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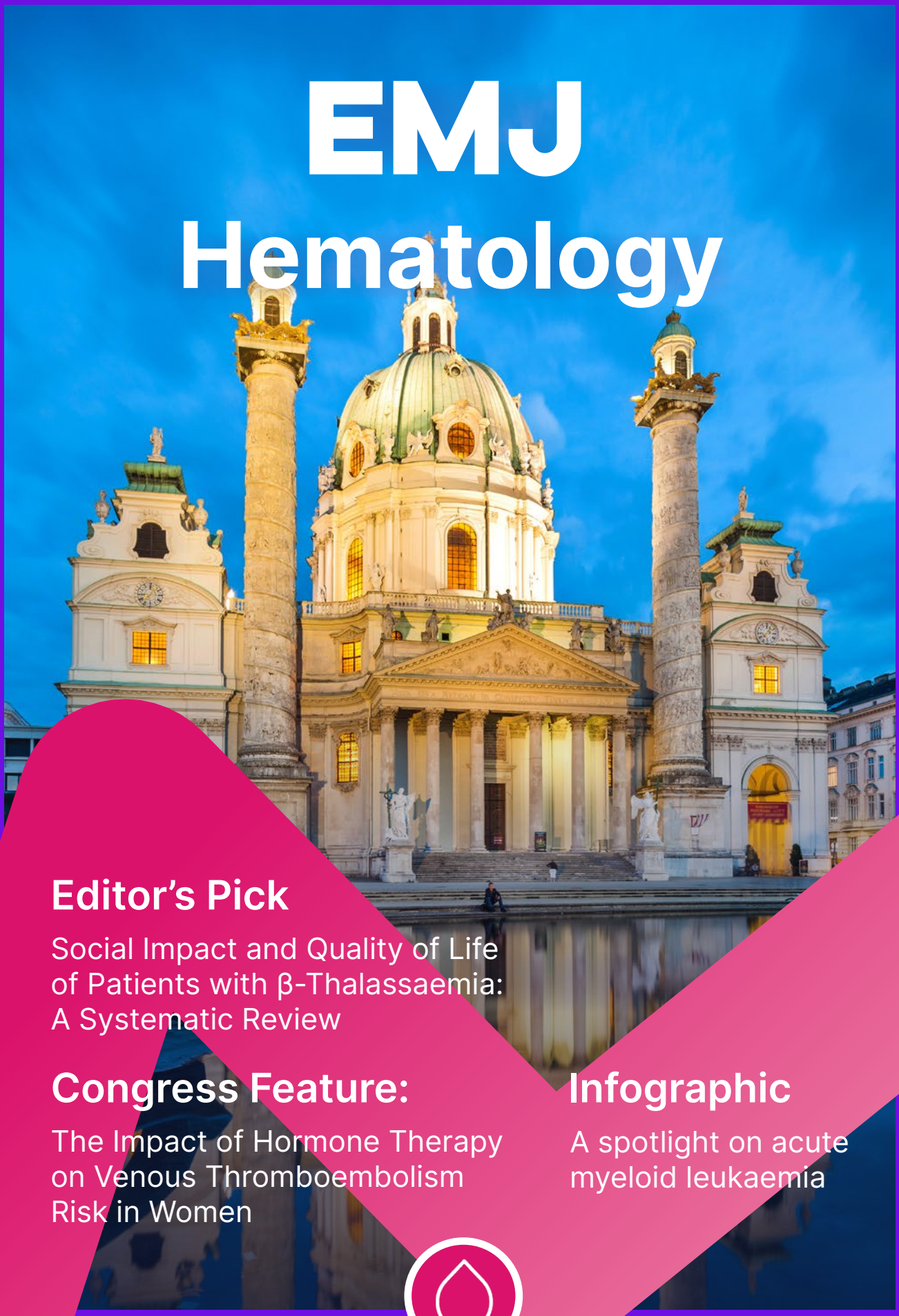

Editor's Pick

Social Impact and Quality of Life of Patients with β-Thalassaemia: A Systematic Review

Congress Feature:

The Impact of Hormone Therapy on Venous Thromboembolism Risk in Women

Infographic

A spotlight on acute myeloid leukaemia

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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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Welcome letter

Koutsouki

Evgenia Koutsouki
Editor

Dear Readers,

Welcome to the 2022 issue of *EMJ Hematology*, covering the 27th Annual Congress of the European Hematology Association (EHA), which took place in Vienna, Austria, this year and followed the overarching theme of 'community'.

We are proud to bring you the key developments from this highly engaging event, spotlighted in our congress highlights section, which features the summary of a study on a new chimeric antigen receptor T cell therapy for patients with relapsed/refractory multiple myeloma. In our abstract reviews section, you can read a summary on the outcomes and responses of the severe acute respiratory syndrome coronavirus 2 vaccine in patients with severe aplastic anaemia. Finally, a highly interesting congress session, focusing on hormone therapy and the risk of venous thromboembolism in females, is covered in detail.

For our Editor's pick, we are proud to feature a systematic review article on the social impact of the disease and quality of life for patients with β-thalassaemia. Among our other articles is a case report of a patient presenting with dyspnoea due to extramedullary haematopoiesis, which was successfully treated with helical tomotherapy, and a paediatric case of Von Willebrand disease-associated angiodysplasia.

I hope you enjoy reading this issue and, as always, I would like to express thanks to our authors for contributing to this journal, and also to our Editorial Board and peer reviewers for ensuring that the content maintains a high quality. We look forward to seeing everyone at next year's EHA Congress.

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Foreword

Dear Colleagues,

The congress for the European Hematology Association (EHA) ended in Vienna, Austria, on 12th June. It was the EHA's first hybrid meeting but, finally, a large number of haematologists were able to meet and speak in person. Most of the speakers attended the congress in person, with only a few speaking remotely, so we had a normal atmosphere at the EHA 2022. Speaking directly to each other is fundamental in our profession and cannot be completely replaced by remote meetings.

The meeting presented notable innovations in all sectors of neoplastic and non-neoplastic haematology. Companies were able to resume their therapeutic and diagnostic developments. Among the many innovations, I would like to list the following: the use of gene editing for gene therapy in haemoglobinopathies, with a large number of cases that finally promise to open new options for these patients; the presentation of the molecular mechanisms for targeting pre-leukaemia; presentations on precision medicine in sickle cell disease and other haematological diseases; new chimeric antigen receptor T cell products; a large clinical series on bispecific antibodies; the introduction of a new classification for myelodysplastic syndromes, including molecular criteria to complete the pre-existing clinical and cytogenetic criteria; and much more! I apologise for leaving out all the other wonderful innovations that were presented this year.

But above all, we have finally presented many speeches and projects that were interrupted by the COVID-19 pandemic. Hopefully, we are, once again, projected into the future and progress in our discipline.

I would like to thank all the authors and interviewees who contributed to this journal, as well as the Editorial Board members and reviewers.

Emanuele Angelucci

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

EHA2022

Review of the European Hematology Association 2022 Hybrid Congress

Location: Vienna, Austria
Date: 9th-17th June 2022
Citation: EMJ Hematol. 2022;10[1]:8-15. DOI/10.33590/emjhematol/10158548. https://doi.org/10.33590/emjhematol/10158548.

THE EUROPEAN Hematology Association (EHA) successfully brought together clinicians and researchers from all over the world to share the latest advances in the field of haematology in its 27th Annual Congress, and its first ever hybrid congress. The EHA 2022 Hybrid Congress was held in Vienna, Austria, with the new format allowing healthcare practitioners to engage both online and in person for the first time since the start of the pandemic. With the EHA celebrating its 30th anniversary, the congress provided a fantastic opportunity for this large network of professionals to connect once again, and advance individual and collective understanding of haematology care.

In her opening ceremony address, EHA President, Elizabeth Macintyre, praised the EHA community: "The pandemic showed that our community is capable of facing challenges, sticking together and delivering excellence in every sense of the word." Discussing the response to another crisis that has arisen since the last EHA Congress, the President went on to address the ongoing conflict in Ukraine, and lauded the Ukrainian people, stating: "Ukrainian people gave resilience a new meaning. In particular, we applaud the efforts of the Ukrainian haematology teams who kept going under extreme circumstances, delivering healthcare to patients who needed it most." A clear theme that arose throughout the Congress was community, with the introduction of a Patient Advocacy Committee representing patients' interests outside of EHA.

The 9-day congress was divided into three hybrid and four fully virtual days, and offered thematic days, as well as more than 180 scientific sessions. These covered a wide range of topics in haematology, including educational sessions. Kirsten Grønbæk, Chair of the Scientific Programme Committee, highlighted: "One of the special topics this year is around Big Data, artificial intelligence, and ethics. The new developments in this field are moving along rapidly." Important for all clinicians were the guidelines sessions on a broad range of topics, such as stem cell transplantation, alongside sessions on how to handle haematological patients in the post-COVID era.

With an outstanding number of abstracts submitted, a variety of research was shared at this year's hybrid congress. Several of these abstracts have been summarised and included in this issue of *EMJ Hematology*. These included a single institution retrospective study into relapses of patients with acute myeloid leukaemia who have received allogeneic stem cell transplant, as well as a study examining the impact of the severe acute respiratory syndrome coronavirus 2 vaccine on severe aplastic anaemia

disease status, and establishing the humoral and cellular response to the vaccine.

While the Committee commended the contribution of a multitude of esteemed professionals to the field of haematology, three major awards were presented at this year's congress. The winner of the José Carreras Lecture and Award 2022 was Marina Cavazzana, in recognition of her role as an established and active investigator who has made an important contribution to haematology. This year, the David Grimwade Award 2022 was granted to Elaine Dzierzak for her outstanding contributions in the field of basic and translational malignant haematology. Finally, the prestigious Jean Bernard Lifetime Achievement Award 2022 was presented to Gert Ossenkoppele for his outstanding contribution to the advancement of haematology.

As last year's wish to walk the Viennese Ringstrasse alongside our haematology colleagues this year became reality, both the speakers and the team at EMJ were excited to be back as a community to share and explore key insights in haematology care. The EMJ team are looking forward to attending the EHA

"The pandemic showed that our community is capable of facing challenges, sticking together and delivering excellence in every sense of the word."

Hybrid Congress in 2023 in Frankfurt, Germany; however, for now, please enjoy our highlights and reviews of the 2022 congress. ●

Quizartinib Demonstrated Promising Potential for Overall Survival in Acute Myeloid Leukaemia

APPROXIMATELY 25% of newly diagnosed cases of acute myeloid leukaemia (AML) carry the *FLT3*-internal tandem duplication (ITD) gene mutation. The mutation promotes disease progression, creating high leukaemic burden, and is associated with the unfavourable prognosis of shorter overall survival and increased relapse risk. New research data has demonstrated quizartinib addition could significantly improve overall survival.

As a highly potent and specific type II *FLT3* inhibitor, quizartinib was developed specifically for *FLT3*-ITD positive AML. The study, carried out at Duke University, Durham, North Carolina, USA, investigated patient outcomes when quizartinib is added to standard induction and post-remission consolidation therapy followed by single-agent continuation of quizartinib. The experiment was trialled for up to 3 years, and improved overall survival in patients diagnosed with *FLT3*-ITD positive AML.

Patients receiving the standard induction therapy with the addition of quizartinib had significantly improved overall survival compared with those treated with standard induction alone. Median overall survival was 31.9 months for patients receiving quizartinib compared with 15.1 months for those on the standard treatment. Furthermore, quizartinib's safety profile was comparable to previous studies with the presence of neutropenia, prolonged QT on the electrocardiogram, and an increased rate of discontinuation due to adverse events than patients on the standard treatment.

From the results, the study authors concluded that statistically significant and clinically meaningful improvement in overall survival could be achieved by the addition of quizartinib to standard induction and consolidation therapy.

"The study, carried out at Duke University, Durham, North Carolina, USA, investigated patient outcomes when quizartinib is added to standard induction and post-remission consolidation therapy followed by single-agent continuation of quizartinib"

Promising Survival Rates with Decitabine Treatment in Acute Myeloid Leukaemia

IN OLDER patients diagnosed with acute myeloid leukaemia (AML), decitabine treatment has been found to result in similar survival rates, and also presents fewer adverse events, when compared to traditional induction chemotherapy.

AML typically occurs in patients over the age of 65. This patient group exhibits a lower tolerance to conventional induction chemotherapy in comparison to younger patients. Older patients receiving induction chemotherapy have poorer long-term survival without haematopoietic stem cell transplantation (HSCT).

Throughout the last decade, DNA-hypomethylating agents like decitabine have been given as a safer alternative treatment for patients for whom induction chemotherapy is unsuitable. Previous research has demonstrated that prolonged (10-day) decitabine treatment is promising in older patients with AML, showing encouraging efficacy. Decitabine may therefore be a more suitable treatment than HSCT in fit patients.

An open-label, randomised, Phase III study, led by the European Organisation for the Research and Treatment of Cancer (EORTC) Leukemia Group, included 606 participants over the age of 60. Researchers compared both efficacy and safety of 10-day decitabine alongside conventional 3+7 induction chemotherapy in patients with recently diagnosed AML.

Although induction chemotherapy achieved overall higher complete remission than decitabine (61% versus 48%), the survival level was comparable, with a median overall survival of 15 months (decitabine) and 18 months (induction chemotherapy). After 4 years, 26% of patients in the decitabine cohort, and 30% from the induction chemotherapy arm were alive.

> **"Decitabine treatment demonstrated lower incidences of oral mucositis, febrile neutropenia, platelet reduction, and diarrhoea."**

Researchers discovered that a notable difference between both treatments was the number of Grade 3–5 adverse advents prior to HSCT. Decitabine treatment demonstrated lower incidences of oral mucositis, febrile neutropenia, platelet reduction, and diarrhoea. The study concluded that in older patients with AML, decitabine treatment signified a superior safety profile in comparison with induction chemotherapy, whilst continuing to uphold similar overall survival and rates to treatment with HSCT. ●

Novel CAR-T Cell Therapy for Patients with Relapsed/Refractory Multiple Myeloma

A NOVEL chimeric antigen receptor (CAR)-T cell therapy, which targets B cell maturation antigen (BCMA), has been found a highly effective treatment for patients with relapsed or refractory multiple myeloma.

CAR-T cell therapy is a type of immunotherapy, in which genetically engineered T cells target a specific protein. Since 2017, when it was first approved by the U.S. Food & Drugs Administration (FDA), CAR-T cell therapy has been used consistently as a treatment for blood cancers, including multiple myeloma. Researchers are continuing to discover new cancer cell targets, which allows CAR-T cells to be further customised to suit specific patients.

In a multicentre study (CARTBCMA-HCB-01), researchers evaluated the safety and effectiveness of a novel autologous CAR-T cell product (ARI0002h), which targets BCMA, in patients diagnosed with relapsed and refractory multiple myeloma. Patients were eligible for inclusion in the study provided they had a refractory disease, and had received >2 regimens previously, including an immunomodulatory drug, an anti-cluster of differentiation 38 antibody, and a proteosome inhibitor.

In total, 35 patients with a median age of 61 years, participated in the trial. Of these patients, 30 were eligible to receive a targeted dose of 3×106 CAR+ cells /kg. The production time of CAR-T cells took an average of 11 days, and the success rate was measured at 100%. Ninety percent of this cohort showed complete remission, and very good partial response. The time to first response took an average of 1 month, and 92% of patients in the minimal residual disease (MRD) cohort were MRD-negative in their bone marrow at Day 100 following infusion. Eighty percent of patients survived for 16 months following treatment, and 53% had no further disease progression. In a cohort of 28 eligible patients, 86% received a second dose of CAR+ cells, and 29% showed an improved response following this reinfusion.

> **"Researchers concluded that ARI0002h is an effective treatment for patients with relapsed or refractory multiple myeloma, and the response may be boosted with a second dose."**

The study's outcome measures included the overall response rate, which was defined as at least partial response according to the International Myeloma Working Group (IMWG) criteria; bone marrow MRD in the 3 months following the initial infusion; and the rate of neurological toxicity and/or cytokine release syndrome in the first 30 days. Researchers concluded that ARI0002h is an effective treatment for patients with relapsed/refractory multiple myeloma, and the response may be boosted with a second dose. ●

Achieving Progression-Free Survival in Patients with Chronic Lymphocytic Leukaemia

CHEMOIMMUNOTHERAPY (CIT) is considered the gold standard for treating patients with chronic lymphocytic leukaemia (CLL); however, it is not suitable for all patients due to adverse side effects. Results from the GAIA/CLL 13 study, presented by Barbara Eichhorst, University of Cologne, Germany, at the EHA2022 Congress indicate that there are superior options available.

According to Eichhorst, venetoclax plus obinutuzumab (GV) and GV and ibrutinib (GIV) are better alternatives to CIT as treatment for patients with CLL who are treatment-naïve. By targeting particular molecules that are associated with the development and progression of CLL, new treatments could reduce the collateral damage to healthy cells.

