be uploaded to the online EHA Campus. The cases are re-edited at this stage to make sure that they can stand alone when the author of the case is not there to answer questions. The online availability means that far more people can benefit than were able to attend the actual tutorial. I usually attend one tutorial a year, as do my colleagues. This lets us see how the cases work in practice and helps us to guide future authors. My most recent expedition was to Kazakhstan where the tutorial was part of the EHA's global outreach programme. The previous year I participated in a tutorial in Warsaw.

Q3 The practice of medicine is becoming increasingly multidisciplinary. How collaborative is modern haematology and with whom do you work most frequently?

Haematology is very collaborative, but at the same time in some countries specialised tests are centralised so that there is a regrettable dissociation between the clinicians treating the patient and the laboratories that are performing specialised tests. I now work intermittently in the laboratory, collaborating with laboratory scientists, clinical staff, and trainees.

Q4 When did you first know that you had a passion for teaching?

This started as early as school. Some of my teachers were not very pleased when they found I was helping other students understand the lessons. Presumably they thought this reflected badly on them. I have continued to teach throughout my medical career. One of the pleasures of haematology is discovery: to look at a blood or bone marrow film or a laboratory result and work out what is going on. If this is done collaboratively with laboratory scientists or trainee haematologists, everyone learns from the experience. Formal lectures help, but sitting at the microscope with others can be more important.

Q5 You have spoken before of the importance of your mentors throughout your career. What do you remember most about their teachings and what qualities do you think make a good medical mentor?

The mentors that most influenced me were those who had both a keen interest in science and a deep understanding of the patient's experience. They dedicated hours each week, in the company of trainees, to diagnostic haematology and to discussing patient management. Like all good teachers they showed intellectual curiosity and continued to inspire others well past the usual retirement age.

"One of the pleasures of haematology is discovery: to look at a blood or bone marrow film or a laboratory result and work out what is going on. ."

Q6 The YoungEHA provides support to young researchers and clinicians throughout Europe. How important do you think groups dedicated to the next generation are for the future of this discipline?

Supporting the next generation is of great importance. The practice of haematology is not getting any easier with the increasing complexity of the subject and the enormous body of knowledge to be assimilated.

Q7 Burnout has recently been recognised as an occupational phenomenon by the World Health Organization and is of growing concern for medical practitioners throughout the world. How have you avoided burnout throughout your career and what advice would you have for aspiring physicians?

I think you need to accept focussing on just a small part of your discipline and work closely with others. A supportive secretary is pretty important. It is also important to have some interests outside medicine and some time when you can escape from the pressures of medical practice.

Q8 What is your opinion on social media as an education tool, especially for haematologists?

I am too old to have much interest in social media. It is all I can do to keep up with the daily flood of emails... No doubt it is important, but not for me.

Q9 What do you think were the main take-home messages from this year's EHA congress?

A large part of the congress was dedicated to understanding the nature of haematological neoplasms and assessing their optimal treatment. New and evolving treatment options will be in the forefront on the minds of many participants. These are continually being evaluated and then introduced into clinical practice. Participants will go back to their day-to-day work armed with the latest information.

Q10 Congratulations on being awarded a lifetime achievement by the British Society for Haematology in 2017 and an inaugural EHA Educational and Mentoring award in 2018! What will be the next milestone in your career as a haematologist?

I am not expecting any milestones, but I should like to keep learning. Teaching helps in this regard. *Docendo discimus*: by teaching, we learn. My advice to the next generation is to always have the courage to have an opinion on a diagnosis or optimal management. It does not matter if your initial opinion is wrong: what is important is to think about the possibilities for yourself and only then discuss it with others and learn from the experience. Of course, sometimes the only honest opinion is "I don't know what is going on here."

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Rebooting the Myeloma Treatment Programme

This symposium took place on 13th June 2019 as part of the 24th European Hematology Association (EHA) Annual Congress in Amsterdam, the Netherlands

Chairpeople: Jesús San Miguel[1]

Speakers: Jesús San Miguel,[1] Katja Weisel,[2] Xavier Leleu,[3] Hermann Einsele[4]

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Meeting Summary

Multiple myeloma (MM), characterised by the clonal proliferation of malignant plasma cells, results in the overproduction of monoclonal immunoglobulins.[1] Genetic heterogeneity of these clones confers treatment resistance and contributes to disease progression. Therefore, the use of combination therapies with different mechanisms of action can target the maximum number of clones simultaneously and may achieve long-term disease control.[2] Current therapeutic strategies, such as chemotherapy, radiotherapy, proteasome inhibitors (PI), immunomodulatory drugs (IMiD), monoclonal antibodies, and autologous/allogeneic stem cell transplantation have resulted in improved outcomes for MM patients. However, these therapies rarely induce long-lasting complete remissions, and patients frequently develop resistance to treatments. As such, the search for novel treatment strategies, including personalised immunotherapies, is ongoing to overcome resistance and improve patient survival.

Steady Stream and Changing Seas in Myeloma

Professor Jesús San Miguel

Treatment of MM requires a multifaceted approach using a combination of therapies targeting the several pathophysiological pathways involved in the disease. PI are a key backbone therapy in the treatment of MM by targeting an integral pathophysiological pathway in myeloma cells and the bone marrow microenvironment simultaneously.[1] However, clonal heterogeneity means that combination therapy is needed to tackle the multiple pathogenic pathways inherent in MM. PI can be synergistically combined with IMiD, another backbone treatment, as well as monoclonal antibodies to improve outcomes.

Overactivation of the ubiquitin proteasome pathway, which maintains cellular homeostasis, results in an anti-apoptotic state and is a hallmark of MM.[3,4] Inhibition of the pathway leads to accumulation of misfolded and regulatory proteins triggering endoplasmic reticulum stress, activation of the unfolded protein response, and apoptosis.[3,5] Furthermore, treatment with PI suppresses the NF-κB pathway, downregulating anti-apoptotic factors and promoting apoptosis of myeloma cells.[5] Additionally, in the bone marrow microenvironment, proteasome inhibition downregulates cytokine secretion; cell proliferation, adhesion, and migration; and decreases tumour angiogenesis.[1]

IMiD exert potent anti-myeloma activity by stimulation of apoptosis and inhibition of angiogenesis, adhesion, and cytokine circuits within the bone marrow microenvironment, as well as enhancement of anti-tumour immune responses through T cell and natural killer cell alterations.[6] Monoclonal antibodies target cell surface antigens to induce apoptosis by alterations in intracellular signalling, growth factor receptor inhibition, adhesion molecule inhibition, as well as direct antibody-dependent cellular toxicity resulting in enhanced myeloma cell death.[7,8] Current treatment regimens, as recommended by the European Society for Medical Oncology (ESMO) guidelines, combine PI with IMiD and/or monoclonal antibodies with corticosteroids to provide synergistic treatment options that target the multiple pathogenic pathways present in MM.[9]

Lenalidomide, an IMiD, and dexamethasone (collectively termed 'Rd') is an established backbone treatment for relapsed MM patients. Evidence from the Phase III ASPIRE study indicates that the addition of carfilzomib, a PI, to lenalidomide and dexamethasone (KRd) significantly improves patient outcomes.[10,11] Median progression-free survival (PFS) was significantly improved in the KRd group (26.3 months) compared to the Rd group (17.6 months).[11] In addition, median overall survival (OS) was 48.3 months (95% confidence interval [CI]: 42.4–52.8) for KRd versus 40.4 months (95% CI: 33.6–44.4) for Rd.[10]

Another treatment approach includes the use of monoclonal antibodies in the treatment regimen. Findings from the Phase III CASTOR study indicated that the addition of daratumumab, a human IgG monoclonal antibody targeting CD38 proteins on myeloma cells, to a PI and dexamethasone backbone provides significant improvements. Patients with relapsed/refractory MM (RRMM) were treated with a combination of bortezomib and dexamethasone (Vd) or a triple combination with daratumumab, bortezomib, and dexamethasone (DVd). Treatment with DVd resulted in significantly longer PFS than Vd alone (16.7 versus 7.1 months), demonstrating the benefits of monoclonal antibody treatment in MM.[12] The combination of daratumumab with a second-generation PI, carfilzomib, is currently being tested in a Phase III randomised CANDOR study.[13]

Recently, concepts such as early detection and intervention, eradication of resistant clones, cytogenetic risk, and personalised medicine have altered the approach to treatment. Evidence from the Phase III QuiRedex study highlights the importance of early detection and treatment with Rd in high-risk smouldering MM patients. Early treatment with Rd significantly delayed the time to progression to myeloma compared to the observation group (not reached versus 23 months).[14,15] Similarly, the CESAR trial, in which high-risk smouldering MM patients were treated with KRd both before autologous stem cell transplantation (ASCT) and post-transplant in the consolidation phase, demonstrated similar improvements: 93% of patients were progression-free at 32 months. Significant improvements in response rates including minimal residual disease (MRD)-negativity, an established prognostic

marker, were observed throughout the treatment sequence. The proportion of patients achieving a complete response (CR) or better during the induction, ASCT, and consolidation phase were 42%, 64%, and 76%, respectively.[16] Importantly, patients achieving durable MRD-negative status were less likely to experience a relapse compared to MRD-positive patients. This is supported by results from the PETHEMA/GEM2010MAS65 study demonstrating improved survival rates in patients that achieved MRD-negativity irrespective of age or cytogenic risk.[17] PFS rates at 3 years were 92%, 70%, 54%, and 44% for patients who were MRD-negative (<10^{-6}), MRD-positive (10^{-6}), MRD-positive (10^{-5}), and MRD-positive (≥10^{-4}), respectively, with only 3% of patients relapsing.[17]

To improve outcomes and overcome treatment resistance, the foundations of disease management have evolved to include a new generation of PI and IMiD, together with monoclonal antibodies. Additionally, recent advances in novel immunotherapy development and the growing understanding of MM pathophysiology are leading to personalised medicine.

An Uphill Battle: Overcoming Treatment Resistance

Professor Katja Weisel

Treating MM is a long-term endeavour requiring a range of therapeutic strategies as the nature of the disease changes over time. The front-line therapy for newly diagnosed MM is evolving with new combinations of PI, IMiD, monoclonal antibodies, and corticosteroids. Extended duration of highly active combinations in early lines is resulting in increased treatment resistance as the disease relapses, which is becoming an important consideration in clinical practice. Development of treatment resistance is multifaceted, including adaptation of malignant cells and alteration of the microenvironment. Overcoming treatment resistance can be achieved by targeting either intracellular or extracellular pathophysiological pathways with novel treatments.

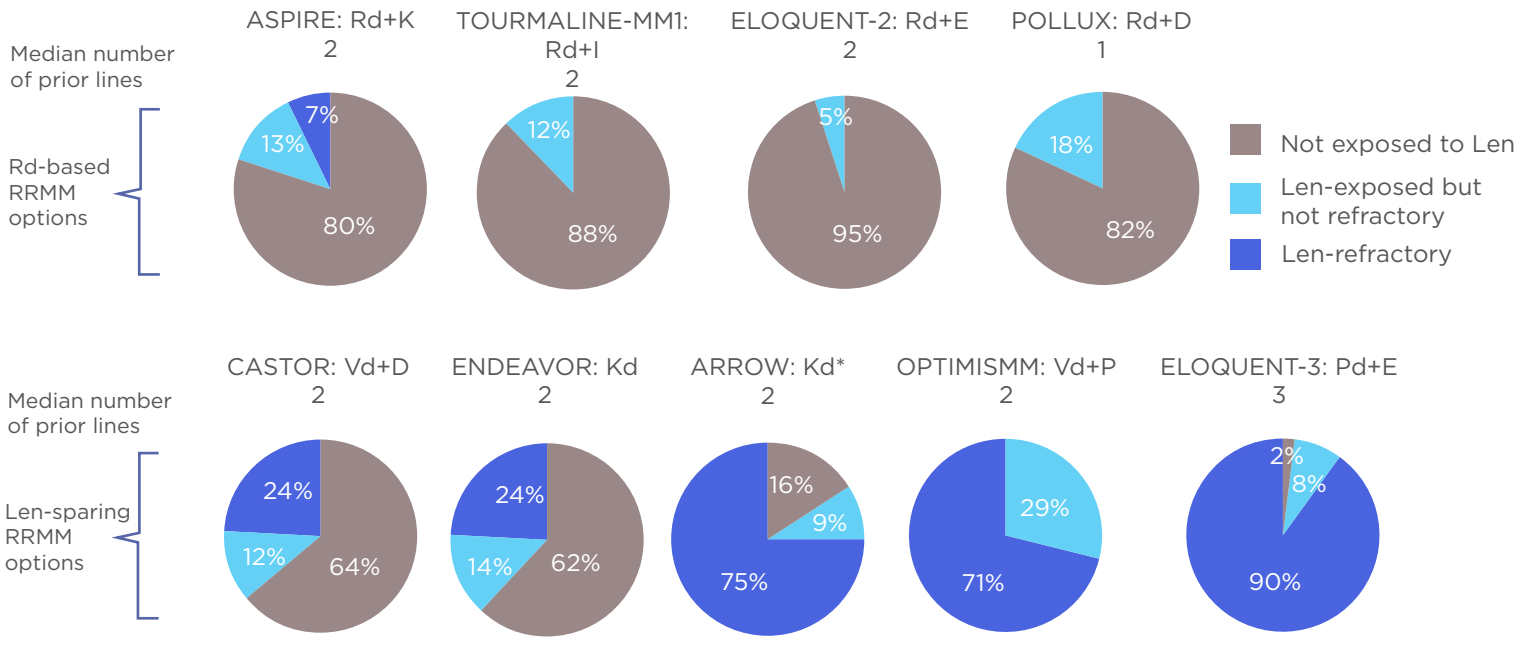

Figure 1: Proportion of patients in relapsed/refractory multiple myeloma drug combination trials exposed to lenalidomide but not refractory, and lenalidomide-refractory. *Kd patients from both study arms are represented.

D: daratumumab; d: dexamethasone; E: elotuzumab; I: isatuximab; IMiD: immunomodulatory drug; K: carfilzomib; P: pomalidomide; R/Len: lenalidomide; RRMM: relapsed/refractory multiple myeloma; V: bortezomib.

The proportion of lenalidomide-refractory patients in early-RRMM combination trials is currently underrepresented. Recent Phase III studies such as CASTOR, ENDEAVOR, ARROW, OPTIMISMM, and ELOQUENT-3 show a growing trend in the proportion of lenalidomide-refractory patients with 24%, 24%, 75%, 71%, and 90% identified, respectively, in their active arms (Figure 1).[18-22] These studies provide evidence on treatment options for the emerging lenalidomide-refractory patient population by excluding lenalidomide from the treatment combinations.

One such trial that represents a lenalidomide-sparing option is the Phase III ARROW study of once-weekly Kd with carfilzomib at 70 mg/m^2 (Kd70), or twice-weekly Kd with carfilzomib at 27 mg/m^2 (Kd27) in RRMM. Of patients enrolled in the ARROW trial, 75% were lenalidomide-refractory.[20] In the overall population, Kd70 once-weekly and Kd27 twice-weekly treatment conferred a median PFS of 11.2 months and 7.6 months, respectively. To address the unmet need of treatment for lenalidomide-refractory patients, a post-hoc meta-analysis of 1,107 Kd-treated patients from the ARROW, ENDEAVOR, and CHAMPION-1 studies was performed to evaluate efficacy and safety of Kd in patients who were previously exposed, or refractory, to lenalidomide.[23] Median PFS of lenalidomide-refractory patients with one prior line of treatment was 15.6 months in both lenalidomide-refractory and non-refractory subgroups.

Lenalidomide-refractory patients can benefit from replacing lenalidomide with pomalidomide in the treatment combination. In the OPTIMISMM study, RRMM patients with 1–3 prior lines of therapy were treated with pomalidomide, bortezomib, and dexamethasone (PVd) or Vd. In total, 71% of the PVd group and 69% of the Vd group were lenalidomide-refractory. Despite this, the median PFS for PVd was 11.2 months compared to 7.1 months for the Vd alone group, indicating significant benefits of alternative IMiD in lenalidomide-refractory patients.[21]

Additionally, PI- and lenalidomide-refractoriness can be overcome by using a novel PI in combination with a monoclonal antibody and lenalidomide. In the MMY1001 Phase Ib study, 82 RRMM patients were treated with daratumumab, carfilzomib (70 mg/m^2 weekly), and dexamethasone, and 74% of patients achieved 12-month PFS, with 84% overall response rate (ORR). In a subpopulation of lenalidomide-refractory patients, 65% of patients were progression-free at 12 months and the ORR was 79%.[24] Furthermore, the median PFS of lenalidomide-refractory patients reached 25.7 months.[24]

Moreover, PI- and lenalidomide-refractoriness can be overcome by combining monoclonal antibodies with pomalidomide and dexamethasone. In the ELOQUENT-3 study, patients with RRMM refractory to lenalidomide and a PI were randomly assigned to receive elotuzumab, a humanised monoclonal antibody targeting SLAMF7, plus pomalidomide and dexamethasone (EPd) or pomalidomide and dexamethasone alone (Pd). Median PFS was more than twice as long with EPd (10.3 months) versus Pd (4.7 months). Furthermore, ORR was significantly higher in the EPd group (53%) versus the Pd group (26%).[22]

As the population of refractory patients increases, treatment resistance is becoming a more important issue in clinical practice. Furthermore, the nature of drug resistance is evolving and diversifying because of changes in treatment standards. Concepts and strategies for tackling treatment resistance represent significant unmet needs. PI remain the foundation of MM treatment, with 2nd generation PI improving response rates, PFS, and OS. With the emerging use of lenalidomide in frontline treatment, and the resulting refractoriness, lenalidomide-sparing options are crucial when the disease inevitably relapses.

A Delicate Balance: Tailoring Treatment for Elderly Patients

Professor Xavier Leleu

As novel treatment options result in improved patient outcomes, the average age of MM patients is increasing reflecting the global trend of ageing populations. There will be an estimated 77% increase in the number of patients >65 years diagnosed with MM by 2030.[25]

Survival of elderly MM patients >80 years has not improved in the past 20 years.[26] Furthermore, very

elderly patients (≥85 years) have a significantly higher early mortality rate highlighting an emerging population with unmet need.[27] Elderly myeloma patients are a heterogenous population with patient-specific challenges including old age itself, frailty, and co-morbidities, as well as cognitive, emotional, and social concerns of the patient's life. Management of elderly patients must also consider the global health status.[28] These considerations are compounded by the myeloma-specific challenges including cytogenic risk, treatment tolerability, poor performance status, and increased risk of adverse events. Furthermore, there is limited evidence from on-going and completed studies to support treatment algorithms in very elderly MM patients.

In a subgroup analysis of the ASPIRE study, patients treated with KRd or Rd were split into two age groups (<70 years or ≥70 years). In the <70 years old group, patients treated with KRd and Rd achieved a median PFS of 28.6 months and 17.6 months, respectively. Patients ≥70 years old achieved similar median PFS when treated with KRd (23.8 months) and Rd (16.0 months).[29] Thus, the benefit of adding carfilzomib to Rd was conferred regardless of age. Furthermore, in a frailty subgroup analysis of the ASPIRE study, KRd improved PFS and OS outcomes versus Rd across frailty subgroups.[30]

The Phase III TOURMALINE-MM1 study examined the efficacy of ixazomib, an orally administered PI, with Rd (IRd) versus Rd alone. In the overall patient population (N=722), median PFS was significantly longer in the IRd group than in the Rd group (20.6 versus 14.7 months). In an age subgroup analysis, younger patients (≤65 years old) showed similar survival rates in the two treatment arms, with IRd patients achieving a median PFS of 20.6 months versus 14.1 months in the Rd group. Elderly patients (≥75 years old) achieved similar PFS rates to the total population, and median PFS was significantly longer in the IRd group compared to the control group (18.5 months versus 13.1 months).[31]

Subgroup analysis of the ENDEAVOR study suggested Kd treatment may confer survival rates in elderly patients comparable with younger patients. Median PFS in the youngest subgroup of patients (<65 years old) was not estimable. However, median PFS in the patients aged 65–74 years old and ≥75 years old was similar (15.6 and 18.7 months, respectively).[32] OS in the age subgroup analysis was similar for patients aged <65 years old and patients aged 65–74 years (47.8 and 49.0 months, respectively), with patients aged ≥75 years achieving a lower OS rate (36.1 months).[33] Furthermore, in a frailty subgroup analysis, Kd with carfilzomib at 56 mg/m^2 improved PFS and OS outcomes versus Rd, across frailty subgroups.[30]

A subgroup analysis of patients <75 years old and ≥75 years old in the ARROW study indicated that once-weekly Kd treatment and twice-weekly Kd treatment result in similar survival rates in both age populations. Median PFS for once-weekly Kd patients <75 years old was 11.1 months compared to 12.2 months in the ≥75 years old patients. Similarly, median PFS for twice-weekly Kd patients was 7.4 months in the younger patient population versus 9.5 months in the elder population.[34]

Because there is limited evidence for the treatment of elderly patients, treatment should be adapted based on the patient profile. If the patient is fit, full dose therapy can be applied, including ASCT, triplet, or doublet regimens with a treatment goal of deep remission. If the patient is of intermediate frailty, the treatment goal should be a balance of safety and efficacy. Therapy options should be reduced to doublet regimens or reduced-dose triplet regimens. However, if the elderly patient is frail, safety and tolerability of treatment should be the highest priority with reduced-dose doublet therapy regimens being the main option.[35]

Key Phase III trials have shown that elderly patients derive clinical benefit from novel drug combinations, such as KRd, Kd, DRd, DVd, and IRd. To date, there are no treatment regimens indicated specifically for the elderly population, therefore treatments should be chosen based on safety signatures. All drugs can be applicable to elderly fit patients and treatment can be the same as for non-elderly patients. Furthermore, all drugs can be considered for elderly frail patients, with a focus on doublet regimens instead of triplets. Elderly myeloma patients should be carefully monitored for the emergence of treatment side effects and managed accordingly.