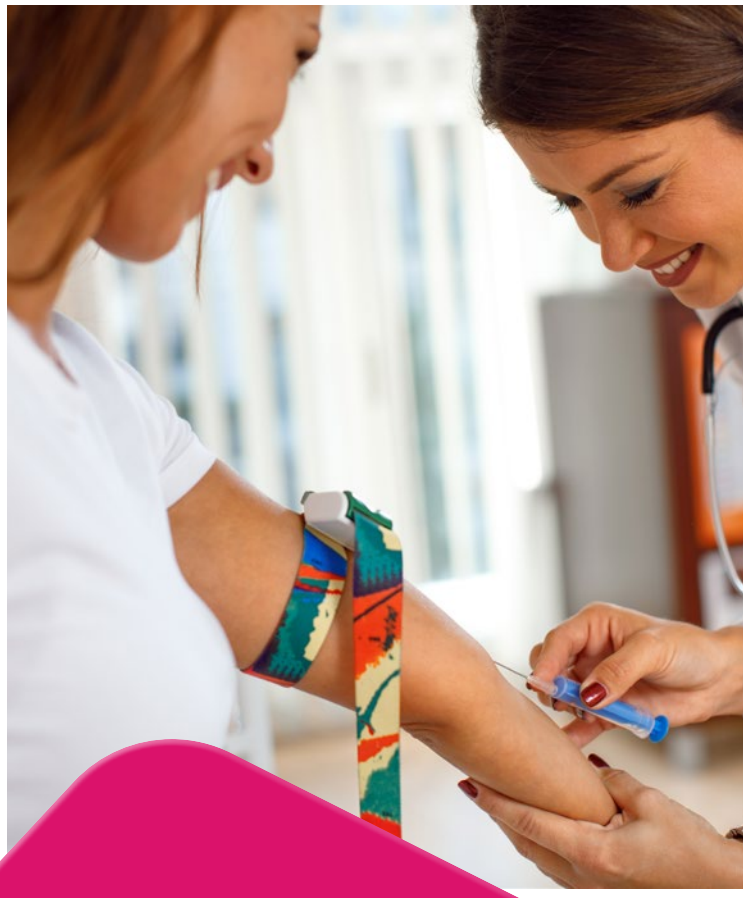
The GAIA/CLL 13 study recruited 926 fit patients with CLL who were treatment-naïve to compare CIT with GV and GIV. In the CIT group, individuals under the age of 65 were treated with a combination of fludarabine, cyclophosphamide, and rituximab. Patients who were older than 65 were treated with bendamustine and rituximab. In the venetoclax group, patients with treated with either a combination of venetoclax and rituximab (RV), GV, or GIV.

An interim analysis of progression-free survival after 61 months proved that treatment with GV and GIV was superior (hazard ratio: 0.32 and 0.42, respectively). However, there was no significant difference in progression-free survival from patients treated with CIT and RV. Overall survival rates were comparable across all groups, with no difference in haematological side effects being observed.

Despite these promising results, Grade 3 and 4 infections were more common in patients treated with GIV (21.2%). Grade 3 and 4 infections occurred less frequently in patients treated with CIT (18.5%), GV (13.2%), and RV (10.5%); however, the rate of secondary neoplasia was increased in patients treated with CIT.

> **"An interim analysis of progression-free survival after 61 months proved that treatment with GV and GIV was superior."**

While the GAIA/CLL 13 study indicates that GV is a superior option to treat patients with CLL than CIT, whether GIV is superior to GV will be tested further. ●



Ribosome Component Overexpression Drives Haematopoietic Stem Cell Exhaustion

RESEARCHERS at the Centro Nacional de Investigaciones Oncólogicas, Madrid, Spain, aimed to analyse and describe how dysregulation of ribosomal components may impact haematopoietic stem cell biology and lead to diseases that cause bone marrow failure. The translation of messenger RNA (mRNA) is a process requiring intricate crosstalk between the nucleoli and the ribosomes. Impairment due to abnormal function or structure of ribosomal components may lead to pathologies, including cancer. The researchers investigated on one such component, hnRNP protein K, a binding protein that processes pre-mRNA in the nucleoli into mature mRNA ready for translation by ribosomes.

The investigators overexpressed the gene *Hnrnpk* in mouse embryonic fibroblasts before exposing them to actinomycin D to trigger nucleolus stress. Confocal microscopy, flow cytometry, and quantitative reserve transcription-PCR were used to assess levels of nuclear stress and investigate underlying molecular mechanisms. Inducible tamoxifen mouse models were used to assess the impact of *Hnrnph* on survival and phenotype.

The results demonstrated that the overexpression of *Hnrnpk* resulted in elevated gene and protein expression of nucleolin, mammalian target of rapamycin, and c-Myc. Furthermore, the cells expressed an increase in global protein synthesis which was inversely correlated to proteasome function. The overexpressed cells showed increased numbers of nucleoli, enlarged total area of nucleoli, and were more likely to display a senescent cell phenotype, all hallmarks of nucleolus stress. The inducible tamoxifen mice models exhibited a reduced lifespan with analysis showing a strong reduction in CD34 cells and B cells, with leukopenia, anaemia, and thrombocytopenia. The shortened lifespan of the mice was primarily due to dysplastic bone marrow and bone marrow failure.

Researcher concluded that this data indicated overexpression of the hnRNP protein K component induced an increase in nucleoli activity through ribosome biogenesis and increased translation followed by cell senescence. This dysregulated phenotype is subsequently linked to bone marrow failure and haematopoietic stem cell exhaustion. ●

"The inducible tamoxifen mice models exhibited a reduced lifespan with analysis showing a strong reduction in cluster of differentiation 34 cells and B cells, with leukopenia, anaemia, and thrombocytopenia."

The Impact of Hormone Therapy on Venous Thromboembolism Risk in Women

Authors: Natasha Meunier-McVey, Editorial Assistant

Citation: 2022;10[1]:16-19. DOI/10.33590/emjhematol/10161940. https://doi.org/10.33590/emjhematol/10161940.

EHA 2022

MILLIONS of women across the world opt for hormone-based therapies for contraception, and as a replacement therapy for relieving symptoms during the menopause. Many of these treatments involve daily ingestion of hormones over extended periods of time. This timely session which took place at this year's European Hematology Association congress 2022 (EHA2022) involved expert discussion and perspectives on the impacts of hormone-associated venous thrombosis (VT) on females, including the effects of different therapies and their progression in recent times. Taking place between 15th–17th June 2022, EHA2022 explored timely content in the field of haematology, both live from Vienna, Austria, and virtually.

MECHANISTIC INSIGHTS INTO HORMONAL THERAPY

Per Morten Sandset, Principal Investigator of Thrombosis and Haemostasis, Oslo University Hospital, Norway, opened this fascinating session with a summary of the indications for hormonal therapy, namely contraception and replacement therapy, and the current types of hormonal therapy available to women. With oestrogen-based therapies and progestin-based therapies primarily offered as the most common forms of hormonal therapies, Sandset highlighted the risks associated with both types, and the progression in the production and dosing of these pharmaceuticals.

Sandset went on to discuss the mechanisms and risks associated with venous thrombosis in the context of hormonal therapy. He presented key angiographic images, including that of an arterial thrombosis of the internal carotid artery that would typically be seen in young women taking oral contraceptives. Sandset highlighted that the risks of developing arterial or venous thrombosis are dependent on the thrombotic threshold: "The haemostatic system must be efficient enough to provide haemostasis in the case of bleeding," which is strongly influenced by age, family history, and factors such as antithrombin deficiency. Oral contraceptives have a major impact on the haemostatic system and coagulation cascade, with a 20–70-year-old woman's risk of VT increasing by 50-fold when taking these hormonal medications.

Sandset presented key studies that have investigated the effects of oestrogen therapies on key haemostatic markers, which demonstrated that even marginal changes in clotting factors and inhibitors leading to an increase in thrombin generation can significantly impact the system, even if prothrombin does not exceed the normal range. Amongst the effects of hormonal therapy on the haemostatic system presented, Sandset

emphasised the impact of these treatments on normalised activated protein C resistance (nAPCsr). Used as a biological marker for the risks of oral contraceptives and post-menopausal hormonal therapy, the data presented displayed the correlation between nAPCsr and the risk of VT. Compared with no combined oral contraceptives, second generation ethinylestradiol treatment led to a medium risk of VT, whereas third generation treatment was associated with a high risk of developing this condition.

CLINICAL RISKS OF VENOUS THROMBOEMBOLISM

A selection of large epidemiological studies highlighted the effects of different hormonal contraception options on the risk of VT; notably, the use of a patch presented with an 8-fold increase in risk compared with non-use. The risk of developing VT in older women undergoing hormone replacement therapy also increased by 8-fold compared with placebo. In terms of continuing hormone therapy alongside anticoagulant therapy to treat occurrence of VT, Sandset remarked the results of a trial, which demonstrated a low risk of VT recurrence with continued therapy.

> **"The haemostatic system must be efficient enough to provide haemostasis in the case of bleeding."**

Sandset presented common mutations that lead to thrombophilia, and discussed whether these should be routinely screened for in women taking combined oral contraceptives. Loss-of-function mutations lead to antithrombin deficiencies, and protein C and S deficiencies, whereas gain-of-function mutations are known to lead to polymorphisms in the prothrombin gene, and the factor V Leiden gene. It was noted that there was a 34-fold increase in the risk of VT in women with specific inherited mutations; however, Sandset explained the lack of benefit to routine

screening for inherited thrombophilia. Key statistics from a study showed that between 10,000 and 100,000 women in the general population would need to undergo screening to prevent one case of VT. A BMI of over 30 was also highlighted as a key risk of VT development from oral contraceptive use, presenting with a 24-fold increase in risk.

PREVENTION AND TREATMENT OF VENOUS THROMBOEMBOLISM IN PREGNANCY

Sabine Eichinger, Associate Professor and Head of Anticoagulation Clinic, Medical University of Vienna, Austria, gave a presentation on VT during pregnancy. The risk of VT is significantly increased throughout pregnancy; however, the highest risk is during the first 6 weeks postpartum, with a 5-fold increase compared with during pregnancy.

Eichinger explained how the risk of VT during pregnancy is increased in the mother entering into a prothrombotic state, influenced by altered haemostasis, vascular injury, and altered rheology. The activation of the haemostatic system leads to increased fibrin generation and increased fibrinolysis due to the surge in various factors. Eichinger presented her findings from a prospective study of healthy females during pregnancy, focusing on levels of the fibrin degradation product, D-dimer. From 12–34 weeks of gestation, the participants' D-dimer levels consistently increased, which Eichinger explained was likely due to the body preparing for childbirth. The risk factors for VT development during pregnancy must also be considered, and those presented included pre-existing VT, a family history of the condition, and pregnancy complications; it was also highlighted that there is an increased risk of VT following a caesarean section.

ANTICOAGULANTS DURING PREGNANCY

The most favourable choice of treatment for VT during pregnancy according to the American Society of Hepatology (ASH) guidelines are low molecular weight heparins (LMWH). The guidelines recommend either once-daily or twice-daily dosing, with observational studies indicating a <1% incidence of VT bleeding with these treatments, and no difference between the two regimens. Eichinger noted however, that the available data in females who are pregnant is very limited.

Although the ASH guidelines do not recommend the routine monitoring of anti–factor Xa levels to guide LMWH dosing in females who are pregnant due to the lack of beneficial evidence, Eichinger explained that she employs this technique in cases of females who are pregnant with extreme body weight, severe renal function impairment, and antithrombin deficiency. In terms of the management of LMWH treatment at the time of delivery, anticoagulant treatment should be halted 24 hours prior to a caesarean section or natural birth, and should only be restarted on a prophylactic dose 6–8 hours following this. It was emphasised that the full therapeutic dose should not be given until 12–24 hours postpartum.

Eichinger concluded the session with information on prophylaxis use in females who are pregnant, both with and without prior VT. The ASH guidelines advise prophylactic treatment both ante- and postpartum in females who are pregnant with prior VT, except in cases of females who have experienced prior provoked VT with non-hormonal risk factors. Several considerations are taken into account when making recommendations in females who are pregnant without prior VT, dependent on the factor causing hereditary thrombophilia, and whether the patient has a past history of VT.

> **"The risk of VT during pregnancy is increased in the mother entering into a prothrombotic state."**

CONCLUSION

Providing expert insight and guidance from guideline recommendations will help both patients and healthcare professionals make informed decisions about prescribing hormone therapies, both during pregnancy and as a form of contraception. ●

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Exploring a Role for Mitapivat in Children with Pyruvate Kinase Deficiency

These posters were presented as part of the European Hematology Association (EHA) 2022 Hybrid Congress, which took place between 9th–12th June 2022 in Vienna, Austria, and virtually.

Presenter:	Rachael Grace Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Harvard Medical School, Massachusetts, USA

Disclosure:	Grace has received research funding from Agios, Dova, and Novartis; and has received consulting services from Agios and Principia.
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Summary

Three posters presented at the European Hematology Association (EHA) 2022 Hybrid Congress focused on the role of mitapivat in the treatment of pyruvate kinase (PK) deficiency, a rare inherited chronic haemolytic anaemia.[1-3] Mitapivat is a first-in-class, oral, allosteric activator of the red blood cell (RBC) PK enzyme, and treats the underlying pathophysiology of PK deficiency.[1-3] Results from a long-term extension study in adults have confirmed the consistency and durability of treatment response achieved with mitapivat, providing the basis for its ongoing evaluation in the treatment of paediatric patients with PK deficiency.[1] Currently, there are no approved pharmacotherapies that target the underlying cause of haemolytic anaemia in children with PK deficiency. To address this global unmet need, recruitment is currently underway into two international Phase III paediatric studies (ACTIVATE-KidsT [NCT05144256][4] and ACTIVATE-Kids [NCT05175105][5]), which will evaluate efficacy and safety of mitapivat treatment in children with PK deficiency who are regularly transfused and not regularly transfused, respectively.[2,3]

Durability of Haemoglobin Response and Reduction in Transfusion Burden is Maintained Over Time in Patients with Pyruvate Kinase Deficiency Treated with Mitapivat in a Long-Term Extension Study

Rachael Grace

PK deficiency is a rare, life-long, hereditary disorder caused by mutations in the *PKLR* gene, which encodes for the RBC-specific PK enzyme.[6,7] Defects in this critical enzyme lead to chronic haemolytic anaemia.[6,7] Patients with PK deficiency are at risk of both acute and long-term disease-related complications, independent of their transfusion needs, including iron overload, pulmonary hypertension, cholelithiasis, and osteoporosis.[8-11] The disease also exerts a substantial negative impact on patients' health-related quality of life.[10]

Mitapivat is an oral allosteric activator of PK that is approved by the U.S. Food and Drug Administration (FDA) for the treatment of haemolytic anaemia in adults with PK deficiency, and has been submitted for regulatory review to the European Medicines Agency (EMA).[12-14] FDA approval was based on positive findings from two global, Phase III, clinical trials (ACTIVATE, placebo controlled [NCT03548220][15] and ACTIVATE-T open label [NCT03559699][16]), both of which met their primary efficacy endpoint.[17,18]

In the ACTIVATE study of patients with PK deficiency who were not regularly transfused, mitapivat demonstrated a significantly higher haemoglobin (Hb) response rate than placebo (40% versus 0%; 2-sided p<0.001, respectively).[17] Improvements in markers of haemolysis and haematopoiesis were also seen, together with an improvement in PK deficiency-specific measures of health-related quality of life.[17]

In the ACTIVATE-T study of patients with PK deficiency who were regularly transfused, 37% of patients (n=10) achieved a reduction in transfusion burden (1-sided p=0.0002, respectively).[18] Mitapivat proved well-tolerated across both Phase III studies, with a consistent safety profile.[17,18]

This poster, by Grace et al.,[1] presented at EHA2022, showcased data from ACTIVATE, ACTIVATE-T, and their long-term extension (LTE) study (NCT03853798).[19] Patients who completed the fixed-dose period in both studies and demonstrated clinical benefit from mitapivat treatment, or were assigned to placebo were eligible to continue in the LTE, where all received mitapivat. The ACTIVATE/LTE analysis assessed duration of Hb response in two cohorts: patients assigned to mitapivat who achieved a Hb response and continued to the LTE (mitapivat-to-mitapivat arm); and patients assigned to placebo who switched to mitapivat in the LTE placebo-to-mitapivat arm) and then met Hb response criteria. The ACTIVATE-T/LTE analysis assessed transfusion response in the LTE, and transfusion-free duration among patients from ACTIVATE-T who achieved transfusion-free status.[1]

In the ACTIVATE/LTE study, patients who were not regularly transfused and randomised to mitapivat showed maintenance of their Hb response for 72 weeks.[1] In total, 13 out of 15 (86.7%) patients who achieved an initial Hb response to mitapivat in ACTIVATE and were evaluable for Hb assessment in LTE sustained those increases in Hb concentration above the response threshold of ≥1.5 g/dL for a period up to 19.5 months.[1] Similarly, six of 17 ACTIVATE patients who had sufficient time in LTE for Hb assessment (35%) who switched from placebo to mitapivat achieved a Hb response which was maintained for the duration of follow-up.[1]

In the ACTIVATE-T/LTE study, transfusion reduction response and extended duration of transfusion-free status was attained in patients who were regularly transfused. Nine patients (33.3%) in the LTE met criteria for a transfusion response. All six patients who were regularly transfused, and who achieved transfusion-free status during treatment with mitapivat in ACTIVATE-T, maintained this status through the LTE for up to 21.9 months.[1]

Collectively, results from the LTE study show the sustained efficacy of mitapivat in improving Hb and reducing transfusion burden in patients with PK deficiency over time.[1] The safety and long-term durability of treatment response with mitapivat support its evaluation in children with PK deficiency.[2,3]

ACTIVATE-KidsT: Mitapivat in Children with Pyruvate Kinase Deficiency Who Are Regularly Transfused

Rachael Grace

In the absence of any approved pharmacotherapy for PK deficiency in children, RBC transfusions remain the mainstay of disease management for children less than 5 years of age.[12,20] Over half (53%) of children with PK deficiency younger than 5 years old require regular transfusions at an average interval of every 5 weeks.[20] Frequent transfusions impose a heavy burden on patients and their families, and can also exacerbate complications such as iron overload.[17] Splenectomy is commonly performed in children aged 5 years or older with PK deficiency in an attempt to alleviate these transfusion needs; however, the procedure itself carries lifelong risks of sepsis and thrombosis, and is only partially effective at improving anaemia.[20,21]

To address the clear unmet need that exists in paediatric patients with PK deficiency who are regularly transfused, recruitment is currently ongoing for ACTIVATE-KidsT, a global Phase III study of mitapivat. In this poster, Grace et al.,[2] presented the study design, key efficacy endpoints, eligible patient population, and geographical locations of this landmark clinical trial.