Big Changes May Arise: Evolution of Immunotherapies

Professor Hermann Einsele

In recent years, targeted immunotherapy has become a major focus for treatment of MM, aiming to personalise therapy, improve outcomes, and bypass the issues of drug resistance. Novel immunotherapies targeting T cell receptor activity, including bispecific T cell engagers (BiTE) and chimeric antigen receptor (CAR) T cells, are currently in clinical development for the treatment of MM.[36,37] Both BiTE and CAR T therapy trigger tumour cell lysis via T cell-mediated cytotoxicity. BiTE molecules redirect cytotoxic T cells toward myeloma cells, and CAR T therapy relies on generating large numbers of tumour-reactive T cells that are capable of initiating myeloma cell apoptosis.[38] Despite promising efficacy of T cell redirection strategies, they are associated with cytokine release syndrome (CRS) and neurotoxicity which need to be carefully managed.

BiTE molecules are created by linking the targeting regions of two individual antibodies with a peptide linker in order to increase tumour-engaging T cell activity. The antibodies are designed to target specific receptors on the tumour cell and endogenous T cells, allowing the T cell to recognise the tumour cell and initiate apoptosis. Early data from the first in human, Phase I study of AMG 420, an anti-BCMA BiTE, showed encouraging results in heavily pretreated RRMM patients. At the maximum tolerated dose of 400 µg per day, 7 out of 10 patients achieved a partial response (PR) or better (5 MRD-negative, 1 very good partial response, and 1 PR), with a median response duration of 9 months, ranging from 5.8–13.6 months. At doses <800 µg per day, no major toxicities of CRS and polyneuropathy were observed, and no anti-AMG 420 antibodies were detected.[39]

CAR T cells are genetically engineered cells generated from the patient's own T cells. Collected cells are transduced with CAR DNA that incorporates into the genome and results in the expression of CAR proteins on the cell surface. CAR T cells are then delivered to the patient to attack the tumour cells. Early analysis of an on-going Phase I study of LCAR-B38M CAR T cells, which targeted BCMA proteins on myeloma cells, showed promising results. Of the 57 patients evaluable at the data cutoff, the ORR was 88%, with 68% patients achieving CR, 5% achieving a very good partial response, and 14% achieving a PR. Overall, 64% of patients achieved MRD-negativity. CRS occurred in 90% of patients, with 4 patients experiencing Grade ≥3 cases.[40,41]

Moreover, data from the on-going bb2121 Phase I study also showed CAR T cells targeting BCMA as potentially clinically efficacious. The ORR was 85%, including 15 patients (45%) with CR, and the median PFS was 11.8 months. The median PFS was significantly longer (17.7 months) in 16 patients who were MRD-negative. In this study, 63% of patients had CRS, which was mostly Grade 1 or 2. CAR T cell expansion was associated with responses, and their numbers persisted up to 1 year after the infusion.[42] CRS can occur up to 16 days after CAR T cell infusion and persist for several days to weeks, contrasting with the rapid CRS response observed following BiTE infusion (within 72 hours of treatment).[43] The safety profile of CAR T cells may be improved by modulating the activity of CAR T post-infusion. Early preclinical animal model work suggests that the CRS response may be mitigated by using tyrosine kinase inhibitors. Moreover, this CAR T cell inhibition is fully reversible to reinstate their function when required.

Novel immunotherapies are highly active in patients with heavily pretreated MM, inducing MRD-negative CR in most patients. However, longer follow-up observations are needed to assess whether long-term PFS can be achieved at least in a subgroup of patients. Target antigen loss will be a major problem for all the T cell redirection strategies, thus simultaneously targeting additional MM pathogenic pathways may be necessary to mitigate this issue, especially in the pretreated MM patient. Moving T cell redirection strategies to earlier lines of therapy is likely to increase the efficacy, and additionally improve patient outcomes.

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Abstract Reviews

The EHA congress showcased a plethora of exciting abstracts submitted from across the globe. The EMJ team has curated a selection of the very best, summaries of which are provided by the presenters.

Tagraxofusp is a Novel Targeted Therapy Directed to CD123

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Keywords: Blastic plasmacytoid dendritic cell neoplasm (BPDCN), CD123, tagraxofusp.

Citation: EMJ Hematol. 2019;7[1]:44-45. AR No. AR1

Blastic plasmocytoid dendritic cell neoplasm (BPDCN), a rare, highly aggressive haematologic malignancy, often with cutaneous and other extramedullary (e.g., lymph node, viscera) manifestations, is derived from plasmacytoid dendritic cells, which express high levels of CD123.[1-3] BPDCN has historically carried a poor prognosis with median overall survival (mOS) ranging from 8–14 months from diagnosis.[4] Tagraxofusp is a novel targeted therapy directed to CD123.[5] In the largest prospectively designed study in patients with BPDCN to date, the efficacy and safety of tagraxofusp was evaluated in a nonrandomised, single-arm, multicentre study evaluating outcomes in both treatment-naïve and previously-treated patients with BPDCN.

Among the 29 treatment naïve patients treated with tagraxofusp (12 mcg/kg), a 90% overall

response rate was demonstrated, in which the majority of responses were complete response (CR), clinical CR (CRc, defined as CR with residual skin abnormality not indicative of active disease). Furthermore, of note, 45% of patients were bridged to stem-cell transplantation, including older patients who might have been excluded from intensive therapy. At the time of the analysis (median follow-up of 25 months), the mOS had yet to be reached. The long-term survival probabilities reached 59% at 18 months and 52% at 24 months. Among the 15 patients with previously treated disease, the overall response rate was 67% (10/15), with meaningful mOS of 8.5 months.

Tagraxofusp has a demonstrated safety profile. The most common adverse reactions in patients with treatment-naïve or previously treated malignancies treated with tagraxofusp at the labelled dose and schedule included: also add decreases in albumin (77%), platelets (65%) and increases in alanine (82%) and aspartate (79%) aminotransferase levels. On the basis of this dataset, tagraxofusp is FDA-approved for treatment of adult and paediatric patients,[6,7] aged 2 years and older, with BPDCN, and is commercially available in the USA. Tagraxofusp is the first and only approved treatment for BPDCN and the first approved CD123-targeted therapy. Tagraxofusp is additionally being clinically evaluated in other indications including chronic myelomonocytic leukaemia, myelofibrosis, acute myeloid leukaemia, and multiple myeloma.

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Post-Transplant Cyclophosphamide in HLA Matched and Haploidentical Transplant Recipients Receiving Myeloablative Timed Sequential Busulfan Conditioning Regimen: Results of a Phase II Study

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Keywords: Matched unrelated donation, post-transplant cyclophosphamide (PTCy), stem cell transplant.

Citation: EMJ Hematol. 2019;7[1]:45-47. AR No. AR2

The authors report a prospective Phase II trial to assess (a) if post-transplant cyclophosphamide (PTCy) could be safely incorporated in a timed sequential Bu-Flu regimen, and (b) whether this approach could be used in patients undergoing matched sibling donation (MSD), matched unrelated donation (MUD), and haploidentical haematopoietic cell transplantation.

Patients with hematological malignancies received fixed dose busulfan 80 mg/m^2 intravenously (i.v.) either on Days -13 and -12 (n=45), or on Days -20 and -13 (n=10). All patients then received fludarabine 40 mg/m2 i.v. on Days -6 to -2 , followed by busulfan i.v. on Days -6 to -2, and were dosed to achieve target area under the curve (AUC) of 20,000 umoL/min for the whole course based on pharmacokinetic studies. Thiotepa 5 mg/kg i.v. was given on Day -7 to the haploidentical group. Graft-versus-host disease (GVHD) prophylaxis included PTCy 50 mg/kg i.v. given on Days +3 and +4, and tacrolimus starting Days +5. Haploidentical and later MUD recipients also received mycophenolate mofetil. Fifty-five patients were enrolled with a median age of 47 years (range, 15–65).

Diagnoses were acute myeloid leukaemia or MSD (n=30), chronic myeloid leukaemia or MPD (n=9), acute lymphoblastic leukaemia (n=6), lymphoma (n=5), and myeloma (n=5). About half had a haploidentical donor (n=26, 47%), one-third had MUD (n=18, 33%), and the rest had MSD (n=11, 20%). Disease risk index was high in 18 (32%), intermediate in 32 (58%), and low in 5 (9%) patients. Hematopoietic cell transplantation specific comorbidity index was >3 in 22 (40%) patients, and there were no graft failures. The median time to neutrophil engraftment was 17 days (95% CI: 13–39) and that of platelets (> 20K/µL, n=49) was 25 days (95% CI: 11–167). The rate of grade II–IV acute GVHD was 38% (95% CI: 25–51%) and that of grade III–IV acute GVHD was 9% (95% CI: 1–17%) at Day 100. Rates of chronic GVHD and extensive chronic GVHD were 10% (95% CI: 2–28%) and 8% (95% CI: 0–15%), at

Table 1: Outcomes.

	Results (95% CI)
	N=55
OS, 1 year	71% (60-84)
MSD	91% (75–100%)
MUD	72% (54–96)
Haplo	62% (45–83)
PFS, 1 year	63% (51–77)
Relapse, year	17% (7–27)
NRM, 1 year	20% (9–31)
Acute GVHD, day 100	
• Grade II–IV	38% (25–51)
• Grade III–IV	9% (1–17)
Chronic GVHD, 1 year	
• Overall	10% (2–18)
• Extensive	8% (0–15)

CI: confidence interval; GVHD: graft versus host disease; haplo: haploidentical; NRM: non-relapse mortality; MSD: matched sibling donor; MUD: matched unrelated donor; OS: overall survival, PFS: progression free survival.

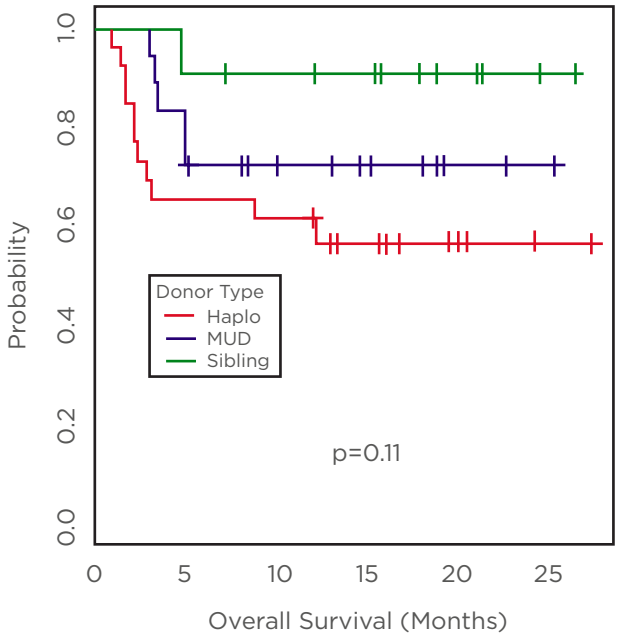

Figure 1: Overall survival.

Haplo: haploidentical; MUD: matched unrelated donation.

1-year respectively. With a median follow up of 17 months (range, 5–28), 1 year overall survival was 71% (95% CI: 60–84%), non-relapse mortality was 20% (95% CI: 9–31%), and relapse rate was 17% (95% CI: 7–27%) (Table 1). One year overall survival in the MSD group was 91% (95% CI: 75–100%); it was 72% (95% CI: 54–96%) in the MUD group, and 62% (95% CI: 45–83%) in the haploidentical group; p=0.11 (Figure 1). Myeloablative-timed sequential busulfan with fludarabine and PTCy is safe in MSD, MUD, and haploidentical HCT. It appears to reduce the incidence of severe acute GVHD and chronic GVHD without an apparent increase in relapse.

Autologous Dendritic Cell Vaccination to Prevent Progression and Relapse in Multiple Myeloma

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Keywords: Dendritic cells, haematology, immunotherapy, multiple myeloma, tumour vaccination.

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Table 1: Characteristics of patients in the study

P	Sex	Yr	MM	Number of doses received	Cytogenetics (FISH)	Pre-vaccine therapy (<2010)	Vaccine post diagnosis (yr)	IMWG response	OS from vaccine 1 (yr)	OS from diagnosis (yr)
1	F	63	IgA λ	4	t(14;16) (q32;q23)	VAD/HDMautoTX/ Thal/Len	7	SD → SD	5	12+
2	F	63	IgG κ	4	del 13q14.3; t(11;14) (q13;q32)	Bort/Dex/ HDMautoTX	6	SD → SD	5	10+
3	M	53	IgG κ	14	Normal	Len/Cyclo/Dex/ HDMautoTX	2	CR → sCR	6	8+
4	M	64	IgG λ	30	del 13q14.3; t(4;14) (p16;q32)	VAD/Cyclo/Bort/ HDMautoTX/Len	8	SD → SD	2	10
5	F	56	IgG κ	4	ampl 1q21; del13q14.3	VAD/Cyclo/ HDmautoTX/IFN/ Thal/Bort/Len	9	SD → SD	2	11
6	M	56	IgG λ	10	Normal	Thal/Dex/Cyclo/ HDMautoTX	1	CR → sCR	4	5
7	M	52	λ	15	Normal	VAD/HDMautoTX/ Bort/HDMautoTX2	7	CR → sCR	5	12
8	M	58	IgG κ	21	Normal	VAD/Cyclo/ HDMautoTX/Thal/ Bort/Len/Dex	11	sCR → sCR	2	13

Ampl: Amplification; Bort: bortezomib; CR: complete remission; Cyclo: cyclophosphamide; del: deletion; Dex: dexamethasone; FISH: fluorescence *in situ* hybridisation; HDMautoTX: high-dose methotrexate + autologous stem cell transplantation; IFN: interferon; IMWG: International Myeloma Working Group; Len: lenalidomide; MM: multiple myeloma; OS: overall survival; P: patient; sCR: stringent complete remission; SD: stable disease; t: translocation; Thal: thalidomide; VAD: vincristine, adriamycine, and dexamethasone; Yr: year

INTRODUCTION

Data from the National Cancer Institute showed that 50% of myeloma patients survive past 5 years post-diagnosis. This is encouraging but also warns the international myeloma community that there is an unmet need for improvement. Dendritic cells (DC) have been used in clinical trials as cellular mediators for therapeutic vaccination in patients with cancer. There are two main trends: the implementation of next-generation DC vaccines that have improved immunogenicity, and the emerging paradigm of combinations of dendritic cell vaccination with other cancer therapies.[1]

OBJECTIVES

The Dendritic Cell Myeloma Project in Antwerp, Belgium is part of a set of clinical trials for diseases with unmet medical needs such as acute myeloid leukaemia, mesothelioma, glioblastoma, and multiple sclerosis. The presented study was performed between 2010 and 2013 while the authors were analysing their pilot study of autologous DC vaccination therapy in acute myeloid leukaemia[2,3] and before the accessibility in Belgium of monoclonal antibody therapies against CD38 and SLAMF7, and chimeric antigen receptor T cell therapy directed against BCMA.

METHODS

In the study, eight myeloma patients were vaccinated, of whom some had high-risk cytogenetics. Median age was 55 years, which is the patient group most in need of better and stronger therapies (Table 1). After leukapheresis, CD14 selection, and 6 days of culturing, white blood cells were uploaded with the WT1 antigen (Figure 1). Vaccination with 10 million DC was performed in the outpatient clinic by intradermal

injections near the axillary lymph nodes. Vaccines were given on a fortnightly basis with a minimum of four doses. To monitor haematological responses, bone marrow biopsies were taken before and after four vaccinations. For immune monitoring, delayed type hypersensitivity test after four vaccinations was performed.

RESULTS

The patients received a median number of 12 vaccinations (range: 4–30). Delayed type hypersensitivity test was positive in all eight patients. International Myeloma Working Group responses after four vaccinations showed a persistent stable disease in four patients, a persistent stringent complete response in one patient, and a conversion from a complete response into a stringent complete response in three patients. Median overall survival was 10.5 years (with a minimum of 5 years and a maximum of 13 years). Three patients are still alive. Median overall survival after the start of vaccination was 4.5 years.

CONCLUSIONS

An induction of DC vaccine-specific T cell immune response was seen in all patients and 5-year overall survival was 100%. With a vaccine production time of 1 week and with total costs of €25,000, DC vaccines are socioeconomically affordable treatment options compared with other immunotherapies. An important issue will be the timing of the vaccination in the whole treatment scheme, especially in the new era of chimeric antigen receptor cell therapy.

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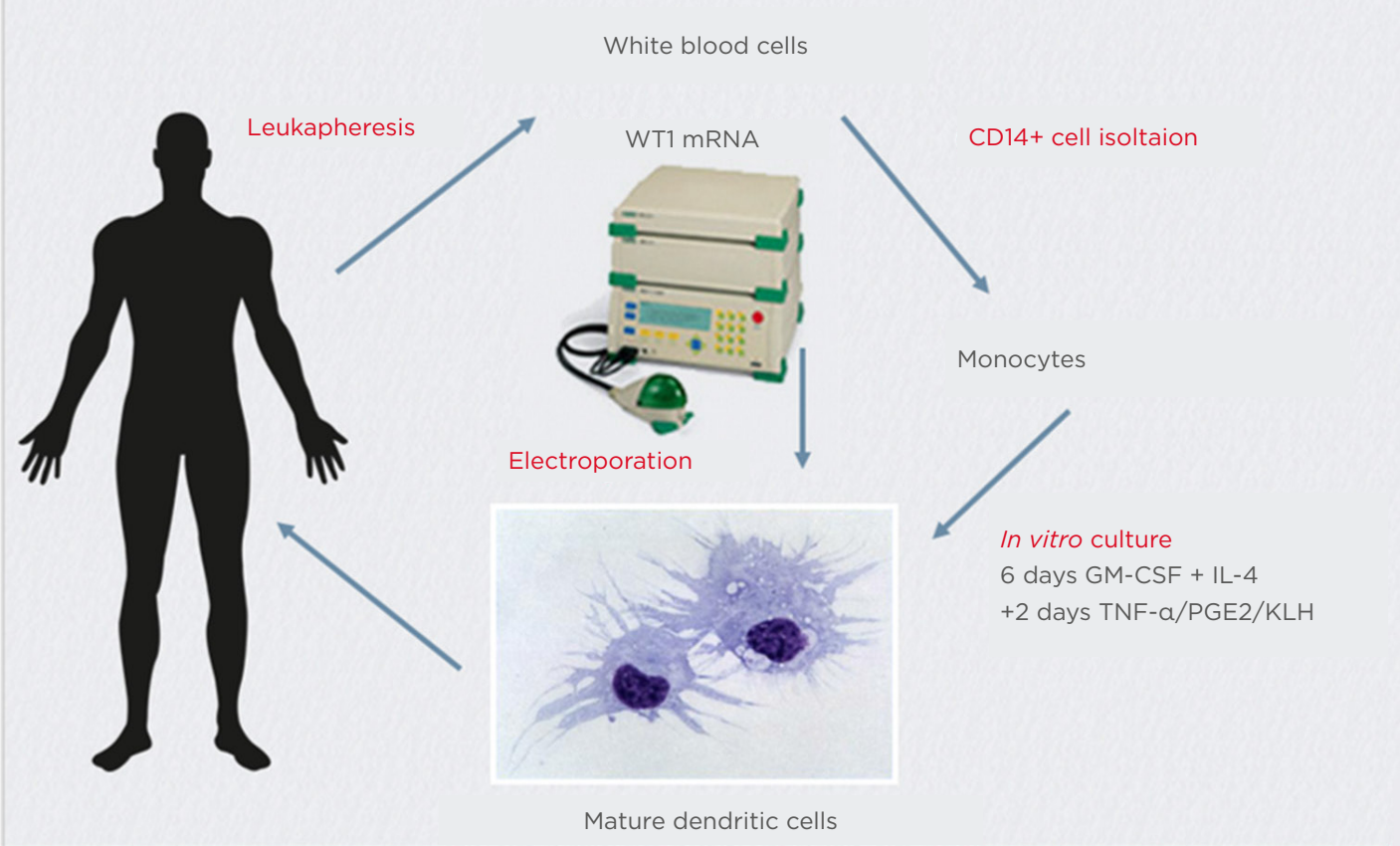

Figure 1: Anti-tumour vaccine manufacturing for multiple myeloma treatment using wild-type mRNA electroporated dendritic cells.

GM-CSF: granulocyte-macrophage colony-stimulating factor; KLH: keyhole limpet haemocyanin; PGE2: prostoglandin E2.