ACTIVATE-KidsT is an international, Phase III, multicentre, randomised, double-blind, placebo-controlled study that will evaluate the efficacy and safety of mitapivat in children aged 1–<18 years of age with PK deficiency who are regularly transfused. 'Regularly transfused' is defined as undergoing between six and 26 transfusion episodes in the 52-week period prior to providing informed consent for the study.[2] In addition to meeting the study transfusion criteria, patients must have central laboratory genotyping confirming PK deficiency, defined as ≥2 mutant alleles in the *PKLR* gene. Additionally, subjects must have ≥1 missense mutation, and not be homozygous for the *R479H* mutation or have two non-missense mutations. Key exclusion criteria for the ACTIVATE-KidsT trial include patients currently receiving haematopoietic simulating agents, or having undergone prior bone marrow or stem cell transplantation.[2,3]

Figure 1 shows the full study design details for the ACTIVATE-KidsT trial. After an initial 8-week screening period, patients will enter the double-blind phase of the study, consisting of 8 weeks of individualised dose titration, followed by a 24-week fixed-dose period.[2] Patients who complete the double-blind period of ACTIVATE-KidsT will also be eligible to receive ongoing mitapivat therapy for up to 5 years as part of a planned open-label extension.[2]

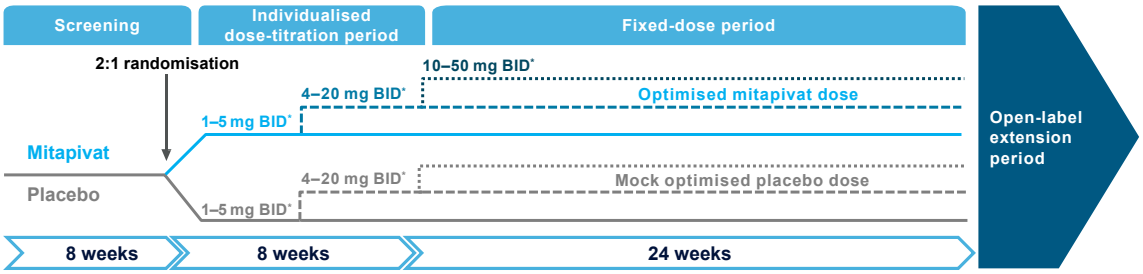
The ACTIVATE-KidsT study aims to enrol 45 children in total, who will be stratified according to their age (1–<6 years; 6–<12 years; 12–<18 years) and splenectomy status (yes or no). A minimum of six patients in each age group will be randomised in a 2:1 ratio to receive either mitapivat or placebo at doses of 1–50 mg twice daily.[2]

Patients will progress through two sequential mitapivat dose increases occurring at approximately 4-week intervals in order to gradually increase Hb levels and maximise efficacy. The specific dose administered at each dose level will depend on the subject's age and weight at the time of randomisation. The drug itself will be administered orally, either as granules or tablets.[2] Paediatric dosing of mitapivat is based on pharmacokinetic modelling and simulation, aimed at reaching similar exposure to adults at the same dose level, adjusted for age and weight.[22]

The primary endpoint of the ACTIVATE-KidsT trial is transfusion reduction response. This is defined as a 33% or greater reduction in the total RBC transfusion volume during the fixed-dose period, normalised by weight and actual study drug duration, compared with the historical transfusion volume standardised by weight and to 24 weeks.[2] The ACTIVATE-KidsT trial will also evaluate secondary and exploratory endpoints of mitapivat efficacy and safety. Secondary endpoints will explore the effect of mitapivat on transfusion-free response, Hb, haemolysis, erythropoiesis, iron metabolism and overload, safety, quality of life, and pharmacokinetics.

ACTIVATE-KidsT will be open at approximately 27 study sites globally including in the USA, Germany, Denmark, the Netherlands, the UK, Spain, Switzerland, Italy, Czechia, and Türkiye (Figure 2).

Figure 1: ACTIVATE-KidsT study design.[2]



Key inclusion criteria

- 1 to <18 years of age with central laboratory confirmation of PK deficiency (presence of ≥2 mutant alleles in the *PKLR* gene, of which ≥1 is a missense mutation)
- 6–26 transfusion episodes in the 52-week period before providing informed consent
- Have complete records of transfusion history for the 52 weeks before informed consent

Key exclusion criteria

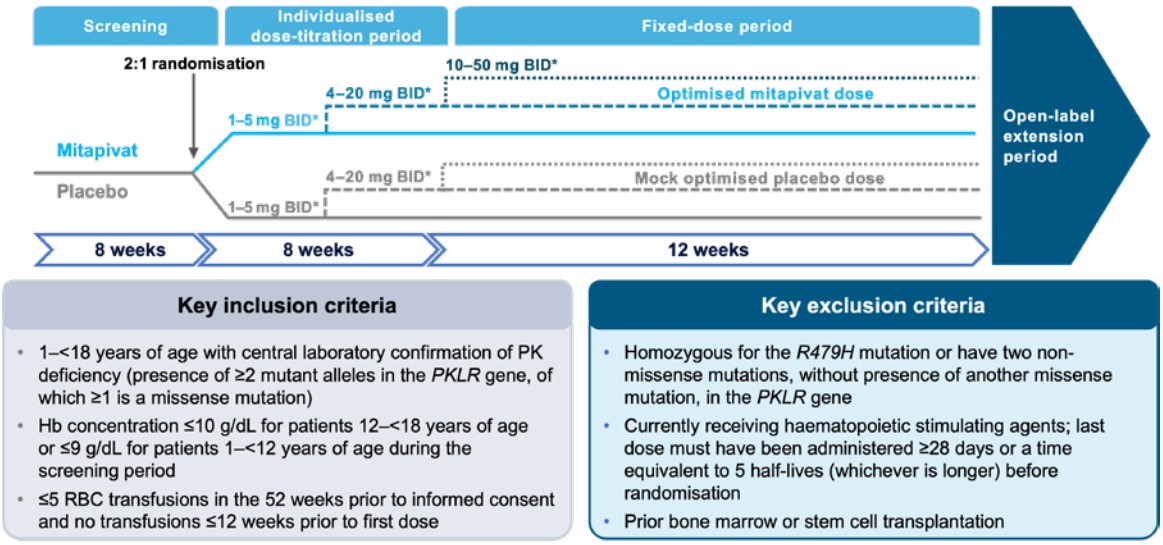
- Homozygous for the *R479H* mutation or have 2 non-missense mutations, without presence of another missense mutation, in the *PKLR* gene
- Currently receiving haematopoietic stimulating agents; last dose must have been administered ≥28 days or a time equivalent to 5 half-lives (whichever is longer) before randomisation
- Prior bone marrow or stem cell transplantation

*Dose of mitapivat or matched placebo based on patient's age and weight.

BID: twice daily; Hb: haemoglobin; PK: pyruvate kinase; RBC: red blood cells.

Figure 2: A) ACTIVATE-KidsT and B) ACTIVATE-Kids Phase III planned study geographic distribution.[2,3]

Figure 3: ACTIVATE-Kids study design.[3]



*Dose of mitapivat or matched placebo based on patient's age and weight.

BID: twice daily; Hb: haemoglobin; PK: pyruvate kinase; RBC: red blood cells.

ACTIVATE-Kids: Mitapivat in Children with Pyruvate Kinase Deficiency Who Are Not Regularly Transfused

Rachael Grace

Children with PK deficiency are affected by the chronic haemolytic anaemia that is the hallmark of the disease and, regardless of transfusion status, they are at risk of developing a spectrum of lifelong disease-related complications.[3] In this patient population, supportive care includes intermittent transfusions and consideration of splenectomy, both of which are associated with the potential for long-term complications.

In this poster, Grace et al.[3] shared details of the ACTIVATE-Kids study, which will evaluate the efficacy and safety of mitapivat in children with PK deficiency who are not regularly transfused. Similar to ACTIVATE-KidsT, ACTIVATE-Kids is a Phase III, global, multicentre, randomised, double-blind, placebo-controlled study targeted at patients aged 1–<18 years of age with two or more *PKLR* mutant alleles, of which at least one is a missense mutation.[3] In order to be eligible to participate in ACTIVATE-Kids, patients much have received no more than five RBC transfusions in the 52 weeks prior to informed consent, and no transfusions in the 12-week period before receiving the first dose of mitapivat.[3] In addition, participants must have a Hb concentration ≤10 g/dL for patients aged 12–<18 years and ≤9 g/dL for patients aged 1–<12 years of age during screening.[3] Patients must have genetic confirmation of PK deficiency and have ≥2 mutant alleles in the *PKLR* gene, of which ≥1 is a missense mutation. Key exclusion criteria for ACTIVATE-Kids are similar to those already described for the ACTIVATE-KidsT trial.[2,3]

The study design for the ACTIVATE-Kids trial is outlined in Figure 3. The screening and individualised dose-titration period are both 8 weeks long, followed by a 12-week fixed-dose period. In total, the double-blind period of ACTIVATE-Kids consists of an 8-week dose-titration period and a 12-week fixed-dose period. ACTIVATE-Kids will be followed by a 5-year open-label period, where all patients will be eligible to receive mitapivat.[3]

ACTIVATE-Kids aims to recruit 30 children with PK deficiency who are not regularly transfused. Patients will be stratified by age (1–<6 years; 6–<12 years; 12–<18 years) and at least six patients in each age group will be randomised

2:1 to treatment with either mitapivat or placebo, dosed at 1–50 mg twice daily. The mitapivat dose-titration and general dosing strategy will be the same as those described for the ACTIVATE-KidsT trial.[2] Dosing will be tailored according to patients' age and weight, and based on pharmacokinetic modelling of adult patients with PK deficiency.[3,20]

The primary endpoint of the ACTIVATE-Kids trial is Hb response defined as an increase of at least 1.5 g/dL in Hb concentration from baseline that is sustained at two or more scheduled assessments at Weeks 12, 16, and 20 in the double-blind period. Patients' Hb concentration at baseline is defined as the average of all available Hb concentrations collected for that patient during the screening period up to administration of the first dose of study drug.[3] Secondary endpoints will also be assessed during the ACTIVATE-Kids trial, and include the effect of mitapivat on haemoglobin, haemolysis, erythropoiesis, iron metabolism and overload, safety, quality of life, and pharmacokinetics.[3]

ACTIVATE-Kids will be a global trial, recruiting patients from approximately 20 study sites in the USA, Canada, Europe, and Israel. Participating centres in Europe are located in Germany, the Netherlands, the UK, France, Spain, Switzerland, and Italy (Figure 2).[3]

Conclusion

PK deficiency is a disease where unmet need remains high in children and therapies targeting the underlying cause of haemolysis are urgently needed. Long-term follow-up of Phase III trials of mitapivat in adults shows a durable Hb improvement and reduced transfusion burden. Mitapivat also proved well-tolerated in these clinical studies, with a consistent safety profile. These results support its evaluation in paediatric patients with PK deficiency. Global site recruitment is currently in progress into two Phase III trials (ACTIVATE-KidsT and ACTIVATE-Kids) of mitapivat treatment in paediatric patients with PK deficiency.

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Zamtocabtagene Autoleucel (MB-CART2019.1): An Investigational CAR-T Cell Product with Tandem Targeting of CD19 and CD20 as a Potential Treatment Option for Patients with Relapsed/ Refractory B Cell Non-Hodgkin Lymphoma

This is a summary of data presented by Peter Borchmann on 10th June 2022 at the European Hematology Association (EHA) 2022 Congress in Vienna, Austria, and online

Presenter:	Peter Borchmann University of Cologne, Germany

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Presentation Summary

Presenting at the European Hematology Association (EHA) 2022 Congress, Peter Borchmann from the University of Cologne, Germany, discussed a novel tandem cluster of differentiation (CD) 19 and CD20 chimeric antigen receptor (CAR)-T therapy for the treatment of patients with relapsed or refractory B cell non-Hodgkin lymphoma. Borchmann presented the 2-year follow up data from DALY 1 trial, which showed that beyond a favourable safety profile, zamtocabtagene autoleucel (MB-CART2019.1) led to durable complete remissions.

Zamtocabtagene Autoleucel

Peter Borchmann

Not all patients with diffuse large B cell lymphoma (DLBCL) achieve durable benefit with approved CD19 CAR-T cell therapies, indicating a significant unmet clinical need.[1-3] Up to 50% of patients relapse after CD19-directed CAR-T cell therapy, possibly due to CD19 antigen escape and T cell exhaustion.[4,5] Targeting one B cell antigen may lead to selective pressure with antigen escape and subsequent relapse,[1,6] suggesting that targeting more than one antigen may improve efficacy by reducing potential downregulation of cell-surface markers and subsequent relapse.

Zamtocabtagene autoleucel (MB-CART2019.1), an investigational medicinal product, is composed of autologous CD4- and CD8-enriched cells, which are transduced with a lentiviral vector encoding the CAR construct for CD20 (Leu16) and CD19 (FMC63) and incorporating a 4-1BB co-stimulatory domain. At the EHA2022 Congress, Borchmann presented the 2-year follow-up data from the Phase I/II trial of zamtocabtagene autoleucel, DALY 1 (NCT03870945).[7,8]

DALY 1 is a first-in-human Phase I/II study conducted to evaluate feasibility, dosage, safety, and toxicity of zamtocabtagene autoleucel-expanded autologous T cells that are genetically modified to express an anti-CD20 and CD19 immunoreceptor. The study population consisted primarily of older patients with relapsed/refractory (R/R) CD20- and CD19-positive aggressive B cell non-Hodgkin lymphoma.

Two dose levels (DL) were tested in the trial. DL1 was 1.0×10^6 CAR-T cells/kg body weight and was allocated to patients with R/R CD20- and CD19-positive B cell non-Hodgkin lymphoma with no curative treatment options. In DL2, 2.5×10^6 CAR-T cells/kg body weight were administered to patients with R/R DLBCL and one prior line of treatment, who were ineligible for high-dose chemotherapy and stem cell transplantation. All patients underwent lymphodepleting chemotherapy using fludarabine and cyclophosphamide and all received an infusion of fresh zamtocabtagene autoleucel 14 days after leukapheresis.

The primary endpoint was the maximum tolerated dose of zamtocabtagene autoleucel, which was defined as the highest dose level at which <33% patients experienced dose-limiting toxicity (DLT) until Day 28 after the infusion of zamtocabtagene autoleucel. Secondary endpoints included adverse events, objective response rate, duration of response, maximum concentration, area under the curve from Day 0 to 28, and the persistence of CAR-T cells assessed by flow cytometry performed during the trial follow-up period.

The trial enrolled 12 patients, of which six were allocated to DL1 and six to DL2. The median age was 72 years (range: 20–78 years), and eight patients were >70 years. The histologies of trial participants distinguished diffuse large B cell lymphoma (n=9), transformed follicular lymphoma (n=2), and mantle cell lymphoma (n=1).

Regarding safety and toxicity, no DLTs were observed, and 2.5×10^6 CAR-T cells/kg body weight is now considered the recommended dose for further trials. No Grade ≥3 cytokine release syndrome (CRS) or neurotoxicity were observed. In addition, haematotoxicity was limited, with no anaemia or thrombocytopenia of Grade ≥3 beyond Day 28, and intermittent neutropenia Grade ≥3 in only two patients beyond Week 8 after treatment.

Turning to efficacy, the objective response rate (complete remission [CR] plus partial remission using the Lugano classification)[9] was 75% (three out of six patients on DL1 and six out of six patients on DL2). CR was achieved in five out of 12 patients (three out of six patients on DL1 and two out of six patients on DL2), according to investigator assessment after PET-CT. All five patients who achieved CR (CR group) had ongoing CR at 12 months, according to PET-CT or CT assessment. At the 2-year follow-up visit, investigator assessment determined that none of the five patients had evidence of relapse. Progression between 2–6 months was observed in the four out of 12 patients who had only a partial response to MB-CART2019.1 as best overall response, as well as in the three out of 12 patients with only stable disease at best overall response.

Immunomonitoring revealed that clinical efficacy corresponded to better CAR-T expansion. All patients with CR had a maximum concentration of ≥460 CAR-T cells/µL, and also a higher area under the curve from Day 0 to 28 as opposed to patients who did not reach CR. Finally, all five patients who achieved CR had detectable CAR-T cells beyond Month 6.

Conclusion

Zamtocabtagene autoleucel (MB-CART2019.1) showed very good safety and the first evidence of promising efficacy in a truly elderly patient cohort. It was successfully manufactured and

infused in all 12 patients, and both DLs were well tolerated, with no DLT. The favourable safety profile comprised no Grade ≥3 CRS events nor neurotoxicity at either DL, leading to the recommended dose of MB-CART2019.1 of 2.5×10^6 CAR-T cells/kg body weight. It was notable that MB-CART2019.1 induced CR in five out of 12 patients. Clinical response was accompanied by higher peak CAR-T cell expansion. Importantly, CRs were durable as all patients who achieved CR had 2-year follow-up visits with no evidence of relapse or need for new anti-lymphoma therapy.

These promising results of zamtocabtagene autoleucel (MB-CART2019.1) in elderly patients with R/R DLBCL represent the rationale for the ongoing randomised Phase II trials, DALY 2-EU (NCT04844866)[10] and DALY 2-USA (NCT04792489).[11] DALY 2-EU is currently enrolling and investigating the superiority of MB-CART2019.1 over conventional immune-chemotherapy in older patients with R/R DLBCL, who are not eligible for high-dose chemotherapy or autologous stem cell transplantation.[10] DALY 2-USA is currently enrolling and investigating MB-CART2019.1 in adults with R/R DLBCL after receiving at least two lines of therapy.[11]

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Abstract Highlights

The following highlights focus on several insightful and innovative abstracts at the European Hematology Association (EHA) 2022 hybrid congress, covering topics such as gene mutations in acute myeloid leukaemia and the use of B cell maturation antigen-targeted chimeric antigen receptor T cells extracted from cord blood in the treatment of patients with multiple myeloma.

Secondary Mutations in Patients with *de Novo* Acute Myeloid Leukaemia

RESEARCHERS have uncovered a number of gene mutations in patients diagnosed with *de novo* acute myeloid leukaemia (AML). Amongst these, a set of mutations such as *SRSF2, ZRSR2, ASXL1, SFB31, STAG2, U2AF1, EZH2*, and *BCOR* have been categorised as secondary AML-type mutations, with a distinct distribution in secondary AML when compared with primary AML.

The aim of the study, carried out jointly by the departments of Haematology, Oncology, and Pathology at the National Taiwan University Hospital, Taipei, Taiwan, and the National Taiwan University Cancer Center, Taipei, Taiwan, was to explore both the clinical significance and prognostic implications of secondary AML-type mutations in patients without non-M3 AML.

The study enrolled 921 patients with *de novo* non-M3 AML, 368 of whom were aged 60 or over. Patients were excluded if they had an antecedent history of haematologic diseases or therapy-related AML. Secondary AML-type mutations were found using targeted next-generation sequencing of 54 myeloid malignancies, which are related to gene mutations.

Researchers found that 243 patients (26.4%) in the ST group had secondary AML-type mutations. This patient group was generally older and, at diagnosis, had lower white blood cell counts, peripheral blast counts, and lactate dehydrogenase levels. Of the patients receiving standard chemotherapy (n=686), those in the ST group had a shorter overall survival rate (median 2.1 years versus not reached; p<0.01) and disease-free survival rate (median 0.4 years versus 0.9 years; p<0.01) with a median follow-up of 4.7 years.

"Secondary AML-type mutations were found using targeted next-generation sequencing of 54 myeloid malignancies, which are related to gene mutations."

Analyses carried out within subgroups discovered that secondary AML-type mutations had impacts on the prognosis of patients, both with regard to overall survival (median years: 5.8 versus 1.5 versus 1.3 for patients with 0, 1, and >2 mutations, respectively), and disease-free survival (median years: 0.9 versus 0.6 versus 0.0 for those with 0, 1, and >2 mutations, respectively). These findings occurred across both younger and older patient groups. Among patients with secondary AML-type mutations, allogeneic haematopoietic stem cell transplantation improved outcomes (median overall survival: 3.0 versus 0.8 years; p<0.01). ●

Acute Myeloid Leukaemia Relapse Following Allogeneic Stem Cell Transplant

A SINGLE institution retrospective study has been carried out by researchers at the Institut Paoli Calmettes, Marseille, France, into relapses of patients with acute myeloid leukaemia (AML) who have received allogeneic stem cell transplant. They focused on a sample of 118 patients from their institution, who relapsed following allogeneic stem cell transplant between January 2009 and December 2019.

Relapse of disease has, in recent years, become the main cause of treatment failure in patients diagnosed with AML, replacing transplant-related mortality. The risk of relapse after allogeneic stem cell transplant is around 30%, but this depends heavily upon both clinical and genomic elements. Due to the variability in disease characteristics, there exists no standard of care for patients, and prognosis is consequently poor; the survival rate after 2 years is reported to be only 20%. In some cases, patients with AML can undergo a first-line treatment of intensive chemotherapy, and then a second-line cellular therapy treatment such as allogeneic stem cell transplant or donor lymphocyte infusion.

In this study, median age was 53. Twenty-two percent of patients had *FLT3* mutations and 53% an adverse genetic risk; 79% had received a transplant; and 21% still had active disease. Forty-five per cent of patients were given an allograft from a related donor; 22% from an unrelated donor; 18% from a haplomismatch related donor; 10% received an allograft from cord blood cells; and 5% from a mismatched unrelated donor.

Researchers found that the median time from allogeneic stem cell transplant to relapse was 4.7 months. Seventeen patients in the group underwent a second round of allogeneic stem cell transplant; 13 of these after intensive salvage, one after non-intensive salvage, and six had active disease. Early transplant mortality following allogeneic stem cell transplant was 25%. The median follow-up of patients alive was 70.2 months (46.3–83.5).

> **"Relapse of disease has, in recent years, become the main cause of treatment failure in patients diagnosed with AML, replacing transplant-related mortality."**

The researchers' data supported the findings of existing studies and confirmed the poor prognosis and outcome of post-transplant relapse in patients with AML. They found that whilst intensive salvage therapy does show a reasonable response rate, subsequent cellular therapy appears to be necessary for long-term disease-free survival. ●

Cord Blood BCMA-CAR-T Cells in Treatment of Multiple Myeloma

RESEARCHERS in China have studied the safety and efficacy of B cell maturation antigen-targeted chimeric antigen receptor (BCMA-CAR)-T cells extracted from cord blood in the treatment of patients with both refractory and relapsed multiple myeloma, the second most common haematologic malignancy worldwide.

The prognosis of patients with multiple myeloma varies. Low-risk patients can survive for more than 10 years with standard care; however, high-risk patients have a prognosis of around 1 year. Whilst CAR-T cell therapy has had promising results in clinical trials, it is not always possible to generate clinically significant amounts of these cells from heavily pre-treated patients and, therefore, it is not a treatment that can be used effectively for every patient.

This study acknowledges that whilst allogeneic CAR-T cell therapy could potentially be used instead, there is a risk of graft-versus-host disease. Cord blood has a good supply of T cells, which have a low immunogenicity, and a relatively low risk for the patient of developing graft-versus-host disease.

Investigators from from the Shaanxi Provincial People's Hospital, Xi'An, China; Shanghai Jiao Tong University, China; and Northwest University, Xi'An, China, have collaborated on a study that incorporates cases recorded between January and December 2021 in Shaanxi Provincial People's Hospital. Cluster of differentiation 3+ T cells were chosen, activated, and modified using lentivirus in order to produce anti-BCMA-CAR-T cells. After expanding for 5–10 days *in vitro*, these cells were then administered intravenously to patients with refractory and relapsed multiple myeloma who had received lymphodepleting chemotherapy treatments 2–3 days previously.

> **"Cord blood has a good supply of T cells, which have a low immunogenicity, and a relatively low risk for the patient of developing graft-versus-host disease."**

Eleven patients were selected for the study (seven male; four female), with a median age of 58 years. Two patients had received previous CAR-T cell therapies and relapsed before enrollment. Seven patients had been given autologous haematopoietic stem cell transplantation. All patients received the average dose of 7.11×106 /kg. CAR-T cells were found to have increased in every patient, with no increase in levels of IL-6, 1L-8, and interferon receptors in peripheral blood 2 weeks after infusion. One patient relapsed after 3 months of follow-up and another patient died from severe pulmonary infection.

The research team concluded that there is a promising safety profile surrounding CAR-T cells derived from cord blood, and the treatment could work effectively for patients who are ineligible for autologous CAR-T cell therapy, as well as preparing them for future treatment regimens. ●

Outcomes and Responses of COVID-19 Vaccine in Patients With Severe Aplastic Anaemia

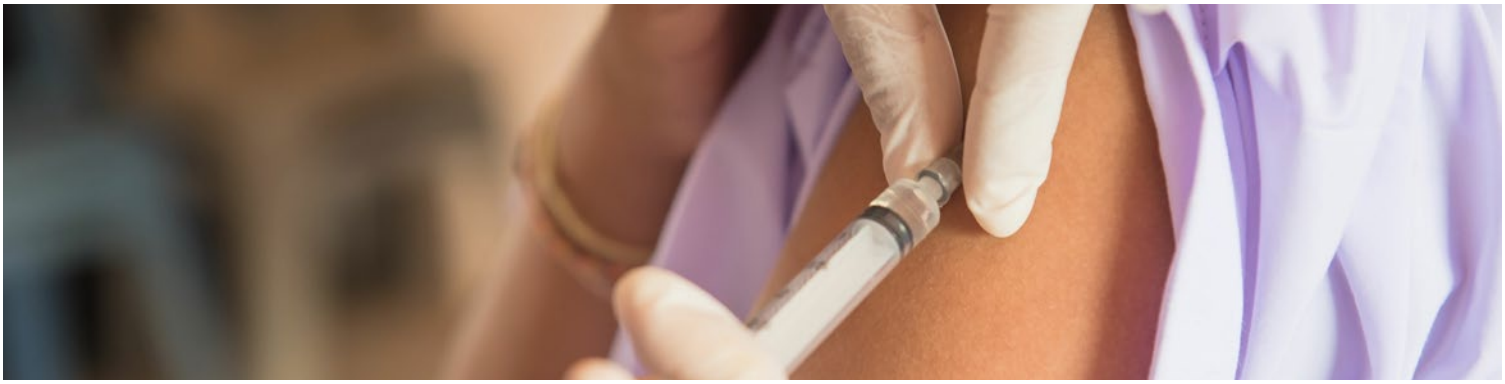
ACCORDING to a study on the COVID-19 vaccine in patients with severe aplastic anaemia (SAA), SAA could result in a temporary decline in blood counts. SAA is a potentially fatal bone marrow failure disorder that presents with pancytopaenia and a hypocellular marrow due to immune-mediated destruction of haematopoietic stem cells. Due to neutropenia and treatment with immunosuppressive therapy (IST) patients are at a higher risk of infection.

The aim of the study was to examine the impact of the severe acute respiratory syndrome coronavirus 2 vaccine on SAA disease status and to establish the humoral and cellular response to vaccine. The researchers analysed the blood samples from 50 patients diagnosed with SAA, involving 29 females and 21 males, with mean age of 42 years (9–78). SAA was managed with IST including horse antithymocyte globulin, cyclosporine, and eltrombopag at the National Institute of Health (NIH). The included participants had received the COVID-19 vaccine between January and November 2021. The SAA disease status during the vaccination time was reported as either response, partial response (PR), and non-response.

The results showed that 94% of the patients did not have changes in the status of the disease after receiving the vaccine. There were 15 patients (30%) receiving cyclosporine as treatment. Progressive or significant decline in blood count, also defined as relapse after receiving vaccine, was reported in 3 cases (6%). The three relapsed patients were deemed weak PR at time of vaccination (platelet count: <50 k/μL) and were 6 months, 3 years, and 4 years from initial IST, respectively. Out of the three patients, two had only received one of the Pfizer (New York City, New York, USA) vaccines and not the second due to a decline in the blood count. The third patient had received the Moderna (Cambridge, Massachusetts, USA) complete set of vaccines and demonstrated a relapse at 4 weeks and a decline in blood counts 6 months before vaccination.

> **"The study concluded that true relapse is rare, but the COVID-19 vaccine could result in temporary decline in blood counts."**

The study concluded that true relapse is rare, but the COVID-19 vaccine could result in temporary decline in blood counts. However, the relapse is more probable in patients who had a blood count decline prior to vaccination. Further research including a risk versus benefit evaluation is needed to confirm COVID-19 vaccination in patients with SAA weak PR to initial therapy. ●



Association Between Vitamin D Levels and Cardiac Iron with Function in Patients with Thalassaemia Major

Researchers from the Fondazione Toscana G. Monasterio, Pisa, Italy, investigated the association between vitamin D (vitD) levels and cardiac iron with function in patients with thalassaemia major (TM). Decreased vitD levels are widely understood to stimulate the expression of transmembrane L-type voltage-dependent calcium channels, which absorb both calcium and iron. However, there is currently little evidence defining the correlation between vitD levels and cardiac iron.

Investigators examined myocardial iron overload in 278 patients with TM pulled from the Extension-Myocardial Iron Overload in Thalassemia Network. They collected further data on left ventricular function parameters using cine images and measured serum 25-hydroxyvitamin D/calcifediol using chemiluminescent immunoassay. Furthermore, vitD supplements were provided to 61.4% of patients.

Results of the investigation demonstrated that vitD levels were deficient in 107 patients (38.5%), insufficient in 96 patients (34.5%), and adequate in 75 patients (27.0%). No significant difference was detected between male and female patients; however, patients with deficient vitD were found to be significantly younger than patients with adequate vitD (36.96±7.64 years compared with 39.63±9.39 years; p=0.042). Pivotally, patients with deficient vitD levels had significantly higher risk for myocardial iron overload than patients with adequate vitD levels (odds ratio: 20.62; 95% confidence interval: 2.67–153.72; p=0.004).

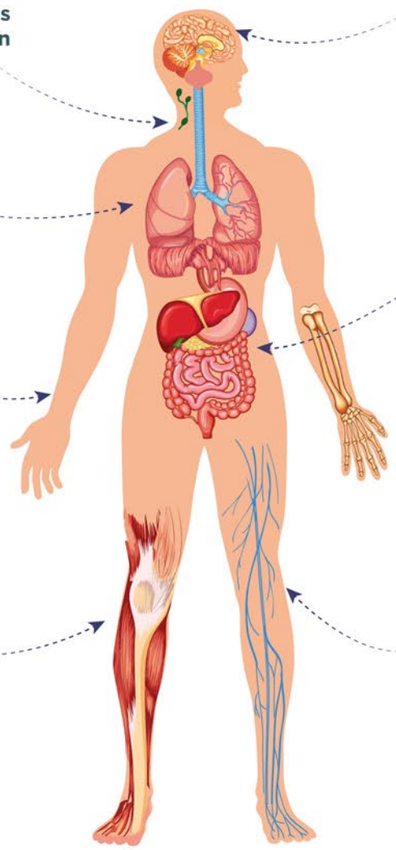
"Regular assessment of vitD levels may contribute to the prevention of both bone disorders and cardiac iron accumulation with its associated dysfunction."