Gilteritinib Plus Azacitidine in Newly Diagnosed *FLT3* Mutated (FLT3^{mut+}) Acute Myeloid Leukaemia Patients Ineligible for Intensive Induction Chemotherapy: Preliminary Findings from the Safety Cohort

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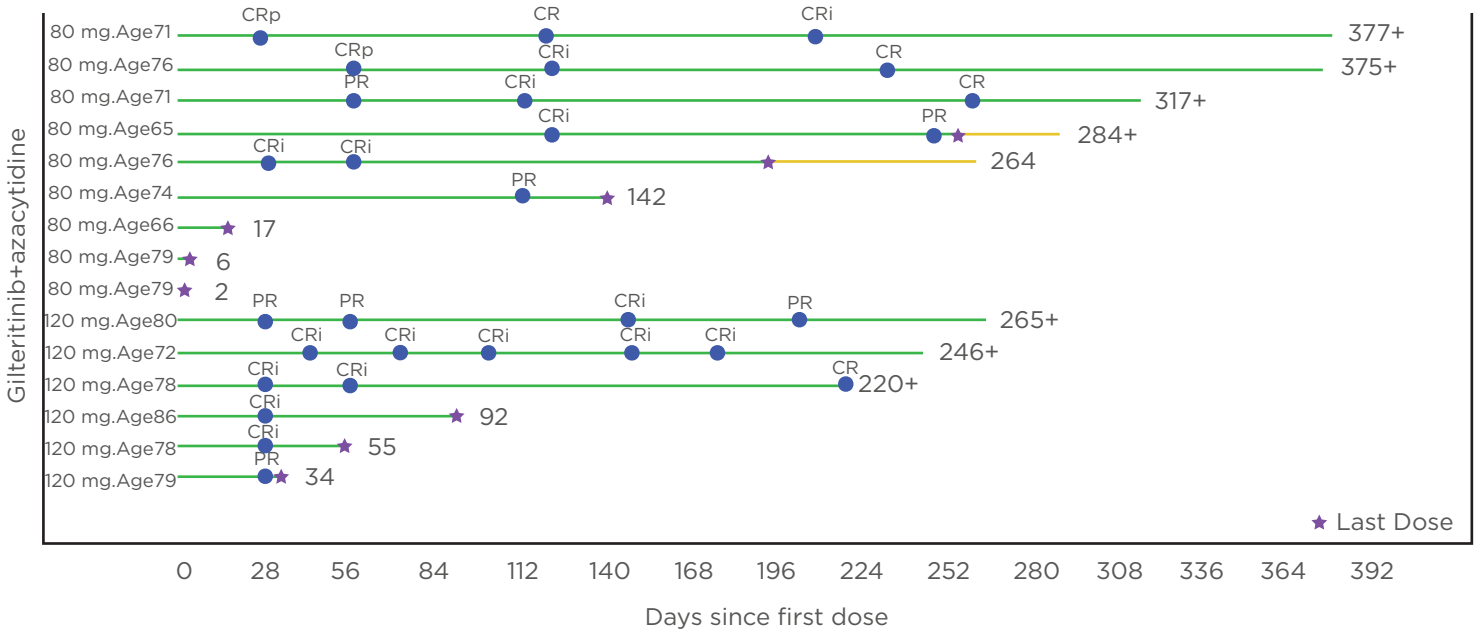
Keywords: Acute myeloid leukaemia (AML), gilteritinib plus aza, ineligible for intensive chemotherapy, safety cohort.

Citation: EMJ Hematol. 2019;7[1]:50-52. AR No. AR4

Search of more effective treatment for patients with acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy remains challenging. Monotherapy with hypomethylating agents (HMT) constitute the backbone therapy in this patient population, associated with a modest clinical benefit.[1,2] Recently, the combination of HMT with agents against determinate novel targets has resulted in unprecedented response rates with a low toxicity profile. In this context, FLT3 inhibitors, targeting one of the most recurrently mutated genes in AML, have demonstrated significant activity in different clinical settings, such as frontline chemotherapy combined with intensive chemotherapy (midostaurin),[3] as monotherapy for salvage therapy (quizartinib, gilteritinib),[4-6] or as maintenance to prevent relapse after allogeneic hematopoietic cell transplantation (sorafenib).[7]

Gilteritinib is a type I FLT3 inhibitor with capability to bind both the monomeric (ITD mutation) and dimeric (D835 TKD mutation) forms of the FLT3 receptor. Pre-clinical work suggests a possible synergistic antileukaemic effect of gilteritinib when combined with azacytidine (AZA),[8] and supports the clinical evaluation of this combination. This was the basis of a Phase I/II clinical trial aimed to explore the added benefit of combination of gilteritinib plus AZA in newly diagnosed FLT3^{mut+} AML ineligible for intensive induction chemotherapy.[9] This trial consisted of an initial phase with a safety cohort, which evaluated feasibility and was aimed to define the recommended dose of gilteritinib in combination to AZA for a randomised phase, currently on-going. In this abstract, the results of a safety cohort of 15 patients are presented. Patients enrolled in this safety cohort received escalating doses of oral gilteritinib (80 or 120 mg/day) on Days 1–28 in combination with AZA (75 mg/m^2/day) on Days 1–7. Treatment was continued in 28-day cycles until lack of a clinical benefit or unacceptable toxicity. Safety and tolerability were the primary endpoints of the safety cohort; antileukaemic activity was also assessed.



Each line represents one subject; green part represents study drug exposure time (days); orange part represents from end of treatment to end of study; + represents overall survival censoring.

Figure 1: Graph depicting response obtained and treatment duration of the combination of azacytidine and gilteritinib in the trial safety cohort.

CR: complete remission; CRi: complete response with incomplete haematological recovery; CRp: complete response without complete platelet recovery; PR: partial response.

Fifteen patients (median age: 76 [range: 65–86]) were enrolled into the safety cohort (80 mg gilteritinib, n=9; 120 mg gilteritinib, n=6). All except one patient harbored a *FLT3* mutation (ITD alone, n=10; TKD alone, n=3; ITD and TKD, n=1; none, n=1). Despite a high frequency of adverse events (AE) observed, frequent (>25% of patients) grade ≥3 AE corresponded to common events in this patient population, such as febrile neutropenia and cytopenias. Eight patients experienced fatal AE, none of which were related to treatment; three patients died in an early treatment phase due to septic shock (Day 2), respiratory failure (Day 6), and cerebral haemorrhage (Day 17). No patient presented a severe increase of liver enzymes (i.e., aminotransferase/alanine aminotransferase >3 X Upper Limit of Normal [ULN] and/or total bilirubin >2 X ULN) or significant QTcF interval prolongation, >500 msec. Only one dose limiting toxicity (DLT) consisting of an early episode of tumour lysis syndrome was observed in a patient who received 80 mg gilteritinib plus AZA, with no further episodes at the same or higher gilteritinib dosing. Given this unique DLT episode from the 11 DLT evaluable patients, the decision to proceed to the randomised portion (AZA plus gilteritinib versus AZA) at a dose of 120 mg gilteritinib for the combination treatment arm was adopted.

In this cohort of patients, 10 out of 15 patients (67%) achieved as best response as composite complete remission (CR; with incomplete haematological recovery: CRi), including four bona fide CR and six CRi. Two additional patients achieved a partial response (PR), giving an overall response rate (CR+CRi+PR) of 80%. Six of these CR/CRi patients maintained their response at last follow-up, between 220 and 377 days after treatment start (Figure 1). More than half (n=8/15; 56%) of the patients had a treatment duration lasting more than 6 months, while nine patients discontinued treatment (death, n=4; relapse; AE; physician decision; sponsor decision; subject withdrawal, n=1 each) and six patients remained on treatment.

In conclusion, gilteritinib was safely combined with AZA without unexpected toxicity in this population of elderly, unfit AML patients, and

120 mg gilteritinib was the chosen dose for the randomised Phase II of the trial. Moreover, this combination therapy induced a significant proportion of antileukaemic responses in newly diagnosed *FLT3*$^{mut+}$ AML patients, suggesting an added benefit and warranting further exploration.

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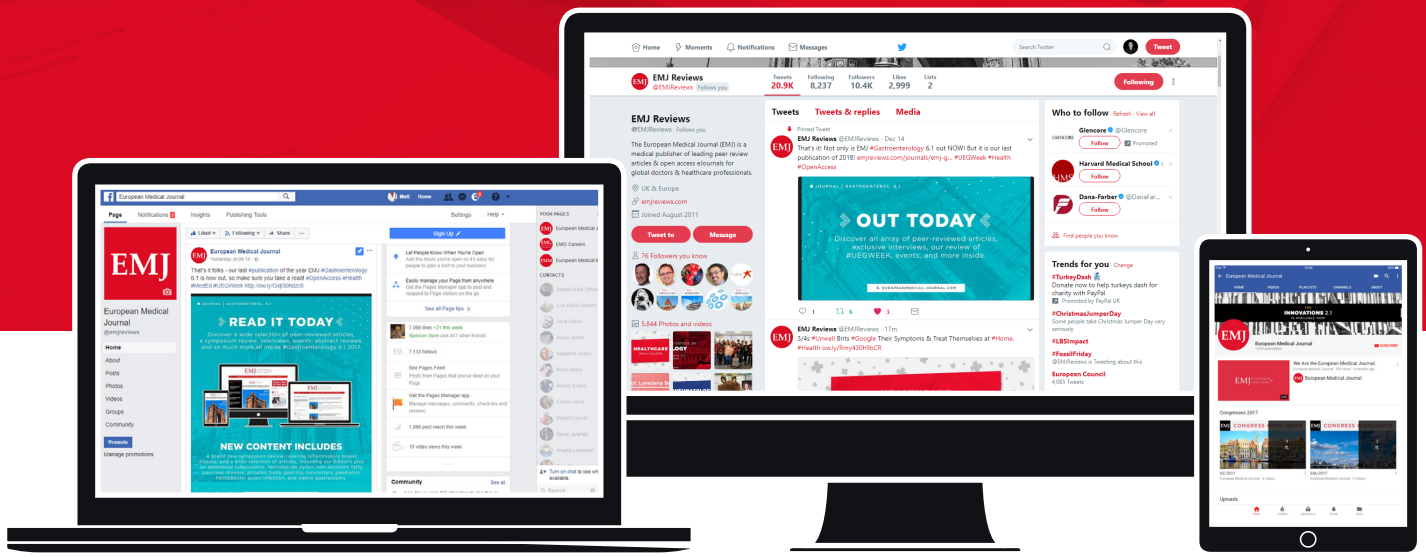

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Umbilical Cord Blood Donation: An Evolving Lifeline for the Stem Cell Field

Michael Dodsworth
Editorial Administrator

The fact that stem cells hold increasingly apparent and still untapped potential for the treatment of a multitude of genetic diseases is undisputed; however, the sources from which pluripotent isoforms are harvested, specifically embryonic, carry significant ethical considerations that have hampered their wide-spread adoption in the clinic. Adult stem cells negate this problem, but are often invasively attained and limited in their potency to produce the various cell types needed to treat complex diseases, whilst induced pluripotent stem cells, despite their impressive innovation, are not (as of yet) a scalable option for the healthcare industry. Could umbilical cord blood banking be meeting some of these challenges head on?

Cord blood can be collected and stored from the placenta and umbilical cord following the birth of a new-born. It is replete with haematopoietic stem cells, identifying it as potential aid in the fight against various immune deficiencies, genetic conditions, metabolic disorders, and cancers. There are currently 37,000 people in the UK requiring a stem cell transplant,[1] but around 70% of patients requiring one do not have a matching donor in their own family:[2] importantly, cord blood-sourced stem cells somewhat bypass this problem due to having less stringent human leukocyte antigen matching and lower graft-versus-host disease burden.[3] This is especially important for non-Caucasian recipients for which finding a suitable match can be desperately hard.[1] Additionally, cord blood collection represents a steady and scalable source of stem cells that could feasibly improve the current long waiting times for patients.

Umbilical cord blood donation is still a relatively young field, beginning with the first donation in 1989 for the treatment of a child with Fanconi's Anaemia.[4] This related donation was quickly followed by the first unrelated donor cord blood transplant in 1990, this time for the treatment of a four-year-old boy with T-cell leukaemia.[5] The advantages cord blood donation offered over conventional stem cell sources in regard to compatibility between donor and host could not be ignored, leading to increased practice in clinics across the USA and UK throughout the 1990s and into the 21st century.[5] The charity sector, including UK-based Anthony Nolan, have taken notice.

Anthony Nolan puts considerable effort into providing support across the entire stem cell spectrum (primary research, matching of donor/recipients, offering support and information for patients), and cord blood donation is no exception. The charity has identified four major hospitals in the UK in which child birth numbers and ethnic diversity are high, and that serve as a primary source of cord blood: King's College Hospital,

London; Saint Mary's Hospital, Manchester; Leicester Royal Infirmary; and Leicester General Hospital. The straight-forward process likely puts mothers' minds at ease, as the cord is clamped as normal following vaginal or caesarean delivery before being taken, together with the placenta, to a separate room for blood extraction. The blood is transferred to a cell therapy centre, assessed for transplant suitability, and then frozen for as long as 25 years or until the cells are matched and needed.[6] The efficiency and simplicity of the charity's pipeline sets a sterling example for other bodies to follow suit.

Both the NHS and Anthony Nolan openly share first-hand accounts and testimonies of the life-saving opportunities cord blood donation has offered to young patients. The former promotes the story of a child who was diagnosed with the rare and life-threatening disease Hurler's syndrome,[7] a condition characterised by accumulation of toxic sulfate compounds in the body that results in severe organ failure.[8] Following the child's diagnosis at 9 months old and initiation of enzyme replacement therapy, their immediate family were screened for bone marrow transplant suitability but to no avail. A match was found through stem cell registries in a cord blood unit in Germany, leading to a successful transplant within weeks. The likelihood that this patient would not have survived into adulthood without an available donated cord blood sample adds weight to the importance of Anthony Nolan's objective, and would undoubtedly resound with mothers contemplating donation of their own cord blood and tissue for charitable purposes.

Complimentary to donative purposes, a growing sentiment to which cord blood collection is undoubtedly tied is the idea of investing in one's child's future, a haematological insurance policy should genetic predispositions manifest as disease later in life. This 'banking' of cord blood is increasingly common, with some 27,028 blood and tissue units being banked privately in the UK in 2018.[9] The British Broadcasting Corporation (BBC) recently published an article discussing the case of a mother harbouring a mutation in breast cancer susceptibility gene *BRCA1* who pre-emptively paid to bank her newly born son's cord blood and tissue.[9] "I've got no control over whether I've passed a faulty gene to them but I feel like I've got a little bit of control now if something was to happen," explained Rosaira Tormey from Sheffield. This outlook is not unanimously supported however, with some claiming that private banks are monetising parent concerns that are not being properly discussed with qualified specialists in regard to accurate disease prediction, or even cell utility.[10] Italy and France have both banned private cord-blood banking, and bodies such as the American Academy of Pediatrics (AAP)[10] and the Royal College of Obstetricians and Gynaecologists[9] have both expressed concern over private, but not public, cord blood donation.

Whilst admittedly there are ethical concerns in the UK around the idea of private banking as opposed to public donations to charities or other NHS-affiliated stem-cell banks, there is regardless a clear change in public perception towards making the most of something that for decades we had discarded. Donor suitability, host rejection, and a limited pool have long been issues facing the public stem cell donation sector, therefore it is not entirely surprising that we are witnessing increased interest in capitalising on cord blood as an elixir for tackling a multitude of pathologies. It is perhaps more surprising that it did not happen sooner.

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New Insights in β-Thalassaemia

EDITOR'S PICK

My pick inside this issue of *EMJ Hematology* is the article on therapeutic advances in transfusion-dependent thalassaemia. Transfusion-dependent thalassaemia has been one of the major fields of advances of medicine during recent years. Since the 1980s, this congenital anaemia has been transformed from a fatal disease in infancy to a chronic disease permitting prolonged survival until adulthood by regular transfusions and iron chelation therapy. Since the pioneering Pesaro experience, haemopoietic cell transplantation has provided for the first time the revolutionary chance to cure this congenital disease. Now, through clinical development of an effective medical therapy that improves erythropoiesis and curative gene therapy approaches, further advances are anticipated. Paubelle and Thomas report in a clear, logical, concise, but complete way these incredible advances impacting on cure rate and on quality of life. An additional note to their fantastic review is that the large majority of thalassaemia patients today are living in low income countries. In this contest, the well-known 'financial toxicity' of these new fantastic approaches remains an important challenge to be met.

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Abstract

Thalassaemia is a hereditary cause of hypochromic microcytic anaemia resulting from defects in haemoglobin production. β-thalassaemia, which is caused by a decrease in the production of β-globin chains, affects multiple organs and is associated with considerable morbidity and mortality. This review aims to highlight the significant progress being made in the areas of ineffective erythropoiesis control, metal chelation, and gene therapy, which is bringing new hope and should change patient management and prognosis in the near future.

INTRODUCTION

Thalassaemia is a hereditary cause of hypochromic microcytic anaemia resulting from defects in haemoglobin (Hb) production.[1] Hb is the iron-containing oxygen-transport metalloprotein in red blood cells (RBC). Its synthesis is controlled by two multigene clusters on chromosome 11 (β-globin) and chromosome 16 (α-globin). A Hb molecule comprises four globular protein subunits; each subunit is composed of a protein chain tightly associated with a non-protein prosthetic haem group which consists of an iron ion (Fe^{2+}) held in a heterocyclic ring, known as a porphyrin. The adult Hb (HbA) that is composed of two α chains and two β chains (α2β2) represents almost all Hb in adults (95.5–97.0%). HbA2, which is composed of two α chains and two δ chains (α2δ2), represents 2.0–3.5% of HbA. Fetal Hb is composed of two α chains and two γ chains (α2γ2) and represents 1.0% of HbA. When a decrease in synthesis affects β chains, a compensatory mechanism leads to an increased elaboration of γ and δ chains, hence an increase of HbF and HbA2. β-thalassaemia, which is caused by a decrease in the production of β-globin chains, affects multiple organs and is associated with considerable morbidity and mortality. The highest prevalence of β-thalassaemia mutations is in people of Mediterranean, Middle Eastern, and Asian descent. Over 200 different thalassaemia-causing mutations have been identified in the β-globin gene, leading to wide genotypic and phenotypic variability of the disease.[2] There are several types of mutations: silent mutations (silent β), mild mutations that cause a relative reduction in β-globin chain production (β+), severe mutations that result in complete absence of β-globin chain synthesis (β0), and the most uncommon, deletion of the gene.[3] β-thalassaemia minor is a heterozygous inheritance of a β-thalassaemia mutation, with patients often having clinically asymptomatic-microcytic anaemia. Patients with β-thalassaemia major, with homozygous mutations, usually present with severe anaemia in infancy and become transfusion-dependent for life, whereas patients with β-thalassaemia intermedia present later in life with mild-to-moderate anaemia and variable transfusion requirements.[2] Both β-thalassaemia major and intermedia can result from the homozygous or compound-heterozygous inheritance of mutations in the β-globin gene. Several modifications can result in patients having β-thalassaemia intermedia rather than major, including ineffectiveness of erythropoiesis or an excess of α-globin.[2] Given the many complications, lifelong care is required.

MICROCYTIC ANAEMIA IN β-THALASSAEMIA

HbA tetramer consists of two α chains and two β chains. A lack of synthesis of β chains therefore leads to an excess of α chains. These α chains can precipitate in the cytoplasm of erythroid precursors during haemoglobinisation at the stage of polychromatophilic erythroblast, instigating a deleterious oxidative cascade.[1] During physiological erythropoiesis, the chaperone heat shock protein 70 (HSP70) accumulates in the nucleus of differentiating erythroblasts, protecting the major erythroid transcription factor GATA-1 from caspase-3 cleavage.[4] This key apoptotic enzyme has an ambivalent action in erythropoiesis. On the one hand, it is essential for terminal erythroid differentiation by selectively cleaving certain targets, which leads, for example, to the condensation of the erythroblast nucleus and to the morphological changes that recede the enucleation, allowing the formation of the reticulocyte.[5] It can, on the other hand, have a deleterious function. In fact, the lack of erythropoietin (EPO) promotes the nuclear release of HSP70, which allows caspase-3 to cleave GATA-1 (which is no longer protected) and blocks erythroblastic maturation.[4] The nuclear localisation of HSP70 thus represents a fine mechanism of regulation for erythropoiesis, which is necessary because this process represents an extraordinary proliferation system. In β-thalassaemia, HSP70 is sequestered in the cytoplasm of mature erythroblasts (stage of intense haemoglobinisation) during erythropoiesis to perform its natural chaperoning of α-globin chains, which otherwise form excessively toxic aggregates. This will result in a lack of HSP70 localisation and, as a result, the destruction of GATA-1, causing maturation arrest and cell death. With the bone marrow producing 200 billion RBC every day, it is necessary to very quickly control excess production, which can lead to polycythaemia, or compensate for a

defect, which would quickly result in anaemia.[6] Microcytosis occurs due to a lack of Hb as a result of defects in either globin or haem synthesis, or iron deficiency, leading acidophilic erythroblasts to enter mitosis once more, reducing the volume of RBC. If, however, the cytoplasm of RBC contains a haemoglobin concentration lower than normal, hypochromia is observed.

IRON OVERLOAD IN β-THALASSAEMIA

Erythropoiesis is governed by erythropoietin (EPO), a hormone primarily produced by the kidney. EPO levels, stimulated by hypoxia, are high in β-thalassaemia. EPO binding to its receptor (EPOR) on the surface of erythroid precursors activates the JAK2/STAT5-signalling pathway and the transcription of several genes involved in proliferation, differentiation, and survival.[7-9] Despite high EPO levels caused by the globin defect, erythroid differentiation is blocked in β-thalassaemia and the resulting hallmarks of the disease are ineffective erythropoiesis and anaemia. Because of the expanded erythropoiesis, the increased erythroid regulator erythroferrone suppresses hepcidin and causes iron overload (Figure 1).[10,11]

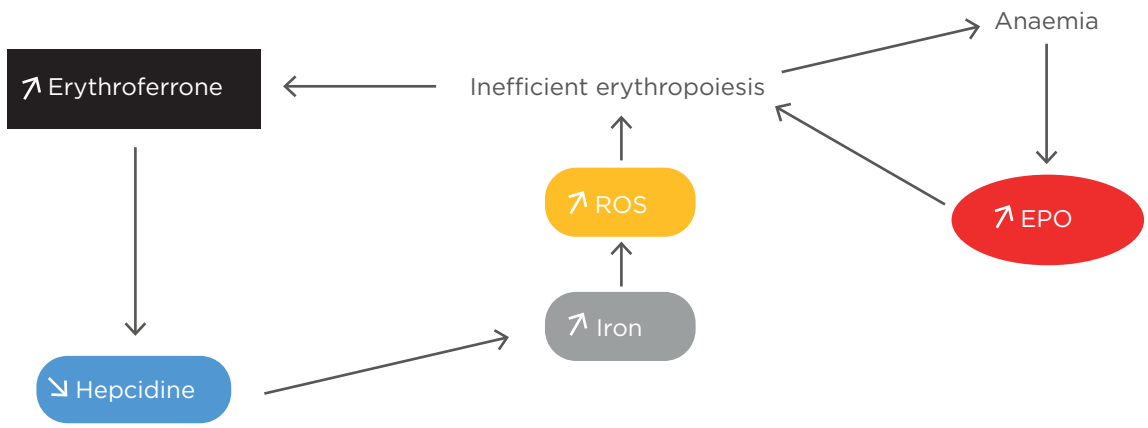

Figure 1: The increased erythroid regulator erythroferrone suppresses hepcidin and causes iron overload.

EPO: erythropoietin; ROS: reactive oxygen species.

NEW INSIGHTS IN THE TREATMENT OF β-THALASSAEMIA

Erythropoiesis-Stimulating Agents

Recombinant human EPO is widely used for the treatment of anaemia, for example, in patients on chemotherapy or on haemodialysis. Treatment with EPO was also tried experimentally in patients with thalassaemia.[12,13] In these patients, despite the state of chronic anaemia, EPO levels are usually low relative to the degree of anaemia.[14,15] Administration of EPO to splenectomised patients with β-thalassaemia intermedia resulted in a dose-dependent improvement in their anaemia.[16] Furthermore, in addition to stimulating RBC and fetal Hb production, EPO might alleviate symptoms of haemolytic anaemias by acting as an antioxidant.[17] However, recombinant EPO is not able to correct inefficient erythropoiesis, therefore its use is not recommended for the treatment of β-thalassaemia.

Sotatercept is a ligand trap that inhibits TGF-β superfamily members including growth differentiation factor 11 (GDF-11) and activin B.GDF-11 is overexpressed in immature erythroblasts in β-thalassaemia.[18] Aberrant GDF-11 production may induce expansion of erythroid progenitors and increase oxidative stress, leading to maturation arrest of late erythroid precursors and ineffective erythropoiesis.[18] Preclinical work has shown that administration of an activin receptor IIA ligand trap decreases GDF-11 concentration, reduces reactive oxidative stress levels, and promotes terminal maturation in immature erythroblasts.[18] Sotatercept is a novel recombinant fusion protein consisting of the extracellular domain of the human activin

receptor IIA linked to the human immunoglobulin G1 Fc domain[19] with interesting efficacy to reduce transfusion requirements in a Phase II trial in myelodysplastic syndromes.[20] A recent Phase II trial with 16 patients with transfusion-dependent β-thalassaemia and 30 patients with non-transfusion-dependent β-thalassaemia showed promising results, with most non-transfusion-dependent β-thalassaemia patients treated with high doses achieving sustained increases in haemoglobin level. Transfusion-dependent β-thalassaemia patients who were treated with high doses of sotatercept also achieved reductions in transfusion requirement.[21]

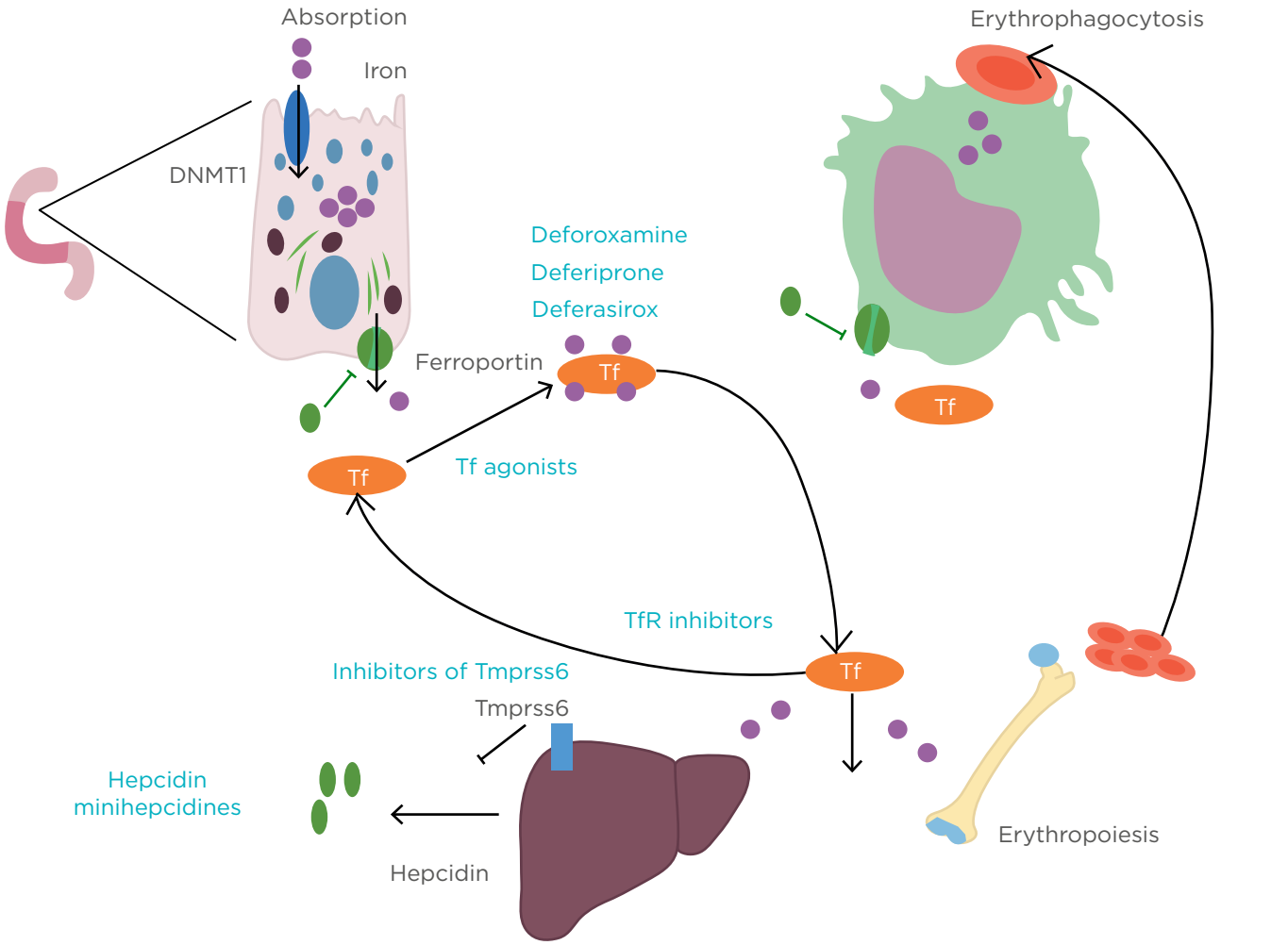

Figure 2: Iron overload-targeting agents.

DNMT1: DNA methyltransferase 1; Tf: transferrin; TfR: transferrin receptor; TMPRSS6: matriptase-2 protease.

Iron Overload Targeting Agents

Transfusion and iron chelation therapy can be a lifelong requirement for many patients with β-thalassaemia. Iron enters the plasma and exceeds the capacity for transport by circulating transferrin. Therefore, non-transferrin-bound iron exists in the plasma of thalassaemic patients causing multiple damages when entering cells through the generation of reactive oxygen species. There is a great interest in developing novel treatments that target iron overload by improving erythroid maturation. Iron chelation therapy can influence the frequency and severity of iron overload-related complications, with demonstrated improvement in organ dysfunction and survival in patients with iron chelation therapy.[2] Substantial progress has been made to improve the compliance of iron chelating treatments. Initially, the patients had a subcutaneous treatment with deferoxamine at their disposal, before the development of oral

treatments such as deferiprone and deferasirox which had a recent galenic evolution.[22] Other approaches to decrease iron overload have been tested and shown to have beneficial effects, primarily in models of thalassaemia intermedia (Figure 2). These include restricting iron for erythropoiesis with the use of hepcidin/minihepcidins[23,24] or transferrins,[25,26] inhibiting the transmembrane protease serine 6, also known as matriptase-2 protease (TMPRSS6),[27-30] and targeting Transferrin Receptor 2 (TfR2).[31] Defining the molecular mechanism of these novel compounds and exploiting potential combinations is a therapeutic challenge for the future.

Allogeneic Haematopoietic Stem Cell Transplantation in β-thalassaemia

Replacement of mutant RBC using allogeneic haematopoietic stem cell transplantation (allo-HSCT) was, until recently, the only existing curative therapy for β-thalassaemia and is now an established approach to correct inefficient erythropoiesis, particularly when matched sibling donors are available.[2] Allo-HSCT is applied with a disease-free survival exceeding 80% with HLA-matched-sibling donors.[32,33] Moreover, improvements in conditioning treatment have encouraged the use of alternative donors and umbilical cord blood for the HSC source in instances where patients do not have a matched-sibling donor. Nevertheless, matched-unrelated transplants for high-risk patients with thalassaemia have a long-term overall survival of <70%.[34]

Gene Therapy in β-thalassaemia

Donor availability and transplantation-related risks have limited the use of allo-HSCT in patients with β-thalassaemia, thus gene therapy is currently evaluated as a new option.[35-37] Gene therapy has been shown to hold promise in β-thalassaemia patients using β-globin lentiviral vectors.[38,39] In two Phase I–II studies, HSC from 22 patients with transfusion-dependent β-thalassaemia were harvested and transduced *ex vivo* with LentiGlobin BB305 vector, which encodes HbA with a T87Q amino acid substitution (human βA-T87Q-globin gene). The cells were then reinfused after the patients had undergone myeloablative busulfan conditioning. This allowed the reduction (19 patients) or elimination (3 patients) of the need for long-term RBC transfusions.[40] Progress is currently being made regarding the use of lentiviral vectors in terms of transduction rate, but the risk of clonal haematopoiesis persists. Genome editing represents an alternative strategy for the treatment of haemoglobinopathies.[41] This is based on the sequence-specific targeting of a nuclease to the genome and the repair of the double-strand break by either non-homologous end joining or homology-directed repair. Non-homologous end joining alters the genome by small insertions or deletions and is induced by targeted double-strand breaks to remove DNA-regulatory elements or to prevent expression of a protein. Therapeutic double-stranded or single-stranded DNA is provided together with a targeting nuclease to mediate homology-directed repair in which a mutant sequence can be replaced by the wild-type sequence. The targeting molecules can either be synthetic DNA-binding proteins like zinc finger (ZF) and transcription activator-like effector (TALE) proteins, or RNA in the context of the CRISPR/Cas9 system.[42,43] ZF or TALE proteins are usually fused to the Fok1 nuclease generating ZF-nuclease or TALE-nuclease. Among the three systems, CRISPR/Cas9 has advantages with respect to ease of design and expense. All three systems have limitations including the possibility of generating off-target double-strand breaks and chromosomal rearrangements.[43] Current efforts focus on generating nucleases with increased specificity. Genome editing holds great promise for the development of new and globally applicable therapies for haemoglobinopathies, especially β-thalassaemia (Figure 3).

CONCLUSION

β-thalassaemia is still a major public health issue. Significant progress in the areas of ineffective erythropoiesis control, metal chelation, and gene therapy is bringing new hope and should change patient management and prognosis in the near future.

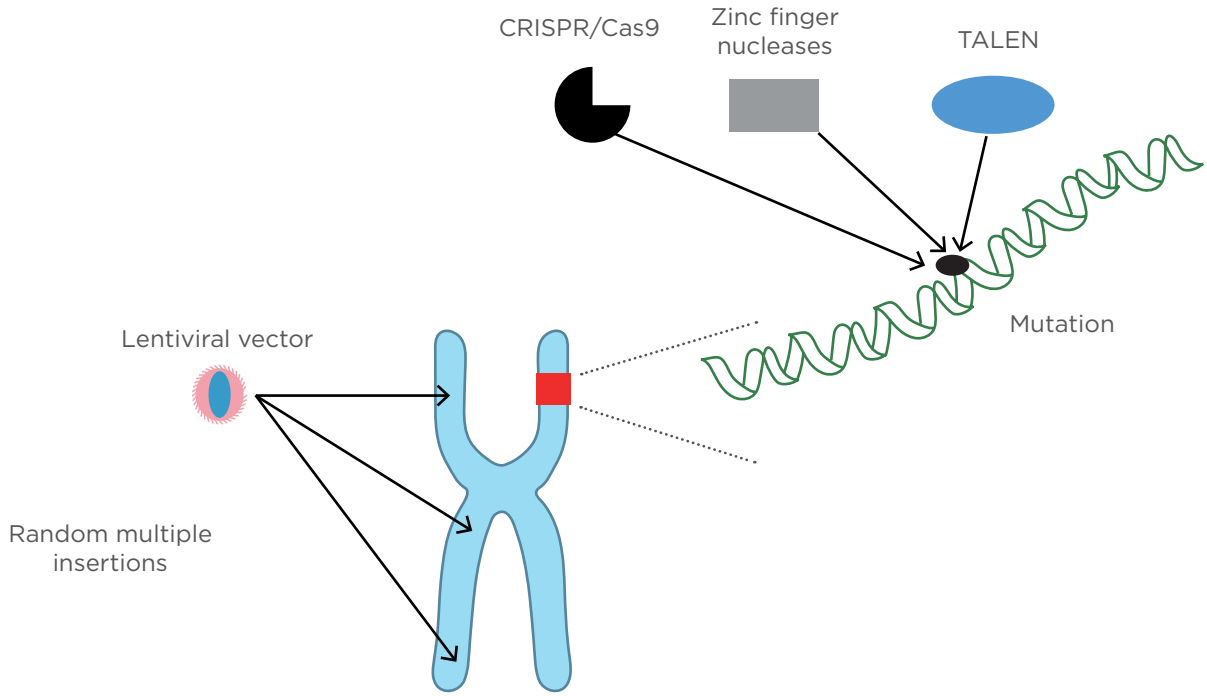

Figure 3: Genome editing strategies.

TALEN: transcription activator-like effector nuclease.

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Retrospective Review of the Role of Abdominal Imaging in Evaluation of Cytopenias

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Abstract

This study consists of a retrospective chart review to evaluate the use of abdominal imaging to aid in the diagnosis of chronic cytopenia. Patients with unclear aetiology of chronic cytopenia often require complex work-up, and it would be beneficial to develop an algorithm to make this process more efficient. Abdominal imaging is a non-invasive procedure that may provide useful clinical diagnostic information as part of an algorithm for this subset of patients. The medical records of 36 patients were reviewed to determine the association between abdominal imaging results and other components of diagnostic work-up. Abdominal imaging was positive for 21 (58.33%) individuals. Following imaging, 8 individuals (22.22%) required bone marrow biopsy and 12 individuals (33.33%) required frequent monitoring, which were non-significant associations. However, positive imaging results were significantly associated with increased BMI as well as severity of thrombocytopaenia. This study suggests that abdominal imaging warrants further study as a potentially useful addition to diagnostic work-up for chronic cytopenia of unknown aetiology.

INTRODUCTION

Normal blood cell count is defined by normal values in all three major haematopoietic cell lineages (i.e., leukocytes, haemoglobin, and platelets) plus normal differential counts in the white cell compartments. The term 'cytopenia' refers to a condition in which one or more lineages show abnormally low counts.[1] In other words, it denotes a quantitative decrease in the white blood cells (neutrophils), haemoglobin, or platelet count. Cytopenia referrals represent a large proportion of referrals to a haematologist, and often require a multistep workup that might be time consuming and costly to the patient. Many algorithms have been proposed to investigate leucopenia, anaemia, and thrombocytopenia, and to determine their aetiologies. These algorithms are often useful but are by no means universally applicable or substitute the haematologist's clinical assessment and judgment.[2-4]

In many patients, the cause of cytopenia is clinically obvious and the correct diagnosis can be established after the initial examination and basic laboratory assessment. However, some patients with chronic cytopenia, especially in the setting of a tertiary referral centre, have less clear aetiology; therefore, workup requires a multi-step, complex approach with specialised testing that often includes bone marrow examination. It would be advantageous for both patient and

physician to develop a refined algorithm to examine and diagnose this subset of patients.

Abdominal ultrasound imaging is a readily available, low cost imaging procedure that does not use ionising radiation, thus posing minimal risk to patients. It is convenient and does not require venous access or administration of contrast material. This modality is effective in evaluating abdominal organs for various indications and aides in evaluating organ dysfunction as a possible aetiology of haematologic abnormality. Abdominal CT and MRI are other possible imaging techniques that can also result in better anatomic definitions of abdominal organs. The role of abdominal ultrasound imaging or abdominal imaging via other modalities has not been investigated as a part of a workup algorithm for cytopenia. The aim of this study was to retrospectively evaluate the use of abdominal imaging in a haematology practice in a tertiary medical centre. Specifically, this study examines the use of abdominal imaging, via an ultrasound or CT scan, to identify the aetiology of haematologic abnormalities. It will also examine the association between abdominal imaging results and need for bone marrow examination for these cases. It was hypothesised that abdominal imaging would lead to more identified aetiologies in adjunct to a thorough history, examination, and laboratory workup for patients referred for haematology evaluation in a tertiary medical centre.

METHODS

This study is a retrospective electronic chart review of patients seen at The University of Kansas Cancer Center, Kansas City, Missouri, USA, which is a tertiary referral centre with a wide referral base that includes primary care physicians as well as medical and surgical subspecialists. This study received Institutional Review Board approval.

SETTING

Patients referred to this haematology clinic were evaluated by thorough medical history, physical examination, review of prescription and over-the-counter medications, and discontinuation of medications suspected to be contributing to cytopenia or medications that are not indicated. Standard laboratory workup includes repeating blood counts; reticulocyte count (if anaemia is present); and peripheral blood smear by a haematologist or haematopathologist. Further workup includes evaluation of nutritional deficiencies including serum iron, vitamin B12, and folate levels; anaemia including direct Coomb's test, lactate dehydrogenase, haptoglobin (if anaemia is present); serum copper (if neutropenia is present); hepatic and renal functions; thyroid function; chronic infections, including HIV and hepatitis viruses (if indicated); autoimmune disorders; and haematologic malignancies if clinical stigmata are present. If this workup fails to identify the aetiology of the cytopenia, abdominal imaging via an ultrasound or CT scan has been incorporated as a second-tier workup to exclude radiologic evidence of organ dysfunction as a culprit for the haematologic abnormality.

If a diagnosis is made, the patient is managed appropriately and discharged to the referring physician. However, if the aetiology of the haematologic abnormality is not evident despite the above workup, the patient is offered a bone marrow biopsy and aspiration, or offered frequent follow up (i.e., at least every 6 months) with a haematologist if bone marrow examination is not indicated or declined.

This review focusses on the medical charts of patients referred to a single haematologist for one or more cytopenias between August 2011 and July 2013. Inclusion criteria included patients who presented for initial workup and subsequently required abdominal imaging for evaluating the cytopenias. Patients with prior abdominal imaging within 2 years and patients with haematologic malignancy at presentation or diagnosed through workup were excluded. The following data were extracted via medical chart review: patient age, sex, BMI, number of cytopenias, severity of cytopenias, 67 results of abdominal imaging, diagnosis after imaging study, and outcome (i.e., patient discharged or followed infrequently; patient had bone marrow biopsy; or patient needed frequent monitoring).

Analyses

The lower limits of normal haematologic parameters were adopted per institutional laboratory references. For this analysis, the authors

defined the severity cut-offs for cytopenias as follows: mild neutropenia was defined as 1,000–1,800x10^6/L; moderate neutropenia was 500–1,000x10^6/L; and severe neutropenia was <500x10^6/L. Mild anaemia was defined as 10.0–13.5 g/dL in men or 12 g/dL in women, moderate anaemia was 8–10 g/dL, and severe anaemia was <8 g/dL. Mild thrombocytopenia was defined as 100–150x10^6/L, moderate thrombocytopenia was 50–100x10^9/L, and severe thrombocytopenia was <50x10^9/L. Descriptive statistics were calculated for subject demographic data and clinical results. Chi-square test (or Fisher's exact test when indicated) was used to examine the association between abdominal imaging and necessity of subsequent bone marrow biopsy. Chi-square test was used to examine the association between number of cytopenias and abdominal imaging result (i.e., positive or negative). Chi-square test was used to examine the association between severity of cytopenias (i.e., mild versus at least one moderate or severe cytopenia) and abdominal imaging result. Chi-square tests examining the association between 1) presence and the Cochran-Armitage test for 2) severity of thrombocytopenia with positive abdominal imaging result were also run.

The Cochran–Mantel–Haenszel test was used to calculate the 88 odds ratio of abdominal imaging and outcome-monitoring frequency, adjusted for bone marrow biopsy. The Cochran–Armitage test for trend and unconditional logistic regression were run to examine association of BMI and result of abdominal imaging test (i.e., positive or negative), treating BMI as categorical and continuous exposure measures, respectively. All data analyses were performed in SAS 9.3.

Table 1: Sample demographics and baseline characteristics (N=36).