Examining other patient parameters, researchers found significantly higher left ventricular (LV) end-diastolic volume index and LV mass index in patients with deficient compared with patients with normal vitD levels. Furthermore, though no statistical difference was detected a tendency towards LV ejection fraction was found in patients with vitD deficiency that the other groups.

From their results, the research group concluded that in TM vitamin D deficiency was associated with increased risk of cardiac iron overload, and that regular assessment of vitD levels may contribute to the prevention of both bone disorders and cardiac iron accumulation with its associated dysfunction. ●

ACUTE MYELOID LEUKAEMIA (AML)

SYMPTOMS



- Swollen lymph nodes and lumps on skin
- Dizziness
- Headaches
- Breathlessness
- Feeling of fullness in the abdomen
- Bruising or bleeding easily
- Pale Skin
- Pain in bones or joints
- General Weakness
- Weight loss
- High temperature
- Frequent infections
- Fatique

RISK FACTORS

- Older age
- Past cancer treatment
- Smoking
- Workplace exposure to benzene
- Genetic disorders
- Other marrow disorders
- Exposure to high doses of ionising radiation
- Autoimmune conditions

EPIDEMIOLOGY

- 80% — Cases in adults
- 15-20% — Cases in children
- 100,000 — 4.2 new cases per 100,000 of population
- 1% — Rare malignancy, constituting only approximate % of all cancers
- 5 : 3 — Slightly more common in men than women
- 45 — 68 — average age of diagnosis at 68 years

SUB-TYPES

Three main sub-types of AML:

1. Favourable group (Inv(16), T(8;21), t(15,17), NPM mutation, CEBPalpha mutations)

2. Intermediate group (unclassified)

3. Poor risk group (complex karyotype, TP53, Inv(3))

TREATMENTS

Two phases for treatment:

Induction therapy

- Employing a '7+3' regimen of cytarabine by continuous intravenous infusion over 7 days
- Taking the anthracycline drugs daunorubicin or idarubicin via intravenous infusion in a single dose for 3 days

Consolidation (post-remission) therapy

- Additional intensive chemotherapy
- Stem cell transplantation
- Oral chemotherapy
- Novel targets: Fms-like tyrosine kinase-3 inhibitors, isocitrate dehydrogenase inhibitors, and immunotherapies

DIAGNOSIS

- Blood tests
- Bone marrow samples

PROGNOSIS

Prognosis for AML is dependent on:

- **Chromosome abnormalities:** Translocation between chromosomes 8 and 21 or 15 and 17 (favourable); translocation between chromosomes 6 and 9 or 9 and 22 (unfavourable)
- **Gene mutations:** *CEBPA* and *NPM1* gene mutations (favourable) or *TP53*, *RUNX1*, and *ASXL1* gene mutations (unfavourable)
- **Age:** Survival rate: 50% for 5 years for patients >40. 2% for patients >80.
- **White blood cell count:** High white blood cell count is linked to worse prognosis

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Social Impact and Quality of Life of Patients with β-Thalassaemia: A Systematic Review

Editor's Pick

My selection for this issue is the article 'Social Impact and Quality of Life of Patients with β-Thalassemia: A Systematic Review' by Greco and Marino. Quality of life is becoming more and more important in the evaluation of clinical trials, and also by regulatory authorities, particularly in chronic diseases (which can be seen by the U.S. Food and Drug Administration's [FDA] recent position on luspatercept). Therefore, understanding its meaning and limitations is very important.

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Abstract

β-thalassaemia (BT) is a hereditary genetic blood disease caused by a mutation in the gene that encodes the haemoglobin protein. In the most severe forms, BT forces patients to undergo frequent blood transfusions, which has a significant impact on the quality of life. Classified as rare, BT is very common in the Mediterranean area, and is also found in the Middle East, Central Asia, India, South America, and North Africa.

This disease does not currently have a definitive cure, although technological progress and new gene therapies are achieving promising results.

This literature review was conducted with the aim to understand how BT affects patients' lives in various social contexts in which they are involved. The authors also aimed to understand which methods are used for this assessment and the possible social actions that can help in the management of the disease.

Electronic databases, including PubMed, Scopus, and Web of Science, were used to search for the articles. Related article titles were selected and reduced to the abstracts of the relevant articles, after which the selected full articles were reviewed.

The reviewed articles showed consistent agreement in observing that the quality of life of patients with BT is considerably lower compared with the healthy population in terms of physical, emotional, social, and functioning at school. The negative results highlight the significance of the introduction of suitable programmes by healthcare providers, counsellors, and education authorities to provide psychosocial support, and improve academic performance. In addition, genetic counselling and intervention programmes would positively impact the lives of patients with thalassaemia.

Key Points

1. β-thalassaemia (BT) is a chronic disease which affects patients' lives in various social contexts as, in its most severe form, the condition involves blood transfusion dependence.

2.The quality of life of people with BT is considerably poorer compared with the healthy population in terms of physical, emotional, and social aspects, as well as functioning at school.

3. It is essential to try to fill the gaps in the psychological support and social introduction of people with BT through a robust network of programmes, including family therapy, genetic counselling, educational interventions, and intervention programmes, emphasising the importance of spiritual growth, physical activity, and interpersonal relations.

INTRODUCTION

Thalassaemia is a group of hereditary microcytic haemolytic anaemias characterised by a defect in haemoglobin synthesis. β-thalassaemia (BT) is a hereditary disease transmitted by an autosomal recessive manner, characterised by deficiency (β+) or absence (β0) of synthesis of the β-globin chains of haemoglobin.[1]

The name thalassaemia derives from the Greek ‘thàlassa’ (sea) and ‘haîma’ (blood), and it was chosen due to the great distribution of this pathology in the Mediterranean area.[1] BT is a condition of highly variable severity; it ranges from a form called thalassaemia minor, which is mostly asymptomatic, to the most severe form, known as thalassaemia major or Cooley’s disease, a condition that involves blood transfusion dependence (transfusion-dependent thalassaemia [TDT]).

Anaemia constitutes the predominant symptom, and transfusions can range from every 2–4 weeks to once every 2–3 months, depending upon the clinical severity of the disease. Repeated blood transfusion also prevents physical abnormalities associated with the bone marrow hyperactivity, which is responsible for the characteristic skeletal changes seen with thalassaemia.

Lifelong transfusions present several possible adverse effects, which include immunological reactions, development of antibodies to red cell antigens, transmission of infectious agents (hepatitis B and hepatitis C), and the accumulation of iron from the transfused red blood cells.[2]

From an epidemiological point of view, BT, together with other forms of thalassaemia, constitute one of the most widespread genetic disorders in the world. Worldwide, approximately 1.5% of the population, or around 90 million people, are carriers of BT, 400,000 of whom are actually affected.[3] According to Orphanet,[4] the annual incidence at the birth of symptomatic BT is estimated at 1 in 100,000 worldwide and 1 in 10,000 people in Europe.

It mainly occurs in the Mediterranean countries, but is also found in the Middle East, Central

Asia, Southern China, India, South America, and countries alongside the north coast of Africa.[5]

In the world, the Republic of Maldives has the highest incidence of thalassaemia, with an 18% carrier rate of the population. The estimated frequency of BT in Cyprus is up to 16%; Thailand: 1%; Iran: 5–10%; China: 3–8%; and India: 3–4%.[5,6] In Italy, about 7,000 people affected by BT.[1] The Piera Cutino Association affirms that there are about 3 million healthy carriers in Italy and 400,000 in Sicily.[7]

Although BT is relatively rare in the USA, there are an estimated 1.25 million carriers, making up 0.4% of the population. Thalassaemia affects approximately 2,000 patients living in the USA, with 1,000 patients having BT major, but data are largely influenced by factors such as population migration.[8]

Additionally, it is estimated that the number of newborns affected each year by BT in the countries of the Mediterranean Basin will increase from 2,479 in 2020 to 2,899 in 2050, for annual average growth of 0.5% over 30 years.

THE VALUE OF PREVENTION

Given the prevalence and severity of BT and the cost of treatment, the World Health Organization (WHO) recommends a prevention-based approach.[2]

The main strategies adopted by national programmes that have shown success and effectiveness include: national policy on prevention that indicates national approval; control and support; public awareness programmes; a screening programme to identify carriers; genetic counselling services; pre-natal diagnosis as a choice for at-risk couples; pre-implantation diagnosis; and new emerging technologies.[9]

Genetic counselling aims to replace misunderstandings about the causes of genetic disease with correct information, and to increase people's control of their own and their family's health by informing them of the resources available for diagnosis, treatment, and prevention. It helps to integrate psychosocial information impacting the family system and relationships, assisting patients in conveying information about genetic risk to other family members, and providing reliable sources of emotional and social support.[10]

Pregnancy management for females with thalassaemia is more complicated than in females without thalassaemia.[11]

Although the fetal outcomes for pregnancies achieved by parents with thalassaemia are remarkably successful, there are some important factors (such as cardiac impairment, liver dysfunction, and the vertical transmission of viruses) that must be seriously considered before encouraging a female with thalassaemia to embark on pregnancy.[12] Moreover, the highly dynamic state of pregnancy needs higher haemoglobin for better oxygen delivery to the fetus, so females with TDT need transfusions as often as every 2 weeks.[11]

The aim of these programmes is to allow involved couples to make 'informed choices' concerning marriage and reproduction, according to the information provided by the professional offering counselling. The number of married patients and proportion of parents amongst patients with BT could be an index for level of management.[11]

Prevention has proven effective in Mediterranean countries strongly impacted by the disorder that have opted for this approach, among them Cyprus, Greece, and Italy.[13]

A combination of implementable structural and functional strategies should help in improving the detection and management of patients with haemoglobinopathies. WHO guidelines recommend that every country should develop, implement, and mandate participation in its own haemoglobinopathy diagnostic and prevention programmes. This would entail planning studies to understand the patterns of mutation in various regions in the country, and then setting up a comprehensive carrier detection programme.[2]

THE BURDEN OF β-THALASSAEMIA

The serious nature of the disease in its most severe form and its wide diffusion imply a social, psychological, and economic impact on the community and healthcare system.

As in all chronic conditions, patients with BT are more vulnerable to emotional and behavioural problems. BT affects emotional conditions, daily activities, family experiences, and occupational capabilities of patients and their caregivers because of lifelong complicated and burdensome therapeutic protocols.[14]

Several studies have reported the occurrence of psychopathologies in subjects with TDT, including incidences of social withdrawal, somatic complaints, and social externalising. Attention disorders were present, with major depression and anxiety being the most frequently seen psychological disorders.[14,15]

In addition, patients with thalassaemia major also suffer from sleep disorders. Sleep disorders could be a result of the short-time and frequent hospitalisation periods these patients have to go through, together with the symptoms caused by anxiety and depression, which can have an infuence on their sleep quality.[15]

In adult individuals, having thalassaemia represents a burden to their employment and working life. The difficulties experienced range from being discriminated against, having unsupportive colleagues and friends, being inhibited from developing to their full potentials, and getting a lower salary, to being fearful of losing their employment due to their frequent time away from work.[16]

These significant factors add to the economic burden associated with a chronic disease, with implications for both the individual affected and the healthcare system overall.

In fact, together with medication cost, there are extra costs that include medical consultation, laboratory tests, diagnostic tests, cost of preventative treatments, side effects of therapies, and many other indirect costs. Indirect costs include travel expenses, the cost attributable to the loss of productivity by patients or their caregivers, the impairment of wellbeing, and all other related aspects.[17]

This aspect becomes particularly pronounced in developing countries, since significant efforts must be invested in improving the medical care of patients with thalassaemia to prolong and improve quality of life (QoL).[18]

FACTORS INFLUENCING THE SPREAD OF β-THALASSAEMIA

The systematic study of thalassaemias began in 1925, when two paediatricians from the USA, Thomas Cooley and Pearl Lee, presented to the American Pediatric Society (APS) the case of five children who displayed anaemia, an enlarged spleen and liver, low-grade jaundice colouration, and the presence of immature red and white blood cells in the blood.[19]

Other notable clinical features included skull and facial bone enlargement, skin discoloration, and "conspicuous changes in the long bones," which led Cooley and his associates to suppose that the symptoms might be due to a congenital malformation of the haematopoietic tissue.[19]

In addition, by examining several other cases, Cooley realised that patients were frequently of Mediterranean origin (mainly Italians and Greeks); the disease had a strong familiarity (i.e., it was transmitted from parents to children); and bone alterations were often related to particular haematological disorders.[19,20]

Between 1943 and 1946, Ezio Silvestroni and Ida Bianco demonstrated that thalassaemia major was caused by a hereditary anomaly of the red blood cells that appear smaller than normal, a condition called microcythaemia. With wide population studies, they proved that the disease was extremely frequent in Italy, and that it appeared only in individuals with two parents with thalassaemia, while children were born healthy when only one of the parents showed a thalassaemic trait.[19]

Once the genetic origin of the disease was recognised, many wondered about its spread, and why it was found mainly in the Mediterranean area. Several factors have contributed to the global distribution of thalassaemias. These factors include malaria resistance, consanguinity, migration, survival rates, and prevention.

Resistance to Malaria

Worldwide, the distribution of malaria and the common haemoglobinopathies have largely confirmed the close relationship between these two pathologies in populations living in highly

malarious areas. The relationship that binds these so different diseases, thalassaemia being a genetic condition and malaria an infective disease, derives from the fact that the subject with thalassaemia, whether homozygous or heterozygous, is more unlikely to be infected by malaria than a subject who does not have thalassaemia. According to what Haldane[21] affirmed in 1948, thalassaemia, although caused by a genetic defect that in normal environmental conditions is disadvantageous and would be, therefore, suppressed by the genetic selection, has represented instead in an environment afflicted by malaria a notable advantage, and has been able to spread widely. This phenomenon coincidentally facilitated the survival of heterozygous individuals, such as in areas in Italy where malaria was particularly widespread or endemic, including the Po Delta area, Sardinia, Sicily, and Lazio regions.[10,12,20,22]

Consanguinity

Consanguineous marriage is especially common throughout the Eastern Mediterranean, North Africa, and the Indian subcontinent, where 25–70% of unions involve related family members.[23] Religious, cultural, and economic factors are commonly perceived reasons for such marriage. In a 2006 study on consanguineous marriages in Italy, Cavalli-Sforza et al.[24] demonstrated that, in some regions of Southern Italy (Basilicata, Calabria, and Sicily), marriages with blood-related partners amounted to over 40% in the years 1935–1939. Some factors such as altitude, village size, population density, and migration have a marked influence on the overall frequency of consanguineous marriages. Increased migratory movements, the changes in communication, transportation, work availability, improved education, and indeed, also the social contacts that occurred in the 20th century, resulted in a rapid decrease in consanguineous marriages.[25]

Migration

The consistent multi-ethnic migrations of the last decades have considerably changed the epidemiology of haemoglobinopathies. Along with the aforementioned factors, it is also necessary to consider the migratory trends characterising the geographical area of the Mediterranean Basin, which has contributed to the spread of this disease in past centuries up to the present day. In 2017, the global number of refugees reached an all-time high of 25.4 million, including many people from regions where BT is endemic such as Syria, Afghanistan, and Myanmar. In recent years, Italy has accepted many refugees who crossed the Mediterranean Sea, demonstrated by the more than 126,000 applications for asylum submitted in 2017.[26]

Survival Rates

Thalassaemia used to be a paediatric disease, but the median age of patients has now increased in European Mediterranean countries as a result of increased survival and birth rate reduction. Population screening, genetic counselling, and the availability of pre-natal diagnosis have been extremely effective. In Sardinia, for example, the number of children born with thalassaemia major children per year predicted on the basis of the carrier rate, assuming random mating, shows a reduction from 1:250 live births to 1:1,660 in 2009, with effective prevention in 85% of cases.[27] In recent decades, several factors have been shown to improve the survival rate of patients with BT, including implementation of the thalassaemia prevention programmes, increased quality of healthcare services, provision of appropriate treatment, and essential services for these patients.[28] According to a recent study, iron chelation therapy resulted in better overall survival of patients with TDT, especially if it is instituted early and compliance is maintained.[29] Other factors that improved survival included better awareness of BT and its management among healthcare providers and patients, and guidelines and screening for safe processing of blood and blood products.[30]

Prevention

Comprehensive prevention programmes include public awareness and education, genetic counselling, and population and carrier screening, accompanied by pre-natal diagnostics, and pre-implantation diagnosis.[23,26] The establishment of a national registry allows the census of patients affected by BT, together with data on morbidity, mortality, and other needed therapies, and it constitutes a valuable tool for the evaluation of the efficacy or weakness of the current prevention programmes,

and for the planning of prevention and social health interventions.[31]

CURRENT AND INNOVATIVE THERAPIES

Currently available treatments for the management of patients with TDT and non-TDT include blood transfusion, splenectomy, hydroxyurea, iron chelation therapy, and, for a subset of patients, haematopoietic stem cell transplantation.[32]

Since blood transfusion is one of the first and most critical components of the clinical management of TDT, it is essential that blood transfusion services in all countries are strengthened, to ensure the availability of a safe and adequate blood supply for all patients who need regular transfusions.[2]

This issue was severely challenged during the COVID-19 pandemic. The COVID-19 outbreak resulted in the disruption of various aspects of blood supply dynamics. Lockdowns imposed by governments to contain the spread of the virus resulted in reduced movement of individuals, and thus reduced the availability of the blood donors. The fear of acquiring infection during the commute to the blood centre and during the process of blood donation also added to the severely compromised situation. These all led to a sharp fall in the blood collection during initial stages of lockdown, which reduced further as the lockdown progressed.[33]

The WHO has published interim guidance on maintaining blood supply during the COVID-19 pandemic. It has recommended that blood transfusion services must be prepared to move quickly in response to changes in managing the demand for blood and blood products, while mitigating the potential risk to staff and donors from exposure to COVID-19. In the event of anticipated blood shortages, there should be local strategies to increase supply, prioritise use, review the transfusion threshold of red cell transfusions for patients who are stable and low-risk, and maximise use of alternatives for transfusion.[34]

Allogeneic bone marrow transplantation can cure TDT, but less than 20% of eligible patients have a related human leukocyte antigen–matched donor.[35] An alternative therapeutic approach is represented by gene therapy, which is the current subject of several clinical trials globally.[36]

Increases in gene editing efficiency, particularly in repair accuracy, will likely translate into an increasing number of clinical applications using gene-edited autologous haematopoietic stem and progenitor cells.

Recently, a therapy currently tested on patients with BT is based upon clustered regularly interspaced short palindromic repeats (CRISPR), one of the most studied examples of genetic editing techniques.

CRISPRs are short DNA sequences with unique spacer sequences that, along with CRISPR-associated (Cas) proteins, constitute an adaptive immune system in many bacteria and archaea against invading bacteriophages. By using short RNA molecules as a template, Cas makes highly sequences specific cuts in DNA molecules that can be exploited to insert genes, or to precisely modify the nucleotide sequence at the cut site.[35]

The CRISPR-Cas technique presents several advantages: it has been found to be able to modify several genes at once, and it is much more precise in cutting DNA at specific sites, allowing a drastic reduction in off-target cuts.[36]

In addition, it recognises its target sequence via guide RNA molecules, which can be easily and cheaply synthesised. An ordinary molecular biology laboratory can now edit genes or entire genomes of many organisms, as the CRISPR-Cas system does not require sophisticated knowledge or expensive equipment.[37]

Therapeutic applications derived from the CRISPR-Cas technique are many and have grown in recent years. Indeed, the annual number of publications on PubMed that have CRISPR in the title and/or abstract increased from 1,000 in 2010 to more than 5,000 in 2020.

To date, only studies on cells and small animals have provided support for the therapeutic efficiency of employing CRISPR-Cas gene-editing technology to rectify pathological mutations that cause genetic diseases. Successful examples include gene rectification in Duchenne muscular

dystrophy, sickle cell disease, BT, and hereditary tyrosinaemia Type 1.[38]

An experimental therapy based on CRISPR-Cas9, CTX001, is currently being studied as a potential one-time therapy for patients with TDT. The study includes 15 patients with TDT who are currently in follow-up to evaluate the safety and efficacy of the therapy, which is already showing reassuring and promising results.[35]

Luspatercept is the most recently approved agent (in the USA and Europe) for the treatment of adults with TDT.[39] It is a recombinant fusion protein that binds to select transforming growth factor β superfamily ligands and enhances late-stage erythropoiesis.[40] A Phase III, randomised, placebo-controlled trial established the efficacy and safety of Luspatercept in reducing the transfusion burden among patients with TDT. The results of all primary and key secondary efficacy analyses were in favour of Luspatercept over placebo. Furthermore, a greater percentage of patients in the luspatercept group than in the placebo group had reductions in the transfusion burden of at least 33%, or at least 50% from baseline during any 12-week or 24-week interval. Now, a 5-year open-label extension Phase is underway to provide long-term data on the safety of Luspatercept, and its effects on the transfusion burden and iron outcomes.[40]

METHODS

The difficulties related to this pathology, which presents a serious clinical framework in its major form, and the absence of definitive therapies make it a burden at an economic as well as a social level. The latter, in fact, is more difficult to address and assess compared to the economic impact due to the disease. Trying to give an answer to how the disease has an impact on the lives of people affected, the authors have conducted a review of the literature on the subject.

Electronic databases including PubMed, Scopus, and Web of Science were used to search for the articles. Related article titles were selected and reduced to the abstracts of the relevant articles, after which the 14 selected full articles were reviewed. Searches for literature on the topic were carried out using these electronic databases and also integrated with a free search on web-based search engines.

These databases were chosen based on the usage of previous similar studies. To capture the wide array of studies that may be relevant to this topic, the authors did not pre-define the study designs of included studies.

All types of study design, such as qualitative and quantitative studies, were included in the search. The selected years range of the publications' search was limited to studies from the year 2010 to the date of writing, because of the fast-paced field of innovations of genetic therapies for the treatment of BT driving attention to this disease, and the resulting most current publications on the topic. In addition, the research focused on the contribution of articles in both Italian and English languages (both being known by the authors). Geographical location limitations were not applied.

Keywords including: 'beta thalassemia', 'beta thalassemia major', and 'transfusion-dependent thalassemia', combined with the terms 'social impact' or 'social burden', were used to achieve relevant studies. A search was completed using AND and OR to combine the results that were found based on each keyword.

The exclusion criteria regarding other works concerned, publications written in languages other than English and Italian, PhD theses, grey literature, and reports. The search resulted in 14 relevant articles that allowed for a discussion of the meaning of social impact of BT, and the possible solution aimed at better advocacy and awareness of this disease.

A total of 79 article titles related to the topic came up in the search. From these titles, 57 studies, which were more closely related to the purpose of the review, were shortlisted and their abstracts were screened. From this, 21 studies were eligible for full-text screening. After thoroughly reading the articles and excluding those that did not directly address the significance and an assessment of the social impact of BT, the final number of articles included in the review was 14. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram below (Figure 1) lays out these procedures in more detail.[41]

Table 1 shows the selected papers, indicating the key words, main findings, and the authors' geographical location.

RESULTS

The results of the review show similar outcomes about the psychological and social burden patients face. It is interesting to remark upon the geographical area of origin of the authors of the studies proposed here, since most are areas where there is a relatively higher prevalence of patients with BT. This consequently allows authors to design studies on the subject, compared with those in other realities that are geographically further away, or that do not experience a similar prevalence of the disease. The limited geographical distribution of BT, along with its rarity, affects the number of studies published on the social impact of the condition, as it limits the number of patients that can be enrolled in studies.

The results of this review show that 78.5% of the selected studies use health-related QoL (HRQoL) as a method of assessing the social impact of BT. HRQoL is a multidimensional concept that includes three broad domains (physical, psychological, and social functioning), which may be affected by an illness and/or its treatment. QoL measurements are increasingly considered important when evaluating disease progression and treatment.[55]

The use of questionnaires and interviews for the assessment of the social impact of BT were found in the studies reported in the review. The WHO Quality of Life questionnaire in its abbreviated version (WHOQOL-BREF) was found to be used in two studies; one study used the Transfusion-dependent QoL questionnaire (TranQoL); five studies used the Paediatric Quality of Life Inventory (PedsQL) 4.0 measurement model; one study used the Thalassaemia Life Index (ThALI); three studies used questionnaires and interviews approved by the ethics committee of the referring institution where the study was conducted.

The self-reported WHOQOL-BREF questionnaire is a short version of the WHO Quality of Life 100 (WHOQOL-100) questionnaire. The WHOQOL-BREF was developed to provide a quick assessment tool for QoL, and it assesses the individuals' perceptions of their position in life in the context of the culture and value system in which they live, and in relation to their goals, expectations, standards, and concerns.[52]

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

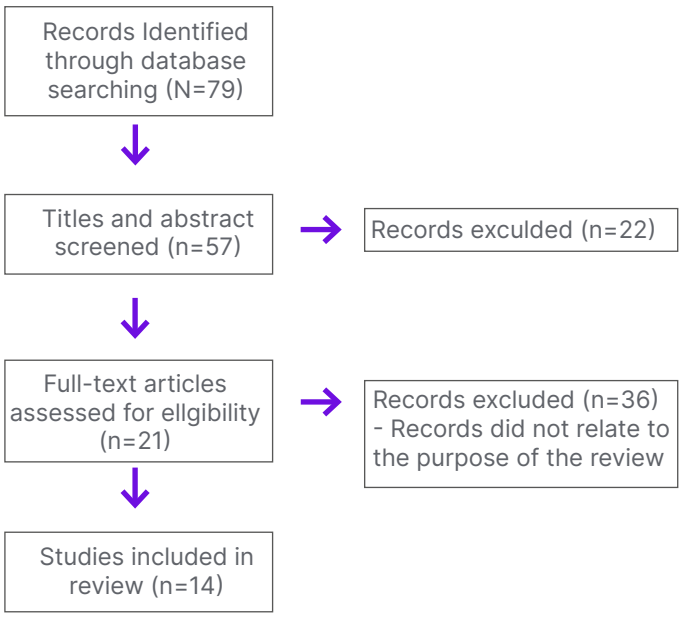

Table 1: Reviewed papers.

Author	Year	Type of study	Authors' geographical location	Keywords	Main findings
Jaffar N et al.[42]	2021	Review article	Pakistan	BT, thalassaemia screening, premarital screening, consanguineous marriage, social impact	Various sociocultural factors, including social stigma faced by families, while breaking off a planned marriage, different ethnicities, low financial status, poor accessibility of programmes, and other various perceived barriers
Kantaris X et al.[43]	2020	Original research article	UK	BT major, QoL	Links exist between the burdensome treatment of BT[1] and increased psychosocial problems, which in turn can lead to poor adherence and in some cases death
Ismail DK et al.[44]	2018	Original research article	Egypt	BT major, QoL, children	Thalassaemia as a chronic disease has a negative impact on HRQoL[2] in terms of physical, emotional, and social functioning, and functioning at school when compared with healthy age-matched children Intervention programmes emphasising spiritual growth, physical activity, and interpersonal relations are necessary for children with thalassaemia
Chen C et al.[45]	2020	Original research article	Iran	Thalassaemia major, QoL, PedsQL	Physical and social aspects and psychological features of Iranian patients with BT major were lower than normal counterparts TDT[3] patients are believed to drop out of school more often, due to recurrently missing school to keep to hospital schedules
Clarke SA et al.[46]	2010	Original research article	UK	Financial impact, HRQoL, thalassaemia major	Poorer child HRQoL was associated with lower socio-economic status, greater travel distance to treatment centres, and greater family financial concerns
Hakeem GLA et al.[47]	2018	Original research article	Egypt	BT major, QoL	Mean physical, emotional, social, school performance, psychological, and total scores were significantly decreased compared with control group
Mevada ST et al.[48]	2016	Original research article	Oman	Children, HRQoL, Oman, PedsQL, thalassaemia major	HRQoL serves as an important domain for children's perception of the disease on physical and psychosocial health functions The low ratings for physical health and functioning at school highlight the significance of introduction of suitable programmes in Oman by healthcare providers, counsellors, and school authorities to provide psychosocial support, and improve academic performance
Arian M et al.[49]	2021	Original research article	Iran	Barriers, BT major, caregiver, HRQoL, qualitative research	Age increase among patients with thalassaemia is associated with increased physical, psychological, and social complications and treatment costs that lead to a reduced HRQoL By increasing age, it is necessary to take measures for employment, education, and marriage of patients with thalassaemia major
Nagiria VRR et al.[50]	2021	Original research article	Papua New Guinea, Australia	QoL, thalassaemia	Children with thalassaemia share many needs with other children with chronic illness, including access to basic specialist services and need for holistic care that promotes optimal growth, development, and QoL Parents of children with thalassaemia in Papua New Guinea are often under financial and social stress to provide the best possible life for their children

Table 1 contined.

Author	Year	Type of study	Authors' geographical location	Keywords	Main findings
Ishfaq K et al.[51]	2016	Original research article	Pakistan	Psychosocial, economic, impact, thalassaemia major, patients, families	The vast majority of parents were facing sociopsychological and financial problems due to the chronic disease Psychosocial health had a comparatively lower score than physical health. The poor psychological score could be explained because of negative feelings, poor self-esteem, and body image
Ajij M et al.[52]	2015	Original research article	India	Adolescent, TDT, QoL	The adolescent with TDT had a poor QoL compared the QoL of their unaffected siblings and healthy unrelated controls
Yasmeen H, Hasnain S[53]	2018	Original research article	Pakistan	BT major, QoL, (TranQoL)	The lowest QoL[4] score was observed in the functioning at school domain; this could be related to insufficient energy, followed by frequent absenteeism from school Paediatric psychiatric services, as well as transfusion and counselling facilities, must be provided for covering psychological aspects of the disease
Foong WC et al.[16]	2022	Original research article	Malaysia	Thalassaemia, QoL, healthy days, employment	Some adults with TDT perceived themselves to be facing more life disruption in a rather non-supportive community, and believe that health services do not meet their needs Having a good income may lead to an increased QoL in physical health, social health, and environmental health
Tuysuz G, Funda T.[54]	2017	Original research article	Turkey	Thalassaemia, QoL, blood component transfusion	Patients with TDT and their parents reported all HRQoL subdomains lower than age-, sex-, and education-matched healthy peers To avoid the school absences of these patients, thalassaemia clinics should reorganise their schedules for blood transfusions on weekends or at night for schoolchildren and help them to overcome this problem

BT: β-thalassaemia; HRQoL: health-related quality of life; QoL: quality of life; PedsQL: paediatric quality of life inventory; TDT: transfusion-dependent β-thalassaemia; TranQoL: Transfusion-dependent quality of life questionnaire.

TranQoL is the first disease-specific instrument that measures HRQoL in patients with TDT. It has four versions: a child self-report; an adult self-report; a parent self-report (measuring the impact of the disease on the parent); and a parent proxy-report (measuring the child's QoL). The adult and parent self-report questionnaires include a fifth category on sexual activity, which represents only one item.[56]

PedsQL 4.0 measures the essential core domains for paediatric HRQoL. It encompasses the essential core domains for paediatric HRQoL measurement, which are physical functioning, emotional functioning, social functioning, and functioning at school. It consists of appropriate forms for ages 2–4, 5–7, 8–12, and 13–18 years.[44,54]

ThALI addresses the multidimensionality of QoL, and encompasses different items such as general physical health, coping, body image, appearance and confidence, social relationships, and autonomy.[43]

If semi-structured interviews and questionnaires are chosen as a method of assessing the social impact of BT, they must be validated by the

ethics committee responsible for the centre in which the study is being conducted, in order to protect the rights, dignity, and integrity of the patients involved, and to adapt the study protocol to meet national standards and guidelines.[49]

HRQoL in children with chronic diseases can be adversely affected as a result of hospital appointments, restricted activities, and general worries.[44,55]

The results indicate consistent agreement in observing that the health and social scores obtained from the various investigations carried out on patients with BT are considerably lower compared with the healthy population. The challenges faced by these patients affect all aspects of their lives economically, physically, socially, and educationally.

The lowest scores, associated with a poorer QoL in patients with BT, are found in the domain of physical and psychological functioning,[45,49,52,54] together with a lower score observed in the functioning at school domain that could be related to insufficient energy followed by frequent absenteeism from school, which had a negative impact on QoL.[44,47,48,53]

Outcomes may also vary depending on a patient's family's economic background and geographical location. In middle- to low-income countries, in addition to economic aspects, religious factors and social stigma also play a role in lowering the level of QoL.[16]

DISCUSSION AND CONCLUSIONS

BT is a rare genetic disease that currently lacks a definitive cure. In its most severe form, BT major, the disease involves frequent lifelong blood transfusions and other complementary therapies that greatly affect patients' lives economically, psychologically, and socially.

The rare nature of the disease hinders the research for a definitive cure, despite recent technological advances and promising results from ongoing trials.[35,40]

A crucial contribution is provided by prevention programmes such as population screening, parental education, pre-natal diagnosis, and genetic counselling,[51] which support raising awareness of the severity and complications of the disease and have been successfully implemented in several disease-prone areas worldwide.[9]

This review herein highlights how the social dimension of patients with TDT is very neglected in studies on the disease, both because as a rare disease its prevalence is low and, therefore, it is difficult to include patients in this type of study, and because the concept of social impact is difficult to analyse and evaluate.