	Number (n)	Percentage (%)
Gender		
Male	18	50.0
Female	18	50.0
Age (years)		
18–49	12	33.3
50–65	13	36.1
>65	11	30.6
BMI		
<20	2	5.6
20–25	4	11.1
25–30	10	27.8
>30	17	47.2
Not available	3	8.3
Number of cytopenias		
1	21	58.3
2	14	38.9
3	1	2.8
Imaging results		
Abnormal	21	41.7
Normal	15	58.3
Bone marrow biopsy		
Performed	8	22.2
Not performed	28	77.8

RESULTS

Descriptive Results

Thirty-six patients met all inclusion criteria. The demographics and baseline characteristics are outlined in Table 1. The average patient age was 54.4 years (range: 21.0–84.0) and average BMI was 31.5 kg/m^2 (range: 18.0–53.0). Table 2 presents a descriptive summary of neutropenia, thrombocytopenia, and anaemia results. In total, 21 individuals (58.33%) had one cytopenia, 14 individuals (38.89%) had two cytopenias, and 1 individual (2.78%) had three cytopenias. Fifteen individuals (41.67%) had only mildly severe cytopenia(s) and 21 individuals (58.33%) had at least one moderate or severe cytopenia. Abdominal imaging consisted of abdominal ultrasound in 33 patients and abdominal CT scan in 3 patients. Imaging identified abnormalities for 21 individuals (58.33%). Abnormalities detected by imaging included splenomegaly (n=14), liver disease or cirrhosis (n=13), renal cell carcinoma (n=2), and ovarian tumour and lymphadenopathy (n=1). Following imaging, eight individuals (22.22%) required bone marrow biopsy and 12 individuals (33.33%) required frequent monitoring.

Inferential Results

Abdominal imaging in the study subjects showed abnormalities that are implicated in blood decreases at a high rate, including three occult, clinically significant malignancies. There was not a significant association between detecting abnormal imaging and necessity of bone marrow biopsy ($p>0.99$). Detecting abnormal imaging and subsequently identifying the probable aetiology of the cytopenia was associated with successful discharge from the haematology clinic or less frequent monitoring, but this did not reach statistical significance ($p=0.14$). The association between BMI and detecting abnormal imaging was statistically significant; specifically, increased BMI was associated with increased probability of positive imaging result when BMI was assessed both as a categorical (ordinal) measure ($p<0.01$) and as a continuous measure ($p=0.04$; see Figure 1).

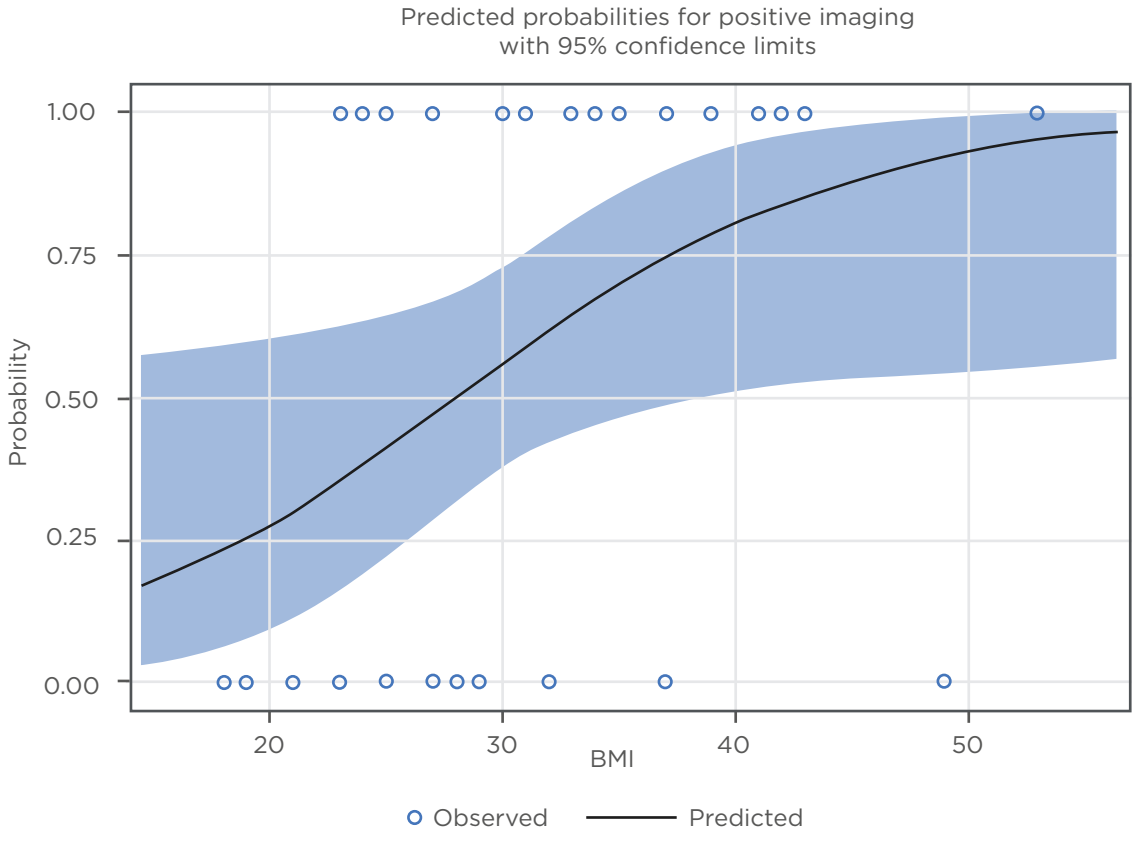

Figure 1: Association between BMI and detection of abnormal abdominal imaging.

Table 2: Frequency (n, and percentage %) of severity of cytopenias (N=36).

	Neutropenia	Anaemia	Thrombocytopenia
None	28 (77.78%)	20 (55.56%)	8 (22.22%)
Mild	5 (13.89%)	9 (25.00%)	12 (33.33%)
Moderate	2 (5.56%)	5 (13.89%)	14 (38.89%)
Severe	1 (2.78%)	2 (5.56%)	2 (5.56%)

There was not a significant association between the number of cytopenias (1 versus ≥2; p=0.86) and detection of abnormal imaging. There was no significant difference in the proportion of positive imaging tests between those with all mild cytopenias compared to those with at least one moderate or severe cytopenia (p=0.23). Thrombocytopenia was significantly associated with detecting abnormal imaging tests. Of those with a diagnosis of thrombocytopenia, 68% had a detected abnormal imaging test result. In contrast, only 25% of individuals without a diagnosis of thrombocytopenia had abnormal imaging (p=0.0461). There was also a significant trend of increasing detection of abnormal imaging, ranging from 25% for individuals without thrombocytopenia to over 80% for those with moderate-to-severe thrombocytopenia (p=0.0094).

DISCUSSION

Blood cell production is tightly controlled by several complexes, interacting biological networks (including the growth factor and cytokine networks), the haematopoietic microenvironment, the immune system, other intercellular communication networks, and diverse intracellular communication networks.[5-8] In addition, genetic, epigenetic, and metabolic factors contribute to the regulation of blood cell production. Each of these mechanisms may act together to control and maintain blood cell counts at a remarkably constant 'physiologic' range in a healthy person throughout his or her lifetime. This process is very sensitive to many physiologic and pathologic processes that include, but are not limited to, nutritional factors; immune disorders; connective tissue disease; chronic diseases and chronic inflammatory conditions; infections; organ dysfunction in the hepatic, renal, and endocrine systems; medication effects or side effects; and haematologic malignancies and paraneoplastic phenomena in association with solid tumours. Disruption in these regulatory factors or acquisition of a disruption in the normal physiologic processes may cause or contribute to the development of one or more cytopenias. This study investigated the role of abdominal imaging in evaluation of the aetiology of cytopenias at a haematology clinic in a tertiary medical centre. Results yielded a notably high rate (58%) of abnormal abdominal imaging detection in this population. The imaging results have led to identifying the aetiology of the cytopenia in many subjects resulting in a final diagnosis and the lack of need for frequent observation. This is supporting the hypothesis that abdominal imaging would be of value in the algorithms of identifying aetiologies of cytopenia(s). Additionally, abdominal imaging in this cohort identified three subclinical malignancies that were resected with curative intentions, and evidence of clinically significant liver disease triggering the need of referral to the hepatology team.

Abdominal imaging was most likely to be abnormal and therefore helpful for workup of patients with thrombocytopenia, possibly by identifying a high rate of occult liver disease.

Notably, abdominal imaging abnormalities were detected more significantly in association with increased obesity. The authors propose that this is plausibly related to more challenging physical examination in patients with obesity, or due to higher prevalence of liver disease in those subjects. Abdominal imaging did not mitigate the need for bone marrow biopsy although the number of bone marrow biopsies performed in this cohort was small.

CONCLUSION

The results of this small, retrospective chart review yielded initial, clinically relevant observations to support a larger, prospective study of the role of abdominal imaging in diagnosis of chronic cytopenias. In this study, abdominal imaging proved to be a high yield test in the workup of cytopenias as a second-tier test. The imaging is most pertinent in patients with thrombocytopenia and in patients with high BMI. Reaching a more acute assessment of the aetiology of the cytopenias, as assisted by abdominal imaging, can have significant clinical impact on these patients and possibly provide a cost-saving advantage by limiting the need for frequent follow up. Prospective study will be needed to confirm this.

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Eltrombopag-Induced Myelofibrosis in Patients with Adult Immune Thrombocytopenia: Scoping Review

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Abstract

Immune thrombocytopenic purpura is a clinical syndrome of thrombocytopenia that manifests as a bleeding tendency, typical skin rashes, easy bruising, or extravasation of blood from the capillaries. Defects in the thrombopoietin-receptor (TPOR)/myeloproliferative leukaemia virus/JAK2 axis leads to haematological diseases such as thrombocytopenia or pancytopenia through the inhibition of the megakaryopoiesis process.

Thrombopoietin-receptor agonists (TPORA), such as eltrombopag, increase platelet count by stimulating the TPOR. Bone marrow (BM) fibrosis has been reported in patients receiving TPORA. Myelofibrosis (MF) may be induced by mutations in *JAK2*, *CALR*, and *MPL* genes. This review gives an insight on MF as a serious side effect induced by eltrombopag.

This review enriches the evidence of MF induced by eltrombopag after long-term administration ranging from 6 months to 7 years. MF is mostly spontaneous and decreases after discontinuation of medication; however, in a few cases it becomes persistent. This major issue should be treated with high concern. The authors recommend that any patient on eltrombopag treatment should be under vigilant observation and closely monitored for any sign of MF by clinical manifestation and any abnormal result from peripheral blood smear examination, and should additionally undergo BM biopsy for confirmation and detection of the severity of MF. The authors recommend discontinuing the medication if this side effect occurs. The authors also recommend to conduct larger studies for longer periods using serial BM before, and periodically after, eltrombopag treatment to evaluate the characteristics of this adverse effect.

INTRODUCTION

Immune thrombocytopenia (ITP) is an autoimmune bleeding disorder that lessens the production of platelets.[1] Despite treatments being available for ITP, first-line treatments fail in 60–80% of adult patients.[2] The initial treatment for ITP is corticosteroid and immunoglobulins (Ig), and splenectomy is then used in cases that fail to respond to steroids. In 2010, the U.S. Food and Drug Administration (FDA) approved anti-RhD Ig as a treatment for ITP patients who are rhesus positive and have not received a splenectomy. Rituximab exerts its therapeutic effect by reducing serum IgG antibody levels and can be used after corticosteroids are tapered and withdrawn. Other second-line treatments include azathioprine, cyclophosphamide, cyclosporine, danazol, mycophenolate mofetil, vincristine, and the novel medication fostamatinib. Recent advances in understanding ITP pathogenesis have highlighted the role of dysfunctional platelet reproduction; this led to a new generation of thrombopoietin (TPO)-receptor agonist (TPORA) therapies, including eltrombopag and romiplostim.[3,4]

Response rates of these treatments are not universal, and each therapy has its own limitations.[2] Myelofibrosis (MF) is a bone marrow (BM) disorder in which the BM is replaced by fibrous tissue, leading to a lack of sufficient blood cells which presents in anaemia, weakness, fatigue, and often, enlargement of the liver and spleen.[5,6]

Eltrombopag is an effective medication for treatment of ITP; however, the development of BM fibrosis is an immense concern and the authors will spotlight this issue in this scoping review.

METHODOLOGY

Arksey and O'Malley's methodology was used.[7]

Identifying the Research Question

This scoping article was conducted to answer the research question: what is known from existing literature about eltrombopag-induced MF in adult ITP patients?

Identifying Relevant Studies

Information Sources and Search Strategy

The search strategy was formulated to identify studies, case reports, meta-analyses, and previous systematic reviews for MF and eltrombopag in adult ITP patients.

This strategy involved searching for research evidence via different sources, including electronic databases like PubMed, Google Scholar, and the Cochran database, as well as reference lists, key journals, relevant organisations such as the American Society of Hematology (ASH), and conference proceedings.

The authors' method for searching the studies involved three steps. The first step was an initial limited search of a selection of relevant databases, followed by an analysis of text words contained in the title and abstract and of the index terms used to describe the article. A second search using all identified keywords and index terms was then undertaken across all included databases. Thirdly, the reference list of all identified reports and articles were searched for additional studies. Key words that were used included 'eltrombopag', 'myelofibrosis', 'immune thrombocytopenia', and 'reticulin'. Articles were analysed using Microsoft Excel® as a data extraction tool. Three reviewers implemented the inclusion and exclusion criteria to all citations searched in all databases. Full articles were obtained for those studies that appeared to be relevant. Only the articles that met the inclusion and exclusion criteria were studied.

The inclusion criteria were:

- Human adult studies written in English.
- Studies for chronic ITP adult patients.
- Articles published from 2008 to 2018.
- Any study design (retrospective or prospective).
- Fully published reports, meta-analyses of clinical trials, or reviews.

Any study seemingly meeting the inclusion criteria based on the title, abstract, or both, were put in for closer inspection.

The exclusion criteria were:

- Trials published in a language other than English.
- Trials that were performed in animals.

- Trials that were performed in children.
- Abstracts.
- Trials outside of the chosen time period (i.e., before 2008 or after 2019).

Study Selection

After an extensive literature search as described, three reviewers applied the inclusion and exclusion criteria to all citations. Full article texts were requested to determine the best article matches with the research question. A deadline was set, after which no more studies could be included in the analysis. The reviewers read the full articles to make the final decision as to whether they should be chosen for inclusion in the review.

Charting the Data

The data was charted and entered into a 'data charting form' using Excel. The study-recorded information was filed under the appropriate title headings: author(s), year of publication, title of the study, study location, study details, methodology, and results (Table 1).

Methodology Outcome

The methodology for the study can be seen in Figure 1. The initial search resulted in a total of 201 articles, which included records identified through searching various databases: 161 from Google Scholar, 27 from PubMed, 2 articles related to the Cochran database, and an additional 11 from article reference lists, relevant organisations such as ASH and the FDA, plus conference proceedings that included references identified through other sources.

Eight articles were excluded because of duplications to give 193 total, after which point only articles from 2008 to 2019 were selected and included to give 118 articles.

Abstracts of each of these articles were reviewed and it was determined that many of the articles were not relevant to the topic of this review but more broadly related to cancer and cardiac problems.

The authors examined 43 articles, of which 21 articles were excluded because they were either animal studies, abstracts, or studies performed in children, leaving 22 relevant articles. Of the 22 relevant articles identified, 3 were case reports, 8 were clinical trials, and 11 were reviews, and are summarised in Table 1.[8-29]

RESULTS

In the study, three case reports of MF that was induced by eltrombopag were included. MF appeared within 6 months to 3 years following eltrombopag administration, two cases showed persistent MF, and the two others did not. Reports recorded MF with Grade 2/3 according to the World Health Organization (WHO) classification (2008).[8,9,30]

The case report by Jayakar et al.[8] in 2015 presented a case of an 87-year-old woman with chronic ITP who was treated consecutively with two TPO mimetics: romiplostim and then eltrombopag. BM evaluation prior to TPO mimetics treatment showed no evidence of fibrosis. Within 6 months of therapy, the patient developed persistent MF (MF Grade 2/3) that was confirmed by BM biopsy (BMB).[8]

The case report from 2016 by Horikoshi et al.[9] presented the case of a 78-year-old man who had been diagnosed with ITP in 2004. Eltrombopag treatment was initiated in 2014 and 8 months after this the patient underwent a BMB that showed Grade 2 MF.[9]

The case report by Moustafa et al.[10] in 2019 presented the case of a 38-year-old man who was diagnosed in May 2015 with chronic ITP and received eltrombopag as a third-line treatment. The patient was stable for 3 years under eltrombopag, after which time the patient developed a severe reduction in platelet count and failure of eltrombopag treatment. The patient underwent BMB that showed Grade 2 MF. The patient's pharmaceutical interventions were discontinued but they developed persistent MF.

In the study, eight clinical trials involving a total of 936 patients were reviewed; a number of points of contention regarding the trials were identified and some had limitations. Two prospective trials were completed by Ghanima et al. in 2011[12] and 2014[13] which studied a total of 91 patients. These studies confirmed that long-term administration of eltrombopag (2–4 years) caused MF-2/3 and that discontinuation of TPORA may prevent the progression of fibrosis in MF-2/3.[12,13] The first trial in 2011 had limitations to the study.

Table 1: Studies from 2008 to 2019 that were included in the literature review of myelofibrosis induced by eltrombopag treatment for immune thrombocytopenia.

Author	Title	Country	Study details	Result/Conclusion
Case report				
Jayakar et al., 2015[8]	Persistent thrombopoietin mimetic induced myelofibrosis in a woman with chronic refractory immune thrombocytopenia.	USA (2015)	One patient (87-year-old woman) 6 months duration MF-2/3	The sequential use of high dose TPO mimetic therapy may have contributed to the development and persistence of MF in this patient.
Horikoshi et al., 2016[9]	Spontaneous thrombocytopenic purpura with myelofibrosis during treatment with eltrombopag.	Japan (2016)	One patient (78-year-old man) 8 months duration. MF-2/3.	Eltrombopag was discontinued, careful observation recommended whilst using TPORA.
Moustafa et al., 2019[10]	Eltrombopag induced myelofibrosis in an immune thrombocytopenic patient: Case report.	KSA (2019)	One patient 3 years MF-2/3	There was a link between eltrombopag and MF.
Clinical trial				
Cheng et al., 2008[11]	Oral eltrombopag for the long-term treatment of patients with chronic idiopathic thrombocytopenic purpura: Results of a phase III, double-blind, placebo-controlled study (RAISE).	USA (2008)	Prospective 197 patients enrolled: eltrombopag, 135; placebo, 62 6 months duration	No evidence of BM fibrosis was detected in clinical or laboratory assessment.
Ghanima et al., 2011[12]	Fibroproliferative activity in patients with immune thrombocytopenia (ITP) treated with thrombopoietic agents.	UK 2011	Prospective 25 patients 4 years duration	Low-grade BM reticulin fibrosis was seen in most ITP patients on TPORA.
Ghanima et al., 2014[13]	Bone marrow fibrosis in 66 patients with immune thrombocytopenia treated with TPORAs: A single-center, long-term follow-up.	USA (2014)	Prospective 66 patients >2 years duration	TPORA induced MF-2/3 in approximately 1/5 of patients with ITP, increasingly with >2 years of treatment.
Brynes et al., 2015[14]	Evaluation of bone marrow reticulin in patients with chronic immune thrombocytopenia treated with eltrombopag: Data from the EXTEND study.	USA (2015)	Prospective 117 patients 5.5 years duration	Reticulin was either absent or mildly increased in 113/115 patients (98%) treated. For most patients with chronic ITP, treatment with eltrombopag was not associated with development of BM reticulin or collagen fibrosis.

Table 1 continued.

Author	Title	Country	Study details	Result/Conclusion
Brynes et al., 2016[15]	A 2-year, longitudinal, prospective study of the effects of eltrombopag on bone marrow in patients with chronic immune thrombocytopenia.	USA (2017)	Prospective, longitudinal study. 162 patients enrolled, 93 completed. 4 patients exert MF-2 after 15 month and 3 patients have MF-3 after 12 months.	Treatment with eltrombopag is generally not associated with clinically relevant increases in BM reticulin or collagen.
Wong et al., 2017[16]	Safety and efficacy of long-term treatment of chronic/persistent ITP with eltrombopag: Final results of the EXTEND study.	Korea (2017)	Prospective 302 patients 7 years duration	MF occurred.
González-López et al., 2017[17]	Use of eltrombopag for secondary immune thrombocytopenia in clinical practice.	USA (2017)	Prospective 87 patients 11 months duration	Patient developed MF-3 but after cessation of eltrombopag this decreased to MF-1.
Fattizzo et al., 2019[18]	Bone marrow characteristics predict outcome in a multicenter cohort of primary immune thrombocytopenia patients treated with thrombopoietin analogues.	Italy (2019)	Retrospective 67 patients MF-1 (24 patients) (35.8%) 3.8 years duration	One third of patients showed reticulinic fibrosis (MF-1.)
Review				
Rice., 2019[19]	Treatment of immune thrombocytopenic purpura: Focus on eltrombopag.	USA (2009)	Review 7/19 patients have MF	Persistent blood smear abnormalities suggesting significant MF. Surveillance bone marrows performed 1 year into treatment revealed mild reticulin fibrosis in 7/19 subjects.
Cuker et al., 2010[20]	Safety of the thrombopoiesis-stimulating agents for the treatment of immune thrombocytopenia.	USA (2010)	Review 2010	11% of patients had MF.
Cook, Cooper, 2010[21]	Eltrombopag – A novel approach for the treatment of chronic immune thrombocytopenic purpura: Review and safety considerations.	UK (2010)	Review	No evidence of clinically relevant BM abnormalities and MF in patients treated for up to 18 months with eltrombopag (EXTEND trial).

Table 1 continued.