Most of the studies have calculated the social impact of BT using the HRQoL. The QoL of people with BT resulted, in all domains considered, lower than healthy people representing the control group. As a chronic disease, BT has a negative impact on HRQoL in terms of physical, emotional, and social functioning, and functioning at school. This highlights the significance of the introduction of suitable programmes by healthcare providers, counsellors, and school authorities to provide psychosocial support and improve cademic performance.[48]

It is essential to address these outcomes and try to fill the gaps in the psychological support and social introduction of these patients, a goal that can be achieved with a robust network of prevention programmes.

Psychosocial support and family therapy are considered as essential aspects of care management to promote HRQOL in patients with chronic disease. Promoting community knowledge and planning for the presence of these patients in the community should be included in the healthcare policies for these patients.[49]

Educatory intervention could help to improve educational levels in patients with BT, and positively affect the social functioning domain.[45] This concern needs to be reviewed by health providers, families, and educational services.

Moreover, as the timing of screening is an important determinant in the success of screening programmes, it is recommended that the test should be performed at an early

stage (prior to engagement), when it is easier for people to make a decision about their marriage, and their desire for parenthood. For this purpose, health education needs to be aimed at adolescents to change their opinion regarding genetic counselling and ensure that this educational process becomes properly structured and effective in society.[42]

Parallel with age increase, it is necessary to plan for patients' presence in society, and specific measures should be taken for employment, education, and marriage of patients with thalassaemia major.[49,57,58] Intervention programmes emphasising spiritual growth, physical activity, and interpersonal relations would have a significant impact on patients with thalassaemia.

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Von Willebrand Disease-Associated Angiodysplasia: Presentation of a Paediatric Case

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Abstract

Von Willebrand disease (VWD) is a bleeding disorder, resulting from a quantitative or qualitative defect in von Willebrand factor (VWF). A regulatory role for VWF in angiogenesis was postulated upon the clinical observation that qualitative or quantitative VWF defects are associated with the frequent occurrence of neoangiogenesis, particularly in the gastrointestinal (GI) tract. Vascular malformations of the GI tract are a cause of digestive bleeding in the form of either acute or chronic haemorrhage and represent a heterogeneous group of lesions, including angiodysplasias and telangiectasias. The management of these patients is challenging due to recurrent and severe episodes of GI bleeding. The mainstay of treatment of angiodysplasia is replacement therapy when this abnormality causes GI bleeding in patients with congenital VWD. When bleeding episodes recur frequently, regular prophylaxis should be implemented, leading to an acceptable degree of prevention of bleeding. The authors had a difficult experience in a 14-year-old adolescent with Type 3 VWD, who had presented with extremely serious recurrent bleeding secondary to duodenal angiodyplasia.

Key Points

1. Gastrointestinal (GI) bleeding from angiodysplasia is a well-known complication of Von Willebrand disease (VWD). While the aetiology of duodenal angiodysplasia is still not clear, it may be a congenital process with increasing incidence as age progresses due to VWF driving the formation of Weibel Palade bodies.

2. The diagnosis and treatment of recurring gastrointestinal (GI) bleeding in Von Willebrand disease is challenging, and associated with significant morbidity, as demonstrated in this case of a 14-year-old with Type 3 VWD, who presented with recurrent bleeding secondary to duodenal angiodyplasia.

3. While acute management of GI bleeding has been successful with Von Willebrand factor replacement therapy, prophylaxis has been less effective for preventing recurrent GI bleeding. Surgical intervention may be necessary in extreme cases, with excision of the culprit lesion and anastomosis.

INTRODUCTION

Von Willebrand disease (VWD) was first described in 1926 by Erik von Willebrand when he cared for a family member with a severe mucocutaneous bleeding problem.[1] Type 3 VWD is inherited in an autosomal recessive fashion, and is the least common (0.5–4 per million in developed countries) and most severe form of the disease.[2,3] Vascular malformations have been documented in patients with VWD since the 1960s, when Armand Quick first reported the presence of dilated blood vessels or telangiectasias in the noses of several patients.[4] This association between angiodysplasia and gastrointestinal (GI) bleeding in patients with VWD was first reported in 1976 by Ramsay et al.,[5] when they described GI vascular dysplasia as a cause of persistently recurring melena in two patients with VWD. Angiodysplasia is most frequently located in the colon, but can also occur in the small bowel and upper GI tract.[6,7] Aggravation to these vessels leads to severe, intractable bleeding that often results in anaemia, hospitalisation for transfusion of packed red blood cells, and a significant decrease in quality of life.[8] However, most of these angiodysplastic lesions will never bleed.[6]

The authors report the case of a 14-year-old male with Type 3 VWD and previous hospital admissions for severe anaemia with no visible blood loss.

Material and Methods

A 14-year-old male, carrier of Type 3 VWD, with a history of surgery for Hirschprung's disease, wearing an ileostomy, was admitted for treatment of several episodes of melena. On admission, the patient was found in average general condition with intense mucocutaneous pallor, with inspection of the ileostomy pouch showing red blood in the pouch approaching 200 cc, and tachycardia at 120 beats/min. The patient would have been transfused several times at the main place of residence.

Results

Several hospitalisations had occurred before at the paediatric hospital of his chief place of residence, where the teenager had benefited from the transfusion of several red blood cells (20 AU total) and substitution in Von Willebrand factor (VWF) without any origin of bleeding able to be identified.

First Hospitalisation in Paediatric Hospital

The patient was readmitted with complaints of fatigue and an haemoglobin level of 4 g/L. Examination of the ileostomy pocket visualised melena-type bleeding. During this admission, the patient was again treated with tranexamic acid, and with transfusion of red blood cells with replacement in VWF. A digestive endoscopy found a DIII seat of a flat relief lesion of 12 mm with sheet bleeding. An injection of 10 cc of serum with adrenaline, followed by the establishment of two clips, allowed the immediate stop of the bleeding.

Second Hospitalisation in Paediatric Hospital

The patient was readmitted with the same problem. Again, stabilisation occurred. The upper GI endoscopy had made it possible to find at the level of the fundus of the stomach a vascular ectasia with a detached adherent clot. After washing with argon and placement of a haemostatic clip, there was also at the level of the D3 a sessile formation of 15 mm in diameter, major axis seat of two clips in place with visualisation of sheet bleeding at the level of the base. An injection of adrenalised serum was performed with placement of three haemostatic clips, which made it possible to control the bleeding.

Third Hospitalisation in Belfort Hospital

Because of the persistent bleeding without an obvious focus, the patient was transferred to the authors' hospital, at 4 g/dL. The authors proceeded to a transfusion packed with red blood cells, with injection of tranexamic acid and substitution by concentrated Willebrand factor (Wilfactin) at a dose of 40 IU/kg every 6 hours. Another endoscopy had been performed, finding at the level of the third part of duodenum D3 a flat relief lesion of 12 mm, with a surface layer with clips in place. An injection of 8 cc of serum with adrenaline followed by the release of two clips. Haemostasis was achieved. Faced with these failures in endoscopic treatment, and given the seriousness of the clinical

Figure 1: Location of the jejunal lesion.

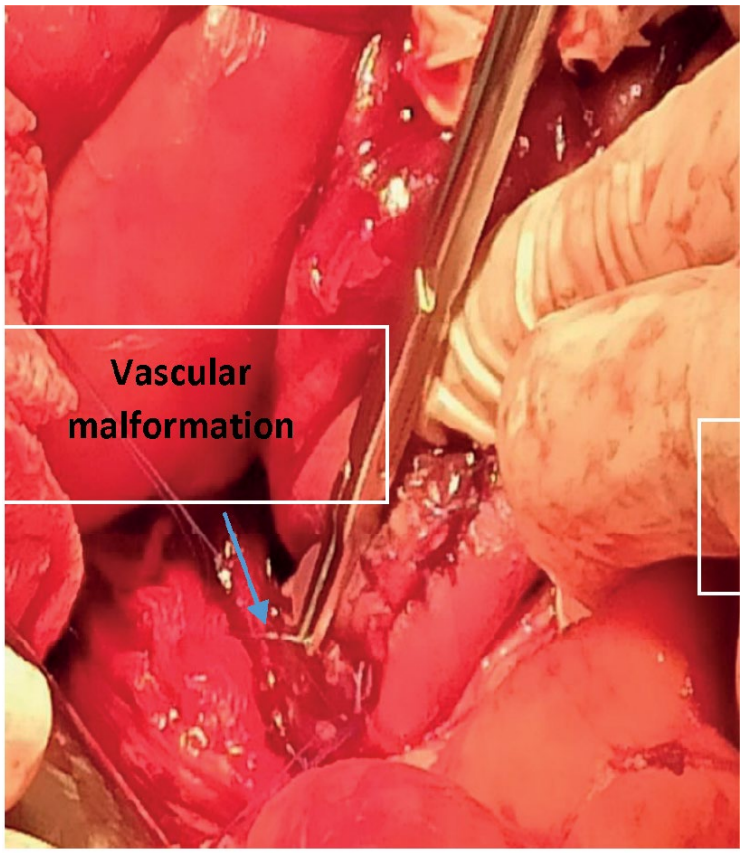
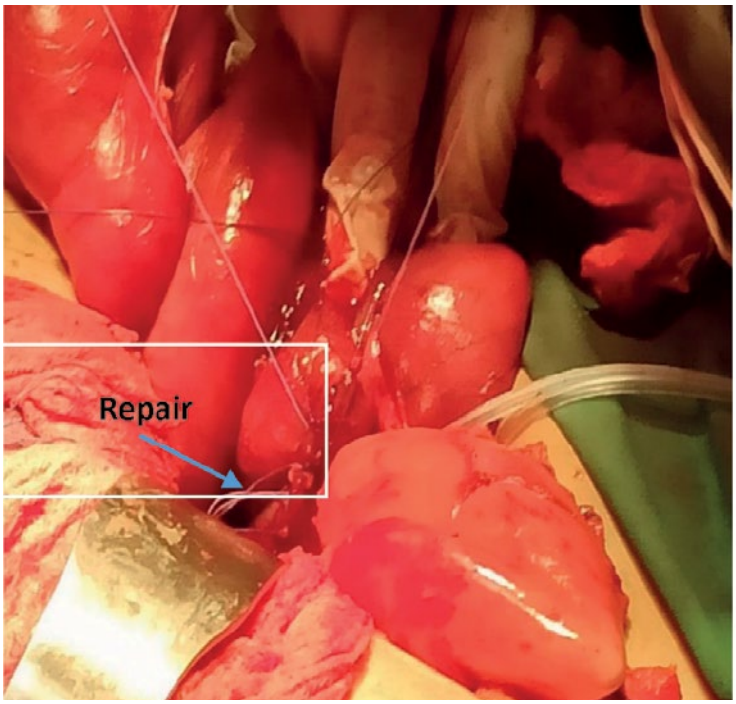


Figure 2: Resection anastomose.



symptoms, the authors decided, along with the paediatric surgery team, to operate on the patient. Chirurgical treatment was carried out with a digestive endoscopy in order to locate the bleeding. This was very laborious and lasted 10 hours, given the pathology itself and the current episode (Figures 1 and 2).

The digestive endoscopy had made it possible to visualise a jejunal duodenum mucous seat due to vascular changes with diffuse inflammatory phenomena. A jejunal resection of 4 cm was carried out, and the part was sent for anatomopathological study. The microscopic study had shown an erosion of the mucous membrane by blood vessels; this mucosa and the submucosa are dilated, and sometimes dystrophic, with large haemorrhagic areas. This aspect is suggestive of vascular angiodysplasia. The postoperative follow-up was good, with a substitution in VWF in per postoperatively for 12 days, associated with tranxenamic acid.

The patient was discharged after 4 weeks of hospitalisation. They have not had any more bleeding after a follow-up of 10 months.

DISCUSSION

The most common clinical manifestations of VWD include epistaxis, bruising, haematomas, and menorrhagia.[9] GI bleeding from angiodysplasia is a well-known complication of VWD.[9,10] In endothelial cells, VWF is constitutively synthesised and stored in Weibel Palade bodies 3.[11,12] While the aetiology of duodenal angiodysplasia is still not clear, some theories were postulated to explain its pathogenesis in the view of its similarity with colonic angiodysplasia. Some considered angiodysplasia to be a congenital process in patients under 20 years old, with increased incidence as age advances, which may be attributed to VWF driving the formation of Weibel Palade bodies, the endothelial storage organelles that contain multiple proteins, including the angiogenesis regulator angiopoietin-2 (Ang-2).

Ang-2 is part of the Angiopoietins/Tie-2 pathway, a crucial system regulating vascular homeostasis and angiogenesis-89. Ang-2 has been shown to destabilise blood vessels and synergise with vascular endothelial growth factor to promote angiogenesis.[14,15] VWF expression has been used extensively to quantify angiogenesis in a variety of tumours.[16,17] However, VWF endothelial expression itself may be regulated in tumour endothelium. Authors reported up regulation of VWF expression by angiogenic factors: vascular endothelial growth factor and fibroblast growth factor 2,[18] which are highly present in the tumour microenvironment. In its many interactions with an ever-growing list of molecules, VWF has come to be known as much more than a haemostatic protein.[19] Angiodysplasia occurs most commonly in middle-age or elderly patients in the cecum and ascending colon, but also throughout the whole colon, small intestine, and stomach.[10] The diagnosis and treatment of recurring GI bleeding in VWD is challenging, and associated with significant morbidity.[20-22] Angiodysplasia is usually detected at endoscopy stage to evaluate GI bleeding but, in some cases, radiographic imaging or surgery may be required for detection.[23,24]

A number of alternative therapeutic measures have been attempted in the last few years for the management of recurrent GI bleeding in VWD.[25] While acute management of GI bleeding has been successful with VWF replacement therapy, prophylaxis has been less effective for preventing recurrent GI bleeding.[21,26]

This patient had benefited from an endoscopic procedure with placement of clips with a replacement by Wilfactin and tranexamic, but after a short response time, this ended in failure. After several hospitalisations in a dramatic picture associating profuse bleeding and deglobulinisation, the authors opted for a surgical cure with excision of the lesion and anastomosis, which seems to have given in the authors' patient with a follow-up of 10 months. Antifibrinolytic amino acids, such as tranexamic and epsilon aminocaproic acid, platelet concentrates, and combined oestrogen-progestogen drugs may be co-administered as adjuvants.[27]

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Atorvastatin, Aspirin, and Hydroxyurea for an Effective and Low-Cost Treatment in High-Risk Polycythaemia Vera

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Abstract

Introduction: Polycythaemia vera (PV) treatment focuses on preventing thrombotic events and delaying transformation to myelofibrosis or leukaemia. According to risk stratification, low-risk patients require therapeutic phlebotomy combined with acetylsalicylic acid, whilst the treatment of high-risk patients with PV relies on cytoreductive therapies, employing hydroxyurea (HU), ruxolitinib, or interferons. However, in low- and middle-income countries, the availability and cost of these drugs poses a challenge in treating high-risk patients, so optimising existing resources is required.

Method: A prospective longitudinal study aimed to investigate the combination of atorvastatin (ATV), aspirin, and low-dose HU as a therapeutic strategy to treat PV in high-risk patients. The study evaluated the effect of statins on erythroid colony proliferation in vitro, as well as the applicability of ATV (20 mg/day), acetylsalicylic acid (100 mg/day), and hydroxyurea (500 mg/day) in high-risk patients with PV from La Paz, Bolivia, residing at 3,600 metres above sea level.

Results: Simvastatin (3.5 µm) inhibited UKE-1 cell (JAK2V617F mutated) proliferation at 33%, and burst-forming unit-erythroid colonies from patients with PV at 61%. Patients receiving ATV, aspirin, and low-dose HU displayed a good response and adequate tolerance to treatment (13-years follow-up). No patients experienced myelofibrosis or transformation to leukaemia, and no severe adverse events were observed.

Conclusions: This accessible, effective, and low-cost therapeutic strategy could improve adherence to treatment and the overall survival of high-risk patients with PV in resource-limited countries.

Key Points

1. Cost and availability barriers to treatments for polycythaemia vera (PV) that prevent thrombotic events and delay transformation to myelofibrosis or leukaemia affect patients in low- and middle-income countries.

2. Combination treatment with atorvastatin, aspirin, and low-dose hydroxyurea demonstrated good response (cytoreduction, inhibition of erythroid proliferation, and prophylaxis of thrombosis) in a prospective, longitudinal study of 14 high-risk patients with $JAK2^{V617F}$ mutations and PV over 13 years follow-up.

3. Lower cost, higher availability, effective treatments could improve adherence to treatment and the overall survival of high-risk patients with PV in resource-limited countries.