Author	Title	Country	Study details	Result/Conclusion
Rank et al., 2010[22]	Evaluation of AMG 531 safety in sple nectomized (S) and non splenectomized (NS) patients with chronic immune thrombocytopenic purpura (ITP) in two randomized placebo-controlled Phase III studies.	Germany (2010)	Review	The significance of reticulin accumulation in BM was unclear.
Cuker, 2010[23]	Toxicities of the thrombopoietic growth factors.	USA (2010)	Review	Recommended larger studies with long-term follow-up and serial BM examinations.
Bascianoa, Bussel, 2012[24]	Thrombopoietin-receptor agonists.	USA (2012)	Review	The significance of MF remains unclear, although it appears in general to be mild and reversible with drug cessation. Long-term assessments will be needed for fibrosis determination.
Sabnani, Tsang, 2011[25]	Changing spectrum of chronic immune thrombocytopenic purpura: New face for an old disease.	India (2012)	Review	Despite TPO agonists showing a favourable safety profile to date, these agents may have potential long-term side effects, such as thrombosis and MF.
Lakshmanan, Cuker, 2012[26]	Contemporary management of primary immune thrombocytopenia in adults.	USA (2012)	Review	Reticulin was observed in <5% of patients receiving treatment for at least 12 months.
Deutsch, Tomer, 2013[27]	Advances in megakaryocytopoiesis and thrombopoiesis: From bench to bedside.	Israel (2013)	Review	Current data suggested that BM fibrosis was seen in a small minority of patients receiving TPO-mimetics; a longer-term clinical evaluation is required to assess the nature of this potential adverse effect.
Rodeghiero, Ruggeri, 2015[28]	Treatment of immune thrombocytopenia in adults: The role of thrombopoietin-receptor agonists.	USA (2015)	Review	The risk of inducing MF seems negligible, at least for treatments shorter than 2–3 years.
Dubis, Collins, 2016[29]	Treatment options in immune thrombocytopenia.	USA (2016)	Review	Previous studies have shown the development of MF; however, BM biopsies from study participants showed no BM abnormalities.

BM: bone marrow; ITP: immune thrombocytopenia; KSA: Saudi Arabia; MF: myelofibrosis; TPO: thrombopoietin; TPORA: thrombopoietin receptor agonist; UK: United Kingdom; USA: United States of America.

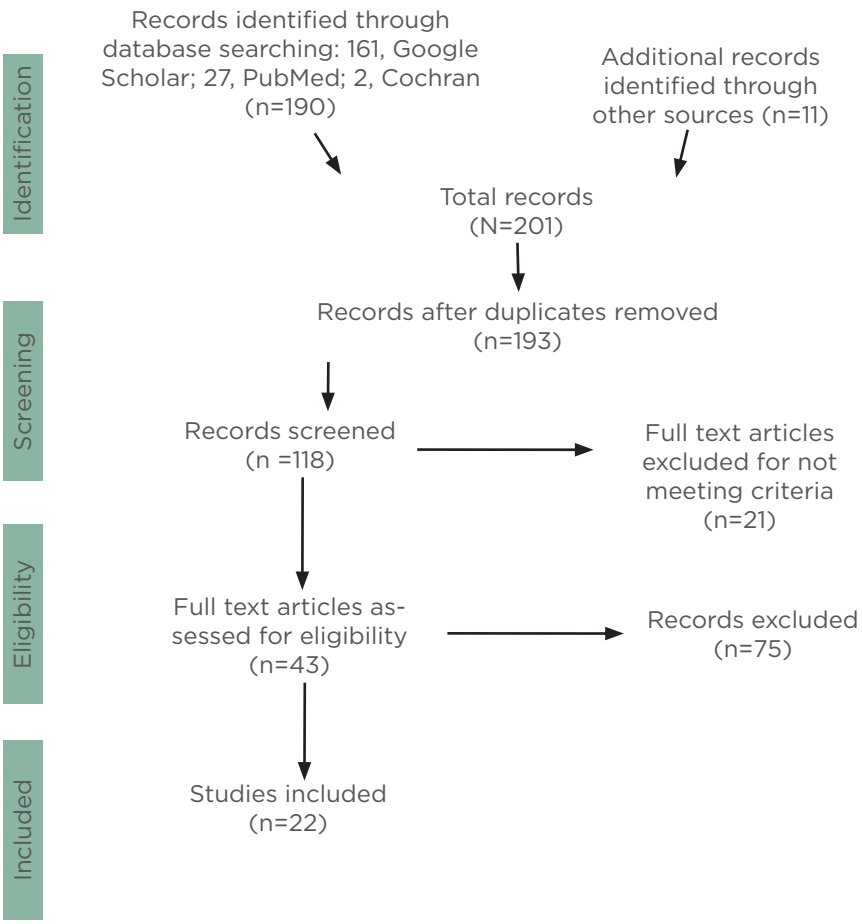

Figure 1: PRISMA flow chart demonstrating literature search and selection of studies.

Ghanima et al.[12] studied 25 ITP patients with TPORA treatment, including 9 patients on eltrombopag, and performed follow-ups on them for 4 years. Eight patients had BMB before treatment in contrast to the other 17 patients. On-treatment biopsies were available in all patients, and five of them were repeated. The results for MF (Grade 1, 2, 3) were significant (19 patients out of 22) but the trial had a small sample size. Some bias appeared in this trial as missing data, particularly related to the pre-treatment BMB for 17 patients. Selection bias appeared in repeating biopsies for patients initially showing extensive fibrosis more than others.

The second trial was done by the same author in 2014 to study 66 patients and provide follow-up for 2–6 years.[13] This study carried some limitations as data was missing for some pre-treatment biopsies. Interruption of TPORA for some patients may have affected the degree of fibrosis in the succeeding biopsy, as well as 5 patients having positive grading for MF-1/2 before initiation of treatment.

Another two trials were performed in 2015[14] and 2017[15] by Brynes et al., however both had limitations. In the first trial, the authors studied 117 patients treated with eltrombopag for 5.5 years. The study concluded that 2 out of 117 patients had moderate-to-marked reticulin fibrosis MF-2 and MF-3 after 25 months. One patient returned to normal after discontinuing eltrombopag whereas the other patient had persistent MF. Over the 5 years, 98% of patients had findings of MF-0 or MF-1. They concluded that eltrombopag is not associated with MF because reticulin was either absent or mildly increased during treatment and the risk of BM fibrosis may be due to TPORA or the disease.[14] No baseline for BMB prior to treatment was identified to be easily compared after treatment.

The second trial from the same author studied 162 patients; 4 patients experienced MF-2 after 15

months and 3 patients had MF-3 after 12 months. From these results, the author concluded that eltrombopag is generally not associated with clinically relevant increases in BM reticulin or collagen.[15] However, there is a conflict between his findings and the conclusion. Both of these trials carried limitations as well as attrition bias because of withdrawal of participants caused by MF, personal prerogative, or other adverse effects.

In the RAISE trial conducted in 2008 by Cheng et al.,[11] 197 patients were studied over 6 months. The study showed that there was no evidence of BM fibrosis detected in clinical or laboratory assessment.[11] As a follow-up study, 6 months is a short duration, especially when, in many cases, adverse drug reactions appear after long-term administration.

The study by Wong et al.[16] in 2017 studied 302 patients. MF was recorded using the European consensus on grading BM fibrosis and assessment of cellularity. MF-1 was reported in 41% of patients, of which 10 patients (6% of total) had progression to MF-2, and 1 (1% of total) progressed to MF-3. The study carries attrition bias because of withdrawal of some patients or missed data at follow-up. No baseline for BMB pre-treatment was found.

The trial conducted by González-López et al.[17] in 2017 studied 87 patients. One patient developed MF-3 after 11 months of being on eltrombopag administration, but after cessation of eltrombopag this decreased to MF-1. Another trial was completed by Fattizzo et al.[18] in 2019 which concluded that 1/3 of the patients had MF-1. No baseline for BMB was found before launching eltrombopag. Some patients had received previous treatment, such as romiplostim, that may have caused MF.

In summary, three trials that studied 476 patients, with follow-up periods of 6–66 months, reported that eltrombopag is not associated with MF; however, 6 other trials that studied a total of 547 patients with a follow-up duration from 11 months to 7 years confirmed the association between administration of eltrombopag and development of MF.

Eleven reviews mostly confirmed MF occurrence with long-term eltrombopag administration and gave several recommendations to support this finding such as the implementation of larger studies with long-term follow-up and serial BM examinations. In contrast, three reviews by Cook and Cooper,[21] Rank et al.,[22] and Bascianoa and Bussel[24] concluded that there was no evidence of clinically relevant BM abnormalities or MF with long-term eltrombopag use, and that the significance of reticulin and MF accumulation in BM is unclear.

To summarise, many studies and reviews showed BM changes (increased reticulin and possible BM fibrosis [MF-1/2/3]). Long-term use of eltrombopag may cause changes in the BM starting from 6 months to 7 years.

DISCUSSION

Immune Thrombocytopenia Purpura

ITP was defined as per Francesco Rodeghiero and the panel of International Hematology Working Group's standardised definitions of primary ITP; an autoimmune disorder characterised by isolated thrombocytopenia (peripheral blood $100x10^9$/L) in the absence of other causes or disorders. The diagnosis of primary ITP remains one of exclusion; no robust clinical or laboratory parameters are currently available to establish ITP diagnosis with accuracy.[3] Defects in the TPOR/myeloproliferative leukaemia virus (MPL)/JAK2 axis leads to haematological diseases such as thrombocytopenia or pancytopenia through the inhibition of the megakaryopoiesis process.[3,31]

Eltrombopag with Immune Thrombocytopenia Purpura

In 2008, the FDA approved eltrombopag (SB-497115, GlaxoSmithKline) for adult patients with chronic ITP.[32] The mechanism of action of eltrombopag remains incompletely understood because it could not be studied in preclinical mouse models.[31] Eltrombopag induces human megakaryopoiesis, the process leading to platelet production in the blood from the differentiation of BM progenitors to platelet precursors called megakaryocytes (MK). The major cytokine regulating megakaryopoiesis is TPO.[31] Eltrombopag selectively binds to the transmembrane domain of the TPOR/MPL oncogene expressed in platelets, MK, and MK-progenitors, that leads to activation of JAK/STAT signalling via STAT5, MAPK, p38, and early response genes. This drives MK proliferation

and differentiation and leads to increased platelet production.[3,20,33]

Eltrombopag may be administered as 30, 50, or 75 mg per day dosages. Eltrombopag increases platelet counts in a dose-dependent manner in patients with relapsed or refractory ITP.[34] Eltrombopag may also increase the risk for development or progression of reticulin fibre deposition within the BM. Long-term use of eltrombopag can cause BM changes by showing increased reticulin and BM fibrosis.[22] Eltrombopag is an inhibitor of OATP1B1 and BCRP (breast cancer resistance protein) transporters (uptake drug transporters expressed on hepatocytes and other cells). Patients should be closely monitored for signs and symptoms of excessive exposure to the drugs that are substrates of OATP1B1 and BCRP (e.g., rosuvastatin) and consider reduction of their dosages.[32] Polyvalent cations (e.g., iron, calcium, aluminium, magnesium, selenium, and zinc) significantly reduce the absorption of eltrombopag; eltrombopag must not be taken within 4 hours of any medications or products containing polyvalent cations such as antacids, dairy products, and mineral supplements.[32]

Myelofibrosis

MF may be induced by mutations in three key genes: *JAK2*, which regulates certain enzymes involved in cell growth and the immune response; *CALR*, whose products are needed for intracellular trafficking; or *MPL*, which is also important for maintaining cell growth.[32] Eltrombopag may increase the risk of development or progression of reticulin fibre deposition within the BM. Long-term use of eltrombopag causes BM changes, shown by increased reticulin and BM fibrosis.[35] Eltrombopag has continuous mimetic action on *JAK2*, *MPL*, and *TPO* with long-term administration. This may lead to genetic mutations which cause secondary MF, but more genetic studies are needed in the future to prove this link.

Analysis of Results

Studies suggest increased reticulin deposition in the BM can be caused by TPORA.[36] TPORA stimulate reticulin deposition via activation of cytokine production by MK. There are reports of MF with abnormal deposition of collagen and reticulin in BMB of ITP patients treated by TPORA. TPORA-induced MF, however, is described as reversible upon discontinuation of TPO-based therapy in most reports.[5,12]

Many studies indicated the possibility of BM fibrosis in patients treated with TPORA but the available data about the degree of marrow reticulin fibrosis in ITP patients under treatment with TPORA are still limited. It is clear that certain patients were susceptible to reticulin accumulation in their marrow. The development of MF-2/3 can occur with a duration of treatment from 6 months and above..

The authors believe that degree of fibrosis may depend on specific factors, including dose of medicine, duration of disease, platelet number and immature fraction, splenectomy, and age at time of starting TPORA agent. The degree of fibrosis in the BM is known to be greater with age. More fibrosis also tended to be related to splenectomised patients and a longer duration of disease. Individual susceptibility to reticulin fibrosis in some ITP patients may trigger the development of MF. The mechanism of these findings is currently unclear. Because MF-2/3 was noticed in patients on both romiplostim and eltrombopag, fibrosis is thought to be a class-effect and not related to a specific agent.

Primary MF is a clonal disorder with progressive fibrosis, cytopenias, cellular abnormalities, and altered cytokine release. TPORA-induced fibrosis is a different secondary disease mostly not associated with cytopenia, clonal abnormalities, high lactate dehydrogenase, morphological changes in blood film, and other abnormal biochemical parameters. No clonal abnormalities showed in any of the patients during treatment with TPORA. The authors believe that the exposure time may still be too short to induce clonal abnormalities. For this reason, longer follow-up is recommended to test these agents in this regard as well.

Some other studies have not clearly produced the same results; but this lower proportion of MF-2/3 could be explained by shorter observation times. Also, the duration of ITP before BMB was shorter in these studies. Patients with chronic ITP under TPORA treatment may be on these agents for as long as 5–10 years, meaning observational follow-up is needed to find out whether prolonged exposure to TPORA would lead to relevant grades of MF in many patients. BMB

were not performed regularly in all patients, on an annual or biannual basis. In some patients, treatment with TPORA was interrupted before biopsies, which could affect the degree of fibrosis in the specimen taken.

Recommendations During Eltrombopag Treatment

Monitoring patients with the treatment of eltrombopag is a big concern. Haematologists have to monitor any clinical signs of anaemia or thrombocytopenia that may be progressed. Severe fatigue is the most common symptom in MF. Fatigue, fever, night sweats, and severe weight loss are signs of hyper catabolism. Hyperuricaemia can also arise secondary to high cell turnover, in which a high white blood cell count and platelet count may be seen: these cells are needed to compensate the marrow underproduction. Hyperuricaemia leads to gout or renal complications, and routine blood checks are very important to explore anaemia. The differentiation picture of full blood count should be monitored monthly. Peripheral blood smear examination is a useful and simple test to detect MF, and is recommended prior to initiation of therapy to establish the baseline level of cellular morphologic abnormalities and to be monitored monthly. If the blood film includes teardrop-shaped red blood cells and a leucoerythroblastic picture, it may be indicative of MF. The authors suggest monitoring BM reticulin biopsy test for MF confirmation and for the detection of the severity of MF.

CONCLUSION

This review is an addition to the evidence that MF may be induced by eltrombopag after long-term administration, starting from 6 months. MF is mostly spontaneous and normally decreases after discontinuation of medication, but in a few cases becomes persistent. This major issue should be of high concern. Any patient on eltrombopag treatment should be under careful observation and be closely monitored. Routine blood check and peripheral blood smear can be used to detect MF, and BMB will be useful for the confirmation and determination of the severity and staging of the disease. Eltrombopag should be discontinued if this side effect is established. Finally, larger studies for longer periods using serial BMB before and periodically after eltrombopag treatment to evaluate the characteristics of this adverse effect need to be conducted.

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Are Successful Pregnancies an Achievable Goal in Patients with Chronic Myeloid Leukaemia?

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Abstract

Since the late 1990s, when the first tyrosine kinase inhibitor (TKI) imatinib was introduced as a front-line treatment for chronic myeloid leukaemia, the disease's course and prognosis has dramatically changed. The development of second-line and further-line more potent generations of TKI has further improved disease control and patients' quality of life; however, during this time, many questions such as the duration of treatment, the depth of response, fertility, pregnancy, and family planning, have been raised. Recent prospective and retrospective discontinuation trials for TKI have shown encouraging results regarding the cessation of TKI treatment and maintaining complete molecular response. The authors report three cases of female patients diagnosed with chronic phase chronic myeloid leukaemia who achieved a long-term deep molecular response; had planned management during pregnancy, including regular molecular monitoring with or without INF-α; and all delivered healthy babies.

INTRODUCTION

BCR-ABL1 positive chronic myeloid leukaemia (CML) is a myeloproliferative neoplasm in which granulocytes are the major proliferative component. BCR-ABL1 CML positive arises in haematopoietic stem cells and is characterised by the chromosomal translocation t(9;22)(q34.1;q11.2), which results in the formation of the Philadelphia chromosome, which contains the *BCR-ABL1* fusion gene.[1] This fusion gene produces a unique oncoprotein named BCR-ABL, which is an active tyrosine kinase. At the very end of the 1990s, CML became a targeted therapy success in oncohaematology due to the introduction of the first tyrosine kinase inhibitor (TKI), imatinib mesylate, which specifically binds to the ATP binding site of the BCR-ABL kinase and inhibits it.[2] Over the following years, second and third-generation TKI were approved as part of the armamentarium for the treatment of CML.

Patients diagnosed in the chronic phase can achieve excellent disease control and therefore

expect many years of good quality of life; furthermore, patients who achieve an optimal response can reach a life expectancy similar to a non-leukaemic population of the same age.[3]

Globally, the median age at diagnosis reported in the literature for patients with CML is about 55–60 years.[2] In Bulgaria, the median age newly diagnosed CML patients is 51.1±14.5 years old, based on data from 499 patients (unpublished data). A number of issues have been raised by patients to physicians regarding contraception, teratogenicity, fertility, and pregnancy. Currently, there is no evidence-based consensus for the management of CML in pregnancy; therefore, clinical observations have become very important. Most of these observations are derived from small case series or case reports.

THE AUTHORS' EXPERIENCE: THREE PREGNANT FEMALE PATIENTS WITH CHRONIC PHASE CHRONIC MYELOID LEUKAEMIA

Between April 2014 and January 2018, three planned pregnancies were managed by the CML team at the Medical University of Plovdiv, Bulgaria. Details of the patients can be seen in Table 1.

Table 1: Characteristics of the three pregnant female patients with chronic phase chronic myeloid leukaemia.

	Phase at diagnosis	Age at diagnosis (years) Age during pregnancy (years)	Months from initial treatment	Drug before pregnancy Drug during pregnancy	Outcome	Delivery	Current status and therapy
Patient 1	Chronic phase	14 24	120	IFN-α Imatinib Nilotinb IFN-α	Successful pregnancy	Healthy girl	MR 4.5 Nilotinib
Patient 2	Chronic phase	28 30	24	Nilotinib IFN-α	Successful pregnancy	Healthy girl	MR 4.5 Nilotinib
Patient 3	Chronic phase	20 24	48	Nilotinib No therapy	Successful pregnancy	Healthy boy	MR 5.0 No therapy

MR: molecular response.

To take part in the planned pregnancy management, several factors were required: patient at the chronic phase of the disease at the time when the diagnosis was established, no history of accelerated or blast phase CML, on therapy with TKI, and stable molecular response (MR: 4; BCR-ABL1 <0.01% IU) for >2 years, as documented on at least four tests performed at least 3 months apart. During the pregnancy, after stopping the TKI, the patients were treated with INF-α, based upon the authors' previous experience in two patients who were treated with INF-α during their pregnancies in the pre-TKI era and gave birth to two healthy children. *BCR-ABL1* transcripts were measured every second month during the pregnancy. The authors have not experienced any unsuccessful or complicated pregnancies in patients treated with TKI.

Patient One

The patient was diagnosed with chronic phase CML (CP-CML) at the age of 14 years (Sokal score: low risk; Hasford score: low risk) and began therapy with IFN-α for 48 months, then switched to imatinib. After 24 months therapy with imatinib, the patient was switched onto nilotinib, a second-generation TKI, due to an adverse event (skin changes). The patient received nilotinib for 48 months before ceasing the therapy due to planned pregnancy. From 2012–2014, her *BCR-ABL1* transcript level was monitored every 3

months and the results showed a stable molecular response (MR) of 4.5. One year after the discontinuation of nilotinib therapy, the patient became pregnant. During the second trimester, a loss of the MR of 4.5 was detected and therapy with INF-α was started. A cytogenetic test for evaluation of the cytogenetic response was not carried out. No side-effects or complications while receiving INF-α therapy were registered. The patient delivered a healthy girl *per vias naturales* and the therapy with nilotinib was restarted soon after. The patient did not breastfeed the baby, and 3 months after the delivery, the patient regained a MR of 4.5.

Patient Two

The patient was diagnosed with CP-CML at the age of 28 years (Sokal score: low risk; Hasford score: low risk) and started first-line therapy with nilotinib. Twelve months after the treatment was started, the patient obtained a MR of 4.5. During the second year of the treatment, she was monitored every 3 months and the results showed a durable MR of 4.5. After 24 months of nilotinib therapy, the patient ceased the TKI therapy because of planned pregnancy. Fourteen months after stopping nilotinib, the patient became pregnant. During the pregnancy, she maintained a MR of 4.5. Pre-emptive treatment with INF-α was started at the end of the first lunar month and the patient remained on INF-α therapy until the delivery; no side-effects or complications were registered while the patient received INF-α therapy. The patient delivered a healthy female baby at gestational Week 39 via caesarean section. The patient did not breastfeed the baby. The child developed normally without any evidence of congenital malformation. The treatment with nilotinib was restarted soon after the delivery and, to date, the patient has maintained a MR equal to 4.5.

Patient Three

The patient was diagnosed with CP-CML at the age of 20 years (Sokal score: low risk; Hasford score: low risk) and started first-line therapy with nilotinib. Twelve months after the treatment was started, she obtained a MR of 5 and maintained the MR for the next 3 years. Treatment was stopped 4 years after starting TKI therapy because of the planned pregnancy. Fifteen months after stopping nilotinib, the patient became pregnant. During the pregnancy, she maintained a molecular response equal to a MR of 5 without any treatment and remained at that level until the delivery. She delivered a healthy male baby at gestational Week 40 via caesarean section and breastfed the baby. The child developed normally without any evidence of congenital malformation. Since the delivery, the patient has not restarted TKI therapy, her *BCR-ABL1* transcript levels are monitored every 3 months, and she is still at a MR of 5.

Case Summary

In summary, a stable MR of 4.5 for 4 years is not always indicative that it is safe to discontinue TKI, as seen in Patient One. However, the patient regained a MR of 4.5 soon after restarting treatment with TKI. Treatment with IFN-α is safe and effective after discontinuation of TKI and during pregnancy.[4-6] As some reports indicate, restarting treatment with imatinib from the second trimester during pregnancy in patients with a high risk of relapse is a feasible approach.[7,8]

DISCUSSION

During the last two decades, the clinical view and management of CML has changed dramatically. TKI have revolutionised the treatment of CML, leading to a substantial improvement in survival, disease control, and quality of life in patients with CML. Considering the fact that treatment with TKI nowadays is recommended to continue indefinitely as far as it is tolerable or the disease is under control, patients frequently raise the question of stopping the therapy.

The main causes for cessation, according to recently published case reports and series, were adverse events, including intolerance (50%), the patient's choice (26%), the cost of drugs (12%), and pregnancy (12%).[9-16] There is currently no official guideline regarding management of CML in cases of pregnancy. The data reported are from several prospective and retrospective clinical trials analysing the discontinuation of TKI in CP-CML.[17-21] Based on the data from the multivariate analysis of these trials, there are some important risk factors that impact the maintenance of complete MR (CMR) after stopping the TKI therapy. A high Sokal score is a significant independent risk factor for relapse

after cessation of TKI therapy. Factors associated with longer TKI free-remission include prior IFN therapy before TKI therapy, longer duration of CMR before discontinuation, and longer duration of imatinib mesylate use before discontinuation (>60 months). Additionally, achieving an early deep molecular response at 3 months is associated with a durable deep molecular response, as indicated by a recently published analysis.[20-26]

An independent algorithm was proposed by Milojkovic and Apperley[8] for the management of CML patients diagnosed during pregnancy. They proposed leukapheresis during the 1st–3rd trimester, the frequency of which is determined by the need to maintain a leukocyte number <100x10^9/L and a platelet count <500x10^9/L. In the second and third trimester, INF-α is indicated as an option for treatment for patients having a suboptimal response to leukapheresis. Patients planning an elective pregnancy who have complete haematological response or a better response with TKI are recommended to collect oocytes for future assisted conception, stop TKI at the onset of their menstrual cycle, and start *in vitro* fertilisation medications 7 days after TKI discontinuation. TKI should be restarted after oocyte collection. Patients planning pregnancy with a stable major molecular response or better MR for 24 months can stop TKI at the onset of the menstrual cycle and should undergo reverse transcription quantitative (qRT-PCR) monitoring in addition to examination of peripheral blood during pregnancy.[8]

Supporting the idea of quiescent residual CML stem cells, qRT-PCR for BCR-ABL1 transcripts is a mandatory test for pregnant patients with a MR of 5. Disease monitoring during pregnancy, according to some published data, should include qRT-PCR every month if a CMR of 4.5 is not achieved and qRT-PCR every 2 months if the patient presents with CMR.[8,27-30] In cases of a loss response, the risk to the mother and the baby should always be considered.

After delivery, all patients can breastfeed for the first 2–5 days postpartum to provide the baby with colostrum. The reason for this is that newborns have very immature digestive systems, and, as such, colostrum is needed to deliver nutrients in a very concentrated low-volume form. Due to its mild laxative effect, colostrum aids the passage of the baby's first stool. It also helps to clear excess bilirubin. Colostrum contains immune cells and many antibodies, immune substances, and a series of cytokines and growth factor. Considering the few days of delay before treatment resumes, it might be important for the newborn to access breastfeeding. After delivery and sustaining a good molecular transcript level, treatment with TKI can be postponed to enable full breastfeeding, according to the haematologist's judgment.[31]

Most of the published cases with good disease control at conception and optimal response while being on TKI stopped during the pregnancy and restarted after delivery confirm the possibility of a safe therapeutic management during pregnancy.[32-34]

CONCLUSION

In conclusion, it is very important to take into consideration that each case of CML in a pregnant patient should be treated as a separate case due to the influence of many factors on the pregnancy outcome, such as the biology of the disease, duration of the treatment, compliance with therapy, and response to the treatment. The willingness of the patient should always be considered and discussed. As a new generation of TKI is incorporated into the clinical practice, the percentage of patients achieving MR ≥4.5 will be constantly increasing. Continuing effort is needed to determine the optimal management of pregnant patients with CML.

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A Review of the Different Haematological Parameters and Biomarkers Used for Diagnosis of Neonatal Sepsis

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Abstract

Neonatal sepsis is a major cause of morbidity and mortality in newborns. It presents a diagnostic challenge to the neonatologists due to a lack of objective evaluation. It may mimic noninfective conditions, such as inborn error of metabolism, birth asphyxia, and even respiratory distress syndrome in preterms. Nonetheless, over-diagnosis and initiating unwanted empirical antibiotics may pose the threat of drug resistance, increasing the hospital stay and cost of treatment. Traditionally, investigations such as white blood cell count, absolute neutrophil count, immature to total neutrophil ratio, C-reactive protein levels, and blood cultures have been used to diagnose sepsis. However, these have low sensitivity and specificity because they may be elevated in conditions other than sepsis. The in-depth understanding of the neonatal immune system's response to early infection has led to the discovery of advanced diagnostic tools, including biomarkers.

This literature review briefs on the various haematological parameters and biomarkers in neonatal sepsis, exploring newer biomarkers and comparing them with their older counterparts. This will help early diagnosis, treatment, and improved prognosis in neonatal sepsis. As there is a spectrum of markers for diagnosing neonatal sepsis, it is preferable to compile these markers and correlate clinically.

A thorough search of this literature was done on the electronic databases PubMed, Elsevier's Web of Science, and the Cochrane Library. The authors found around 90 relevant articles: 84 were from PubMed, 4 from Elsevier, and 2 from the latest Cochrane database. Of these articles, 57 were selected from between early 2000 and January 2019.

INTRODUCTION

Neonatal sepsis has been a leading cause of high morbidity and mortality in newborns and is recognised as a global health challenge.[1-3] The definition of early onset sepsis (EOS) is variable from <3 days (American Academy of Pediatrics [AAP] definition) to <7 days (Centers for Disease Control and Prevention [CDC] definition based on epidemiology studies).[4] The incidence of neonatal sepsis in India was 30/1,000, as per the Neonatal Perinatal Database (NNPD).[5] The incidence of total sepsis was as high as 14.3% in

a recent cohort study conducted by the Delhi Neonatal Infection Study (DeNIS) collaboration in India, of which culture-proven sepsis was 6.2%. Nearly two thirds of these cases were EOS (<72 hours).[6] The total neonatal mortality rate was 28/1,000 live births with early neonatal mortality rate being 22/1,000 live births, of which sepsis contributed to a quarter of the deaths.[7] Therefore, neonatal sepsis constitutes a significant health burden. To combat this, it is vital to understand the fragile neonatal immune system and its response to infection in the form of biomarkers.[8] Timely identification of neonatal sepsis and initiation of appropriate antibiotics form the cornerstone in preventing these neonatal deaths.

Even though there are recent sophisticated biomarkers to diagnose sepsis, it is still challenging to curtail sepsis mortality by timely intervention.[9-11] Moreover, establishing early diagnostic markers will extensively reduce antibiotic abuse and help in rationalising a unit policy for the judicious use of antibiotics, thus preventing the emergence of multidrug-resistant micro-organisms. The current gold standard microbiological blood culture screen may produce false-negatives because of low yield when a lesser amount of blood is collected, in addition to high turnover time.[12,13] Additional haematological tests used traditionally, such as white blood cell count (WBC), absolute neutrophil count (ANC), immature to total neutrophil (I/T) ratio, and C-reactive protein (CRP) measurement, also have a poor sensitivity and specificity and may need serial monitoring.[14] For better prediction of sepsis, recent evidence suggests the use of age-specific nomograms rather than fixed normal ranges of WBC, ANC, and I/T ratio.[15] Thus, diagnostic tests that are rapid and accurate in guiding the management of septic newborns are needed.[16] Empiric use of unnecessary antibiotics will be withheld by the use of tests that have a high negative predictive value, therefore preventing the adverse effects of antibiotics on unaffected neonates.[17,18] The immune system of a neonate remains incompletely understood; however, with the robust development of molecular characterisation of this immature immune system, it has now been possible to identify an array of biomarkers that are produced by these ill infants in response to the offending organism aiding the prompt diagnosis of sepsis.[19-21] The objective of this review is to provide a summary of biomarker developments for early diagnosis and treatment of neonatal sepsis, simultaneously comparing them with older markers for the condition.

METHODS

The authors completed a computer-based search of the literature using the words "neonatal", "sepsis", "biomarkers", "hematological", and "omic", along with combinations of these words in PubMed, Elsevier's Web of Science, the Cochrane Library (including January 2019), and Google. The results revealed around 90 studies in the English language from early 2000 to January 2019; most of which were single-centred, small studies conducted in tertiary care neonatal units in middle and low-income countries. Of the 57 articles included in the review, most of them were cohort, cross-sectional studies, and previous reviews and articles retrieved from their references. This was followed by detailed, extensive analysis of these studies elaborating each of the biomarkers including both the traditional and newer ones (Table 1), comparing them (along with their sensitivity and specificity), and describing their practical utility in a resource-limited set up.

THE REQUIREMENTS OF AN IDEAL BIOMARKER

1. Levels of the biomarker should aid not only in early diagnosis but also in optimising management. Thus, biomarker levels should change early in the disease and remain altered for a period of time.[8]
2. High sensitivity and negative predictive value of nearly 100%, with a preferable specificity and positive predictive value of 85%.[9,22]
3. Guide in starting and/or stopping antimicrobial treatment and also monitor disease course.
4. Discriminate a specific pathogen or a category of pathogens, e.g., viral, bacterial (gram-positive organisms versus gram-negative organisms), and fungal organisms.
5. Be able to predict severity of the disease as well as prognosis.
6. Volume of specimen needed should be small (e.g., <0.5 mL of blood), low cost, and readily available.

7. Quantitative values of biomarker concentration with nomograms or well-defined cut-offs must be easily available.

OLD MARKERS

Cultures

The definitive diagnosis of sepsis is the isolation of the organism from any bodily fluid, such as blood, urine, or cerebrospinal fluid. Although the sensitivity of blood cultures is 98%, results normally take up to 72 hours. Furthermore, prior antibiotic treatment and low volume of collection can result in false-negative reports. Nevertheless, BACTEC culture system has now made early detection within 48 hours possible, even with low volumes of blood and a low colony count.[23]

Haematological Indices

Traditionally, the following parameters have been used as the initial markers of neonatal sepsis, either individually or in combination:

- Total leukocyte count (TLC).
- ANC.
- I/T ratio and morphological or degenerative changes in neutrophils, such as vacuolisation, Döhle bodies, intracellular bacteria, and toxic granules.
- Platelet count.

Total Leukocyte Count

TLC has been conventionally used in the sepsis screen. Based on the fact that there are few reserves of white blood cells in the neonatal bone marrow, leukopenia can represent an overwhelming infection.[24,25] However, TLC has a poor predictive value in diagnosis of EOS. Moreover, in EOS, neutrophil indices are more reliable if obtained after 6–12 hours, thus delaying the diagnosis.

Absolute Neutrophil Count

Blood ANC varies in a neonate, with the lower limit being <1,800/µL at birth, <7,800/µL at 12–14 hours of age, and falling again to <1,800/µL at 72 hours.

Table 1: Old and new biomarkers for the diagnosis of sepsis.

Old markers for sepsis	Newer markers for sepsis
Cultures†	SAA
Haematological indices: • WBC and differential count* • ANC • I/T ratio* • Platelet count	Cytokines and chemokines***
Micro ESR*	Cell surface markers
Acute phase reactants: • CRP* • PCT**	Omics†† • Genomics • Metabolomics • Proteomics

*Forms the conventional septic screen.

**Excellent early marker, especially if combined with PSP, thus forming the best marker for EOS.

***IL-6 early biomarker in EOS.

†Gold standard.

††Promising markers to be explored.

ANC: absolute neutrophil count; CRP: C-reactive protein; EOS: early onset sepsis; I/T ratio: immature/total neutrophil ratio; Micro ESR: micro erythrocyte sedimentation rate; PCT: procalcitonin; PSP: pancreatic stone protein; SAA: serum amyloid A; TLC: total leukocyte count; WBC: white blood cell count.

Immature to Total Leukocyte Ratio

I/T ratio is calculated as 'immature polymorphs/mature plus immature neutrophils' and is the most sensitive indicator of sepsis. Values >0.27 in term and >0.22 in preterm neonates are significant. In general, the abnormal leukocyte ratios, including an I/T ratio of ≥0.2, tend to have a high sensitivity of 90% and negative predictive value of 98%, whereas abnormal leukocyte counts, such as leukopenia and neutropenia, tend to have high specificity.

Platelet Count

Thrombocytopenia has been seen quite often in sepsis, especially fungal sepsis, but has not been a promising early marker.

The haematological scoring system (HSS) suggests that the higher the score, the greater the sensitivity, and that sepsis is probable with a HSS score ≥3. This test has a high sensitivity of 96%, but a low positive predictive value of 31%. Although it is a complex scoring method, studies have complied HSS data with biomarker usage to obtain better results.[26]

Increased mean platelet volume (>8.6 fL) has been studied recently as a marker of EOS and a predictor for mortality, especially in preterm neonates with a sensitivity of 97.14% and a specificity of nearly 100%. However, elevated levels of this marker may also be seen in bronchopulmonary dysplasia and respiratory distress.[27] In addition, recent studies have shown that increased (20%) red blood cell distribution width within 6 hours after birth has been associated with EOS and also predicts a poor outcome.[28]

Micro Erythrocyte Sedimentation Rate

Micro erythrocyte sedimentation rate (Micro ESR) is a technique that has been used traditionally in the septic screen; however, it lacks sensitivity because it takes a few days for ESR to rise and the value varies significantly within the first few days of life. Furthermore, the levels take a significant amount of time to return to normal again. A rough estimate of calculation can be achieved through permiting an additional 2 or 3 days to the age of the neonate being tested.[29]

Acute Phase Reactants

C-Reactive Protein

CRP, a component of the septic screen, is an acute phase reactant produced by the liver in response to an inflammatory/infectious process. It also helps to predict disease severity and guide the antibiotic duration.[30] CRP levels increase at least 6 hours after onset of acute inflammation and decrease faster than any other acute phase reactant.[31] Rather than a single value, serial monitoring at 24 and 48 hours after the onset of sepsis improves sensitivity (by 82% and 84%, respectively). However, CRP may be elevated post-surgery, in meconium aspiration cases, and in those who have recently had vaccinations, thereby reducing its specificity. Since CRP may not be increased immediately at the onset of sepsis, other biomarkers are highly warranted for timely initiation of the treatment. In preterms, for whom CRP production may not be sufficient, the high sensitivity assays of CRP (hs CRP) form a vital marker because it can detect an even lower grade of inflammation.[32] A recent review concluded that serum CRP levels at initial evaluation in suspected late-onset infection is neither sufficiently accurate for early diagnosis nor selecting of neonates that need further investigation and antimicrobial therapy.[33]

Procalcitonin

Procalcitonin (PCT) is the prohormone of calcitonin and is produced by monocytes and hepatocytes in response to sepsis. In contrast to CRP, PCT levels rise 2 hours after infection, peak at 6–8 hours, and normalise after 2–3 days.[34] Although levels are unaffected by gestational age, specific nomograms need to be referred to for the reference ranges in early days of life. PCT has higher sensitivity compared to CRP and other biomarkers, such as IL-6 and hs CRP, especially in early detection of infection.[35] PCT in early-onset infection has been reported to have a sensitivity of 92%, specificity of 97%, positive predictive value of 94%, and negative predictive value of 96%.[36] As evidenced by meta-analyses with pancreatic stone protein (PSP), PCT forms the best marker for EOS.[37] Nonetheless, false-positive increases in PCT may be seen at times in neonatal hypoxia and intracranial bleeding.[38]

NEW MARKERS

Serum Amyloid A

Serum amyloid A (SAA) is an early acute phase reactant and is produced in the liver as apolipoprotein (Apo) SAA in response to infection and inflammation.[39] However, the hepatic and nutritional status may affect the values, limiting SAA's use in late-onset sepsis.[40] SAA has not only proved to be a more sensitive and specific marker, with sensitivity and specificity of 96%, but has also helped in prognosticating patient mortality.[41,42]

Cytokines and Chemokines

Among the various cytokines released by the immature neonatal immune system, the major ones are TNF-α, IL-6, and IL-8.[10] IL-6 is a proinflammatory marker synthesised by mononuclear, chorion, amnion, and trophoblastic cells, and proves to be an early marker in sepsis. This protein triggers the production of CRP and thus its levels elevate prior to CRP. The disadvantage, however, is its short half-life.[43,44] TNF-α, a proinflammatory cytokine, stimulates IL-6 production but is not as sensitive as IL-6 itself.[23] It has been studied that the combination of IL-6, TNFα, and CRP has a sensitivity and negative predictive value of approximately ≥90% for diagnosing EOS.[45] The proinflammatory cytokine IL-8 mediates leukocyte migration and activation and its level rises and falls within 4 hours of infection; it also has a sensitivity of 90%, and has a varied specificity between 75–100%.[46]

Cell Surface Markers

In response to sepsis, various inflammatory cells express cell surface markers, such as CD11b, CD116, CD64, and CD45RO, which can be detected by flow cytometric analysis. This is useful in diagnosing intra-abdominal infections as well as EOS. Amongst these, CD64 plays an important role because it binds to the Fc region of the immunoglobulins that increase in infection. The sensitivity of CD64 in diagnosing EOS is 80% and negative predictive value is 89%;[47] however, combined with CRP and IL, its sensitivity may reach 100%. Another new, promising marker is soluble CD163 in EOS with sensitivity up to 100%. In addition, it helps to differentiate between infectious and non-infectious conditions.[48,49]

'Omics' as Future Markers

The various newer approaches in 'omics' include the following:

- Genomics
- Metabolomics
- Proteomics

Genomics

Micro-organisms' genomes, including their response to infection, can be studied, forming the basis of microbial genomics. PCR plays a key role in this process. Even though PCR takes longer to detect organisms, it has been found to be useful in diagnosing viral as well as fungal infections.[50] However, quantitative PCR (qPCR) can rapidly detect any infection. By using the probe specific qPCR, many bacterial species can also be identified. The limitation to this, however, is the non-availability of the entire genome of the microbiome and resistant cell walls of some bacteria, making the DNA unavailable for sequencing.[51]

Metabolomics

The metabolites produced by the micro-organisms in response to sepsis can be studied by spectrometric analysis (such as magnetic resonance spectrometry, nuclear magnetic resonance, and gas-chromatography mass spectrometry), reflecting the interaction between environment and the gene. Apo C2 and SAA were found to be especially elevated in necrotising enterocolitis and hence Apo SAA score was made in a study by Ng et al.[12] Further studies are warranted for the wide acceptance of this score. However, compiling this core can be time consuming, thus it may not be appropriate in EOS. Nevertheless, it has a wide scope in the future to explore the interactions between host and defence and would enable the identification of more biomarkers for septicaemia.[52,53]

Proteomics

Similar to genomics, exploring the proteins produced by the immune system's defences in response to organisms can be evaluated using proteomics. One example is S-100 (calgranulin), which along with heat shock proteins and altered matrix proteins, forms a part of the group of

proteins called damage associated molecular proteins. These are produced by the fetus in response to inflammation and have a protective role. Buhimschi et al.[54] generated a mass restricted score on the amniotic fluid to predict EOS and found elevated levels of matrix metaloprotease-8 (MMP-8) in the amniotic fluid of mothers with prolonged rupture of memebrane. Similarly, another study had reported increased levels of IL-8 mRNA expression in neonates exposed to perinatal infection.[55]

To summarise, these modern molecular markers are not only definitive, but also rapid in diagnosing neonatal infections (Table 2).[56]

Table 2: The advantages and disadvantages of old and new haematological markers and other new biomarkers for the diagnosis of sepsis.

Marker	Advantage	Disadvantage
Blood culture.	Gold standard.	Time consuming. High false-negative results.
Haematological indices.	N/A	N/A
Old haematological parameters		
TLC.	Part of the traditional sepsis screen.	Poor predictive value in EOS.
I/T ratio.	Most sensitive indicator of sepsis screen.	Less specific .
Platelet count.	HSS ≥3. Sensitivity up to 96%.	Low positive predictive value.
New haematological parameters		
MPV.	Increased in sepsis. Specificity nearly 100%.	Elevated levels may also be seen in bronchopulmonary dysplasia and respiratory distress. Requires serial monitoring.
RDW.	Higher values, alongside EOS, are a good predictor of poor prognosis.	Prematurity, delayed cord clamping, and low maternal iron status may be confounding factors.
Micro ESR.	Part of the septic screen.	Less sensitive and takes time to rise.
CRP.	Prediction of disease severity and antibiotic duration.	Serial monitoring needed and may not rise early in the disease.
PCT.	Early rise in infection.	False-positive in hypoxia and intracranial bleeding.
Recent markers		
SAA.	Sensitive and specific.	Hepatic and nutritional status limits value.
Cytokines and chemokines. E.g., IL-6 and TNF-α.	Rise early in infection.	Short half-life.
Cell surface markers.	Useful in EOS and intra-abdominal infections.	Needs sophisticated technology.
'Omics'.	Helps to understand host–infection interaction.	More studies needed. Uses complex datasets so requires skilled analysis.

CRP: C-reactive protein; EOS: early onset sepsis; HSS: haematological scoring system; I/T ratio: immature to total neutrophil ratio; Micro ESR: micro erythrocyte sedimentation rate; MPV: mean platelet volume; N/A: not applicable; PCT: procalcitonin; RDW: red blood cell distribution width; SAA: serum amyloid A; TLC: total leukocyte count.

MORE MARKERS IN THE PIPELINE

Flow cytometric analysis of various body fluids may be helpful in early diagnosis. Among them are IL-8, inducible protein (IP10), and MCP-1. The sensitivity and specificity of IP10 plasma values of ≥1,250 pg/mL are 93% and 89%, respectively, in neonatal sepsis, especially in preterms.[57]

Markers for Early Onset Sepsis

CRP, PCT, and PSP in combination with the traditional markers are markers for EOS, as mentioned in this review. Other markers for EOS are lactoferrin, alpha-1-acid glycoprotein, haptoglobin, and neopterin. In addition, visfatin and resistin have been used similarly for diagnosing EOS, along with chemokines and cytokines.

Markers for Late Onset Sepsis

SAA, ischaemia-modified albumin, and hepcidin are the newer markers advocated in late onset sepsis. They can be combined with the old markers of sepsis to yield a better result in diagnosing late onset sepsis.[58]

CONCLUSION

Though ample new markers have been explored, much of the population in developing countries may not be able to afford them, because they require sophisticated technology. In such situations, PCT would be an apt marker, especially in EOS, thus aiding in timely intervention and reducing the mortality. This is extremely crucial in low and middle-income countries where EOS is fulminant and is caused by gram-negative micro-organisms leading to early mortality. Despite being costly, the governing bodies of such nations should reconsider the need of including these modern biomarkers in the septic screen of these fragile neonates, as they are more specific and help in prompt diagnosis. This, in turn, would reduce the overall burden on the healthcare system and would therefore prove to be more cost effective in the long run due to curtailing the cost of prolonged hospital stays, mortality, and morbidity burden. In conclusion, despite of an array of biomarkers being available, it is crucial to select the appropriate combination of these markers that allows only minimal blood loss in the neonate for a timely, precise diagnosis of sepsis.

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Resistant Bilateral Chylous Effusion as a Late Adverse Effect of Dasatinib Treatment in Chronic Myeloid Leukaemia

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Abstract

Pleural effusion is a common adverse effect of dasatinib, but chylous effusion is rarely reported. Herein, the authors report the case of a 21-year-old imatinib-resistant patient who presented with bilateral massive chylous effusion on Month 44 of dasatinib treatment. The patient was managed with dasatinib withdrawal, bilateral thorax tube insertion, nasal oxygen support, diuretics, corticosteroids, a fat and oil free diet, and sandostatin. The patient required total parenteral nutrition and albumin infusion. The patient's right lung collapsed as a result of pleural thickening. A subsequent switch to nilotinib was well tolerated. The authors highlight that patients on dasatinib treatment must be carefully followed for adverse effects.

INTRODUCTION

Dasatinib is a potent and efficacious second-generation oral tyrosine kinase inhibitor, frequently used for imatinib-resistant or intolerant *BCR-ABL*+ chronic myeloid leukaemia (CML) and for Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukaemia (ALL).[1] Pleural effusion (PE) is a common adverse effect of dasatinib with a reported frequency of 14–32% in the published clinical trials.[2-5] Pulmonary hypertension and parenchymal opacities are also reported adverse effects of dasatinib therapy, but dasatinib-related chylothorax is quite rare.[1]

CASE REPORT

A 21-year-old female patient with chronic phase CML presented with a 3-week history of dyspnoea, cough, and oedema. The patient had received dasatinib treatment for 44 months.

Initial presentation with CML was at the age of 17 years, with malaise and splenomegaly. A complete blood count revealed haemoglobin levels of 9.5 g/dL, white blood cell count of 850,000/µL, platelet number of 180,000/µL, and a peripheral smear that showed 16% promyelocytes, 21% metamyelocytes, 38% band forms, 17% neutrophils, 6% lymphocytes, 1% monocytes, and 1% basophils. A bone marrow smear revealed 20% promyelocytes, 13% metamyelocytes, 43% band forms, 10% neutrophils, 6% lymphocytes, 3% monocytes,

1% basophils, 1% erythroblasts, 2% normoblasts, and 1% blasts. Too few metaphase samples were obtained to perform conventional cytogentic analysis at diagnosis, but molecular diagnosis revealed a BCR/ABL 210-kDa protein (p210) international score (IS) of 555.9664% and showed 90% positive BCR/ABL fusion with fluorescence *in situ* hybridisation (FISH). After cytoreductive treatment with hydroxyurea, 400 mg/day imatinib treatment was started. Haematologic remission was achieved at 3 weeks, partial cytogenetic remission was achieved at 3 months, but no complete cytogenetic response or molecular response by Month 12 of treatment (FISH BCR/ABL p210 11%). Dasatinib 100 mg/day treatment began on the 13th month after diagnosis. Complete cytogenetic remission was achieved by Month 17, but a major molecular response was not achieved (BCR/ABL p210 IS 0.38%). The patient tolerated dasatinib well until Month 44.

Physical examination of the patient found, bilateral respiratory sounds were diminished. Thorax X-ray revealed bilateral pleural effusion (Figure 1A). Diagnostic thoracentesis showed chylothorax (pleural triglycerides 1133 mg/dL and serum triglycerides 79 mg/dL) (Table I); as a result, dasatinib was stopped at once, a left thorax drainage tube was inserted, which drained 2,500 mL of chylous fluid, and, following the drainage of the chylous fluid, nasal oxygen was administered. Thorax and abdominal CT showed no lymphadenopathy, tumour mass, or any evidence for tuberculosis and ductus thoracic injury (Figure 1B). An oral and oil free diet, total parenteral nutrition, and albumin were administered due to hypoalbuminaemia. Methyl prednisolone 1 mg/kg/day was administered in three doses and furosemide put on the same line please was started.

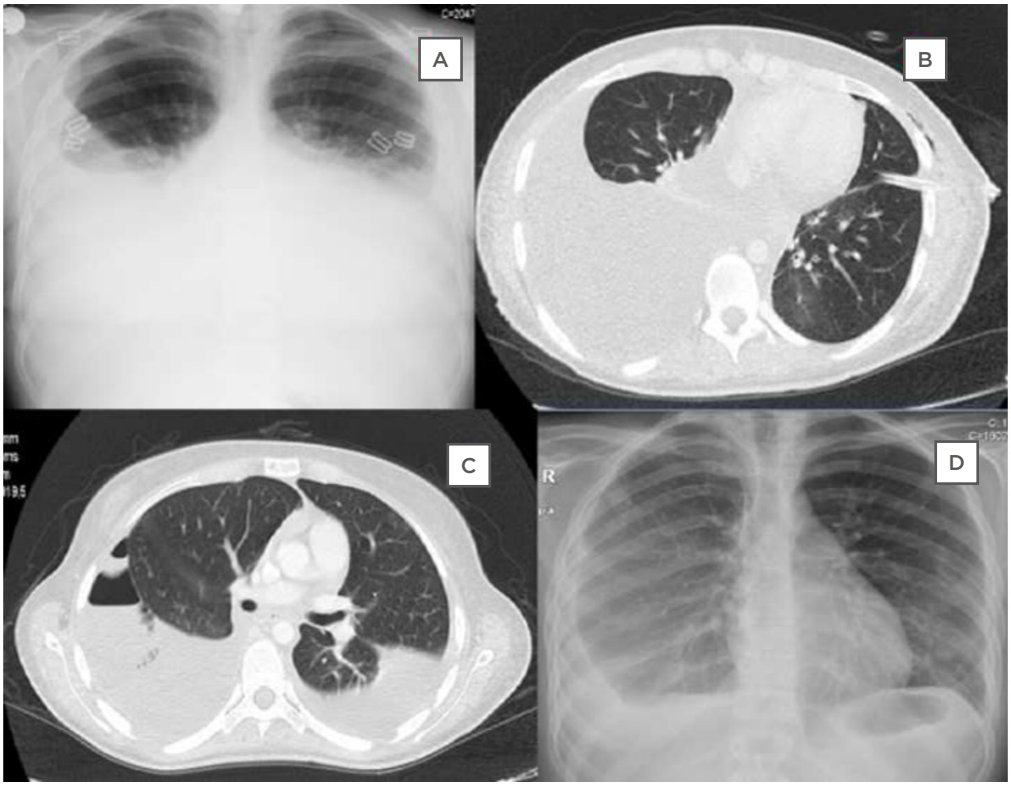

Figure 1: X-ray and CT images illustrating the progression pleural effusion exhibited by the patient and the interventions used by the authors.

A: Initial thorax X-ray showing bilateral pleural effusion.

B: Thorax CT imaging after insertion of the left thorax tube.

C: Thorax CT before insertion of the right thorax tube showing bilateral effusion and left pneumothorax.

D: Thorax X-ray at 6-month follow-up showing collapse of the right lung due to pleural thickening.

Table 1: Characteristics of patients with dasatinib-related chylothorax.

Patient number	1 (Huang et al., 2015)[2]	2 (Ferreiro et al., 2006)[3]	3 (Baloch et al., 2017)[4]	Presented case
Age (years)	40	71	69	21
Gender	Female	Female	Male	Female
Diagnosis	CML	Ph+ ALL	CML	CML
Dasatinib dose (mg/daily)	100 (in two divided doses)	140 (single dose)	100 (single dose)	100 (single dose)
Period for chylothorax development	40 months	2 months	10 months	44 months
Pleural involvement	Bilateral	Bilateral	Right pleura	Bilateral
PF protein (g/dL)	6.4	Right 4.2 Left 4.1	4.8	127.0
PF LDH (U/L)	244	Right 247 Left 254	120	149
PF glucose (mg/dL)	ND	133.0/120.0	157.0	102.6
PF triglyceride (mg/dL)	Right 263 Left 536	Right 625 Left 378	405	1,133
PF/S protein	ND	0.63/0.61	ND	20.32
PF/S LDH	ND	0.67/0.59	ND	0.76
PF/S triglyceride	3.28/6.70	ND	ND	14.34
PF cytology	Lymphocytes, macrophages, mesothelial cells	No cell	ND	Blood elements
Management of chylothorax in addition to dasatinib withdrawal	Diuretics, CS, repeated TS, switch to nilotinib	Dasatinib dose reduction, CS, diuretics, TS	Dasatinib dose reduction, TS, switch to bosutinib	Diet, TPN, diuretics, CS, bilateral TT, sandostatin, switch to nilotinib

CML: chronic myeloid leukaemia; CS: corticosteroids; LDH: lactate dehydrogenase; ND: not defined; PF: pleural fluid; Ph+ ALL: Philadelphia chromosome-positive acute lymphoblastic leukaemia; S: serum; TPN: total parenteral nutrition, TS: thoracentesis; TT: thorax tube.

On Day 4, drainage from the thorax tube was 500 mL/day. Octreotide 0.5 mcg/kg/hour was also administered in escalating doses but stopped on Day 9 due to no decrease in the chylous drainage.

At the end of the second week the patient had a febrile episode, but the fever subsided after piperacillin/tazobactam administration.

The tube was taken out after 20 days, the pleural liquid samples remained sterile, and no mycobacteria were detected. Methyl prednisolone and furosemide treatment was stopped at the end of the 4 weeks. The patient was discharged 28 days after initial admission with some pleural effusion in the right thorax. After 2 weeks she presented again with dyspnoea (Figure 1C) and a right thorax drainage tube was inserted. She was discharged with the thorax tube (100–200 mL drainage daily). After 2.5 months of dasatinib withdrawal, molecular genetics study of the peripheral blood showed BCR/ABL p210 IS of 2.83% (402 copies). Nilotinib was started (two 400 mg doses per day). After 3 months of chylous effusion, the right thorax tube was removed. There was no dyspnoea, but X-ray of the thorax showed partial collapse of the right lung due to pleural thickening (Figure 1D). After 5 and 8 months of nilotinib treatment, molecular genetics anlysis showed that BCR/ABL p210 IS was 0.19% (214 copies) and 0.38% (191 copies), respectively. Informed consent was obtained from the patient for publication of the paper.

DISCUSSION

The presented case details a 21-year-old female with chronic phase CML who received dasatinib 100 mg once per day for 44 months. It was reported that a single dasatinib dose of 140 mg per day was associated with significantly less PE compared with a 70 mg twice a day regimen (20% versus 39%; p<0.001) and a lower need to withdraw the drug.[6] In other studies that compared 100 mg/day and 140 mg/day dasatinib treatment in single and two divided doses, no significant difference was found in the development of PE.[7] In a study by de Lavallade et al.,[8] a history of autoimmune disease and hypercholesterolaemia were factors associated with a higher risk of PE during dasatinib treatment.[8] In reported patients, PE fluid was generally an exudate, and PE was neither related to fluid retention nor kidney failure or cardiac failure. The exact mechanism of PE remains unclear; the predominance of lymphocytes seen in most cases could indicate an immunological mechanism. Inhibition of the platelet-derived growth factor receptor beta (PDGFR-β) expressed in pericytes, which is involved in the regulation of angiogenesis, was also suggested.[9] Src kinase inhibition by dasatinib was also possibly related to changes of vascular endothelial growth factor-mediated vascular permeability and stability of the pleural epithelium.[10] The platelet-derived growth factor-signalling pathway stimulates tumour cell proliferation, angiogenesis, and pericyte recruitment to tumour blood vessels. Furthermore, ligated integrins recruit several nonreceptor tyrosine kinases, including focal adhesion kinase, integrin-linked kinase, and Src-family kinases, among others. If the presentation of Src kinases changes, it may lead to defects in integrin and further chylothorax.[11] Chylothorax typically results from disruption of the normal lymphatic flow. Damage to the thoracic duct or its tributaries may cause leakage of the lymphatic fluid into the thoracic cavity. According to Light's criteria, chylothorax is defined as a turbid PE with triglycerides >110 mg/dL.[12] A visual inspection of the pleural fluid should be conducted, and milky pleural fluid should always be investigated for chylothorax. Not all chylothorax is exudative, with 20% of the cases being transudative.[13] Generally, aetiology of the chylothorax is either traumatic or nontraumatic.[14] The thoracic duct may be damaged by non-iatrogenic methods, such as subclavian vein catheterisation, fracture, dislocation of the spine, childbirth, and penetrating trauma from knife or gunshot injuries. Catheter-related venous thrombosis may also impair lymphatic drainage.[15]

Nontraumatic aetiologies include malignancy, sarcoidosis, retrosternal goiter, amyloidosis, superior vena cava thrombosis, benign tumours, congenital duct abnormalities, and diseases of the lymph vessels, such as yellow nail syndrome, lymphangioleiomyomatosis, and haemangiomatosis.[14] Haematologic malignancies, including lymphoma, chronic lymphocytic leukaemia, and Waldenström macroglobulinaemia were reported to be associated with chylothorax.[2] Imaging studies and history excluded such aetiologies. In the present case, analysis of the pleural fluid revealed chylothorax. Infection was not likely because the pleural fluid culture for tuberculosis and other bacteria remained sterile.

In Table 1, characteristics of the three reported patients with dasatinib-related chylothorax and the present case have been outlined.[2-4] In the reported cases, management of the dasatinib-related PE involves the cessation of dasatinib therapy or reducing the dose and administration of diuretics and a short course of prednisone (40 mg daily for 4 days). Multicentre studies that enrolled many patients with dasatinib-associated PE, reported no cases with chylothorax.[16,17] An Italian multicentre study investigated if dasatinib dose reduction after the first PE would prevent the recurrence of this adverse event. Dasatinib was temporarily interrupted in 71.9% of 196 cases, with a dose reduction in 59.2% of patients; however, recurrence was observed in 59.4% of the cases. Treatment was discontinued due to PE in 29.1% of the cases. Dasatinib dose reduction after the first episode of PE did not prevent recurrence of this adverse event. Therefore, the authors suggest that, once a major molecular response or a deep molecular response is achieved, different strategies of dasatinib dose management can be proposed prior to the development of PE, such as daily dose reduction or, as an alternative option, an on/off treatment with a weekend drug holiday.[16]

In a study by Hughes et al.,[17] frequency, risk factors, and outcomes associated with PE were assessed in two Phase III trials (DASISION and 034/Dose-optimization) and a pooled population of 11 trials that evaluated patients with CML and Ph+ ALL treated with dasatinib. Pleural effusion developed in 6–9% of patients at risk annually in DASISION, and in 5–15% of patients at risk annually in 034/Dose-optimisation; with a minimum follow-up of 5 and 7 years, drug related PE occurred in 28% of 256 patients in DASISION and in 33% of 662 patients in 034/Dose-optimisation, respectively. A significant risk factor identified for developing PE, by a multivariate analysis, was advanced age.[17] However, the age of the presented case is quite young.

There are no firm guidelines detailing when to shift from one treatment to another. Due to respiratory distress, the authors conducted a thoracic tube insertion. The presented patient exhibited cyhlotorax and received 100 mg once-daily dasatinib. In the English literature reviewed by the author, seven patients with dasatinib-related chylothorax were reported.[2-5,18] There was persistent chylous effusion in one patient which required 12 thoracentesis procedures.[18]

CONCLUSION

In the present case, administration of a reduced dasatinib dose was not trialed, due to life threatening chylotorax, with treatment shifted to nilotinib instead. At Month 10 of nilotinib therapy, the patient was in haematologic remission and her tolerance to the therapy was good, but respiratory function tests are still impaired.

Severe adverse events of dasatinib may be observed even during the fourth year of the therapeutic regimen. Dasatinib-related chylous effusion may be large and persistent; thus, shifting to another tyrosine kinase inhibitor may be required.

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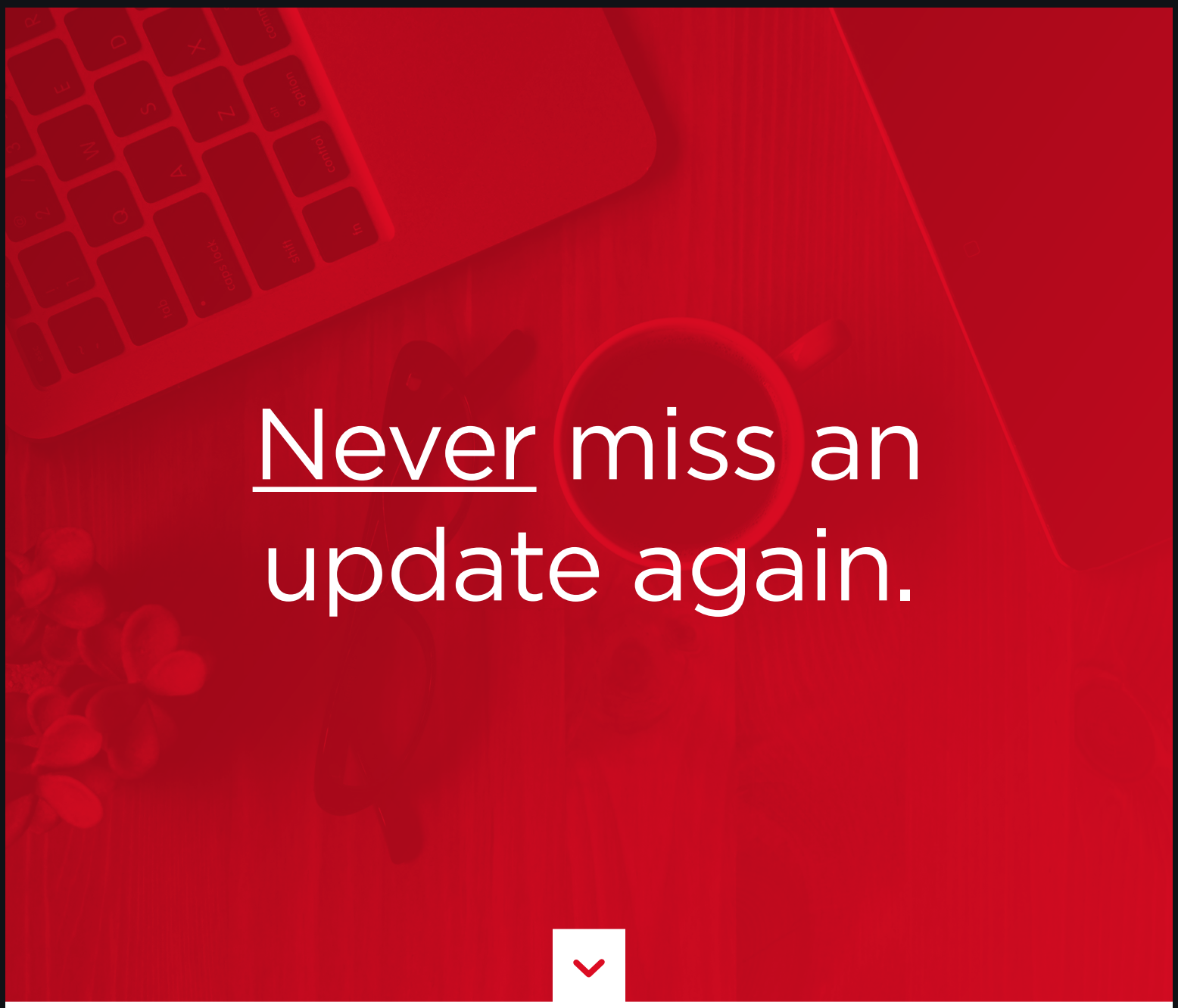

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