INTRODUCTION

Polycythaemia vera (PV) is a clonal myeloproliferative neoplasm that is characterised by the *JAK2*^{V617F} mutation in more than 95% of patients. The overall median survival is 13.5 years,[1] but risk stratification in PV can identify high-risk patients with a median survival of 10.9 years, intermediate-risk patients with a median survival of 18.9 years, and low-risk patients with a median survival of 27.8 years.[2] The primary goals of current PV therapies are preventing thrombotic events and delaying transformation to myelofibrosis (MF) or acute myeloid leukaemia.[3,4]

Treatment for PV aimed at maintaining haematocrit or haemoglobin (Hb) levels within the normal range has been associated with a reduction in cardiovascular deaths and thrombotic events.[5-7] Currently, low-risk patients with PV (<60 years and without previous thrombotic events) are treated with acetylsalicylic acid (ASA) and phlebotomy, whereas high-risk patients with PV require additional cytoreductive therapy, generally with hydroxyurea (HU), interferon-α, or ruxolitinib.[8-11] In the low- and middle-income countries of Latin America, high-risk patients with PV have difficulty acquiring treatment due to the high cost and lack of availability of drugs; therefore, optimising existing resources to provide more accessible, adequate, and effective treatment protocols should be considered.

Atorvastatin (ATV) is a common drug used in clinical practice. It has pleiotropic effects in erythroid proliferation and differentiation, as well as in the prevention of thrombotic events, and sensitises cells to HU's mechanism of action, thus allowing for lower doses to be used.[12-16] As part of the treatment protocol for PV, ASA works as an antiplatelet agent to prevent thrombosis, and also acts as an inhibitor of the nuclear factor NF-κ-B p105 (NFKB1) protein,[17-20] an activator of hypoxia inducible factor (HIF)-1α.[21] Down regulation of NFKB1 by ASA may decrease erythropoiesis by decreasing HIF-1α activity.[22,23] HU, in turn, is a well-known cytoreductive drug in the treatment of PV.[24-26]

The combination of the aforementioned drugs may be an alternative for treating high-risk PV in settings of limited economic resources, improving both adherence to treatment and overall patient survival. This study aimed to investigate the combination of ATV, ASA, and HU as an accessible and low-cost therapeutic strategy for high-risk PV.

METHODS

In Vitro Assays

Assays of erythroid colony proliferation *in vitro*, with or without simvastatin (3.5 μm) were performed in cell lines (UKE-1 and K562) and

bone marrow mononuclear cells obtained from patients with PV, as well as from healthy donors (normal controls) as previously described.[27,28] The assays were focused on showing the effect of simvastatin on neoplastic cells, since HU cytotoxic action and ASA activity are well known.

Patients

After human research committee approval, a prospective longitudinal study was conducted from January 2008 to April 2020. Of a total of 91 patients diagnosed with PV, 14 high-risk patients with *JAK2*^{V617F} with PV were evaluated. All treated patients were high-altitude dwellers (>3,600 meters above sea level) from La Paz, Bolivia, where normal Hb levels in healthy subjects range from 15–18 g/dL in males and 14–17 g/dL in females.[29] The diagnosis of PV was made according to standard diagnostic criteria,[30] and risk stratification was performed by the Griesshammer algorithm, in which 'high-risk' refers to patients 60 years of age or older and/or with a previous thrombosis.[31,32] Laboratory studies (blood count, blood glucose, uric acid, creatinine, bilirubin, transaminases, lactate dehydrogenase, and erythropoietin) were performed, and thrombotic events were confirmed by echo-Doppler and computed tomography. Patients included in this study did not have previous treatment with other medications.

Evaluation of the *JAK2*^{V617F} Mutation

Evaluation of the *JAK2*^{V617F} mutation was performed through a PCR assay using the common reverse primer JAK2 R (5'-CTGAATAGTCCTACAGTTTTCAGTTTCA-3') at 50 µM and two forward primers at 25 µM, namely JAK2 F mutation (5'-AGCATTGGTTTTAAATTATGGAGTATATT-3'), specific for the mutant allele, and JAK2 F WT (5'-ATCTATAGTCATGCTGAAAGTAGGAGAAAG-3'), which amplifies the wild-type allele. PCR was performed at an annealing temperature of 59 °C for 35 cycles. Amplification resulted in a 203-base pair product for the mutant allele and a 364-base pair product for the wild-type allele.[27,28]

Treatment

Phlebotomies of 450 mL were performed in patients until Hb levels were <17 g/dL in females and <18 g/dL in males. Then, after informed consent, high-risk patients with PV received HU (500 mg/day), ATV (20 mg/day), and ASA (100 mg/day) orally. A monthly outpatient follow-up was carried out. Possible adverse events related to each drug were monitored. The dose of HU was adjusted as needed to maintain neutrophils >2,000/µL and platelets >100,000/µL. The dose of ATV was reduced for muscle pain or an increase in creatine phosphokinase. The dose of ASA was modified if bleeding occurred, particularly epistaxis, gingivorrhagia, or petechiae.

Statistical Analysis

Descriptive analysis, using means and standard deviation, was performed through GraphPad Prism Version 6.0 (GraphPad Software Inc., California, USA), and included a Student t-test to evaluate the significance of any differences in the blood count. Figures were created using Microsoft Office Excel Version 16.23.190309 (Microsoft Corp., Washington, USA). A p-value of <0.05 was considered to be significant.

RESULTS

Inhibition of Cell Proliferation

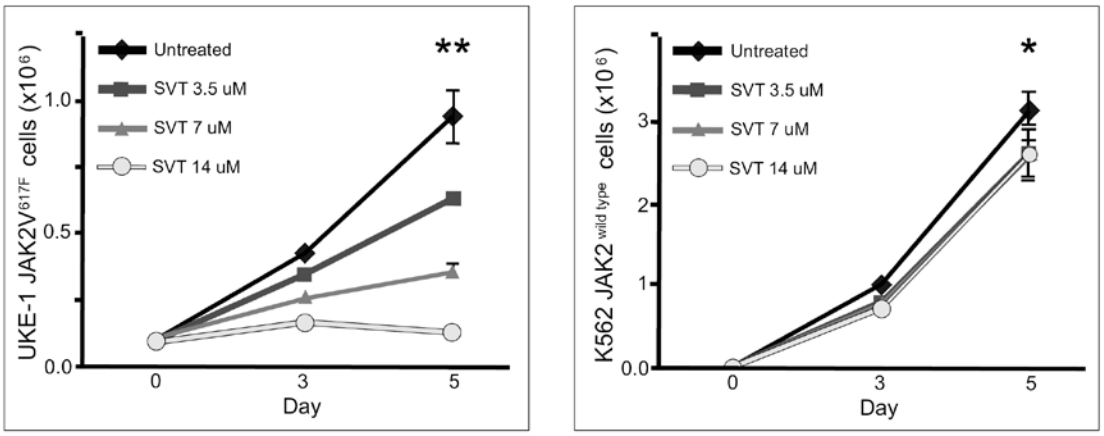
In vitro studies performed in cell lines UKE-1 (JAK2^{V617F} mutated) and K562 (BCR-ABL positive) displayed that simvastatin (doses of 3.5–14.0 µM, added over 5 days) induced a 33–100% dose-related inhibition in UKE-1 cell proliferation, and a 5% inhibition of K562 cell proliferation at all doses (Figure 1A).

Inhibition of Burst-Forming Unit-Erythroid Colonies

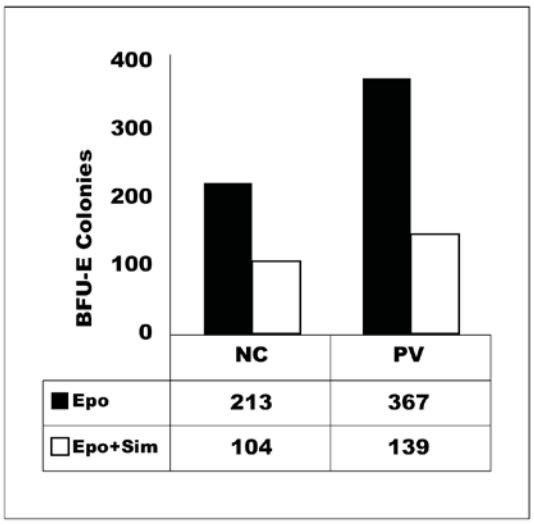
Based on the results reported above, similar assays using bone marrow mononuclear cells from PV patients and from healthy subjects as normal controls were performed. The addition of simvastatin (3 µM) induced a 61% inhibition in burst-forming unit-erythroid colonies from patients with PV and a 51% inhibition in normal controls (Figure 1B).

Figure 1: Inhibition induced by simvastatin.

A



B



A) Inhibition of cell proliferation in UKE1 and K562 cell lines. UKE-1: homozygous cell line with *JAK2* gene mutation obtained from a patient with essential thrombocythemia. K562: Immortalised cell line from chronic myeloid leukaemia (BCR/ABL) in blast phase.

B) Inhibition of burst-forming unit-erythroid colonies with simvastatin. Methylcellulose-based semi-solid culture of bone marrow haematopoietic progenitor cells to different simvastatin concentrations.

*p<0.001

†p<0.05

‡2 UI/mL

§2 µm

**n=3

Epo: erythropoietin; NC: normal controls; PV: polycythaemia vera; Sim: simvastatin; STV: simvastatin statin.

Atorvastatin, Acetylsalicyclic Acid, and Hydroxyurea in High-Risk Patients with Polycythaemia Vera

The 14 patients at high-risk of PV included 7 males and 7 females, with an average age of 65 years. Five of them had a history of thrombosis (1 deep vein thrombosis, 3 portal vein thrombosis, and 1 stroke). Comorbidities such as diabetes (n=1), dyslipidaemia (n=1), systemic arterial hypertension (n=3), and a history of

Table 1: Baseline characteristics of treated patients.

Subjects	N	Age (years)	Hb (g/dL)	WBC (10^9 /L)	PLT (10^9 /L)	Throm (n)	Diab (n)	Dys (n)	SAH (n)	Smok (n)	PTB (n)
Males	7	64.0 (±9.0)	19.1 (±2.5)	16.2 (±8.5)	481.9 (±256.0)	3	0	1	1	1	7
Females	7	63.0 (±12.0)	18.6 (±2.1)	16.7 (±6.2)	558.9 (±205.4)	2	1	0	2	0	6
Total	14	65.0 (±10.0)	19.1 (±2.2)	16.8 (±7.4)	707.3 (±236.7)	5	1	1	3	1	13

Results are displayed in mean and standard deviation (±).

Diab: diabetes; Dys: dyslipidaemia; Hb: haemoglobin; PLT: platelets; PTB: phlebotomy; WBC: white blood cells; SAH: systemic arterial hypertension; Smok: smoking; Throm: thrombosis.

smoking (n=1) were identified. Almost all (13 out of 14 patients) had a history of previous phlebotomies. Baseline characteristics of the high-risk patients treated with ATV, ASA, and low-dose HU are shown in Table 1.

Six follow-up evaluations were conducted from 6 months to 13 years (Table 2). Characteristics of response, progression, and tolerance to treatment were considered.

After 10 years of treatment, two patients needed to increase the dose of HU to 1,000 mg. A 67-year-old patient (10-years follow-up), who presented with deep vein thrombosis, had their dose of HU increased to 1,000 mg/day followed by rivaroxaban 20 mg daily. A 72-year-old patient (13-years follow-up), who presented with leukocytosis (16,900 /µL) had their dose of HU increased to 1,000 mg/day. Both patients had a good response, with performance statuses of 1 and 0, respectively, at the time of writing. However, a 65-year-old patient (5 years follow-up), with a history of smoking, died as a consequence of lung cancer.

The Hb, leukocyte, and platelet levels decreased progressively in patients, with statistical significance in Hb and platelet counts evaluated at 2 and 5 years of treatment (Table 2). Phlebotomies were required during up to 5 years of follow-up. None of the patients experienced progression to MF or transformation to leukaemia. No severe adverse events requiring discontinuation of treatment were observed. Leukocytes and platelets remained over 10,000/µL and 200,000/µL, respectively.

DISCUSSION

Statins are effective for inhibiting the growth and differentiation of *JAK2*^{V617F}-dependent cells by altering the lipid rafts where JAK2 resides.[14,33] The use of statins inhibiting cholesterol synthesis combined with JAK inhibitors may provide a more effective therapeutic strategy for patients with high-risk PV than the use of JAK inhibitors alone or the use of HU alone.[34]

Exposure to statins in patients with PV reduces the odds of requiring high intensity phlebotomies by 84%, possibly because statins inhibit JAK2 pathway-dependent cell proliferation.[12] Statins reduce the location of JAK2 in lipid rafts, negatively regulate JAK2/signal transducer and activator of transcription 5 activation, and inhibit cell growth in cell lines containing *JAK2*^{V617F}.[13,14] A potential role for statins as an adjuvant treatment of patients with PV has been supported by findings that statins inhibit erythroid colony formation, contribute to JAK inhibitors (JAK1, JAK2) such as ruxolitinib, and reduce proliferation of *JAK2*^{V617F} positive cells.[35]

Table 2: Patients follow-up.

Follow-up	N	HU 500 mg	HU 1,000 mg	Hb (g/dL)	WBC (10^9 /L)	PLT (10^9 /L)	Throm (n)	PTB (n)	Transf (n)	Death (n)
Onset time	14	0	0	19.1 (±2.2)	16.8 (±7.4)	707.3 (±236.7)	0	13	0	0
6 months	14	14	0	14.7 (±2.9)	12.4 (±7.2)	481.9 (±256.0)	0	1	0	0
1 year	11	11	0	16.2 (±3.0)	13.8 (±5.9)	361.9 (±116.1)	0	2	0	0
2 years	11	11	0	15.5 (±3.9)§	14.1 (±6.3)**	338.5 (±116.8)††	0	2	0	0
5 years	8	8	0	16.1 (±3.1)§	12.9 (±6.3)**	209.9 (±152.7)††	0	1	0	1‡
10 years	3	1	2*†	13,4 (±3.2)	11.5 (±2.5)	336.7 (± 202.0)	1* (DVT)	0	0	0
13 years	1	0	1	18.1	12.6	353.0	0	0	0	0

Results are displayed in mean and standard deviation (±). HU dosage change is depicted, there was no dose change in ATV (20 mg) and ASA (100 mg).

*A 67-year-old patient who presented DVT and splenomegaly increased HU to 1,000 mg/day, followed by rivaroxaban 20 mg daily. The patient had a good evolution.

†A 72-year-old patient who presented leukocytosis (16.9×109 /L) increased HU to 1000 mg with good evolution.

‡A 65-year-old patient with history of smoking died as a result of lung cancer.

§Hb: p<0.0077 at 2 years follow-up; p<0.015 at 5 years follow-up.

**WBC: p<0.34 (NS) at 2 years follow-up; p<0.22 (NS) at 5 years follow-up.

††PLT: p<0.0001 at 2 years follow-up; p<0.0001 at 5 years follow-up.

ASA: acetylsalicylic acid; ATV: atorvastatin; DVT: deep vein thrombosis; Hb: haemoglobin; HU: hydroxyurea; NS: not significant; PLT: platelets; PTB: phlebotomy; WBC: white blood cells; Throm: thrombosis; Transf: transfusion.

In addition, the antithrombotic action of statins is relevant in PV[35,36] where risk for thrombotic events is high.[23,36-38] In this regard, the thrombotic problem is likely to be greater at high-altitude regions, where HIF is increased by hypoxia and the expression of several HIF-regulated thrombo-inflammatory genes increases the thrombotic risk.[23,39,40] Patients with PV at high altitudes are at a particularly high risk of thrombosis due to population Hb and haematocrit levels being above the normal ranges found at sea level.[41,42]

ASA is recognised as an antiplatelet drug and as a *NFKB1* inhibitor; in its role as an inhibitor of *NFKB1*, it potentially decreases erythropoiesis by inhibiting HIF-1α.[43] The use of ASA in PV is safe and widely known.[17,44]

Regarding HU, the cytotoxic drug has been the conventional treatment for PV in high-risk patients, despite studies that employ HU alone without combining other drugs displaying few encouraging results.[1,45] HU is usually well

tolerated. It influences several critical factors contributing to the reduction of hyperviscosity and to blood rheology, including haematocrit, haemoglobin, and erythrocyte morphology.[45-48]

In this study, high-risk patients with PV who received the combination of HU (low-dose), ATV, and ASA displayed a good response and adequate tolerance to treatment. The most long-standing patient in the study has received this treatment combination for 13 years, and others have received it for at least 10 years. One case for this drug combination presented with a thrombotic event, and this was after 10 years of treatment. Only two patients had to increase their dose of HU to 1,000 mg after 10 years of treatment, and considering such a length of time, no results statistical variations were noticed. After 5 years follow-up, a favourable response to treatment was reported to be 87.5%. This is much higher than in other studies where 1,000–2,000 mg of HU alone was administered, which reported a response of 79% at 2 years follow-up[49] and 63% at 4 years follow-up.[50] Similarly, a good response was observed in the patients within 10 years follow-up (n=4).

The low rate of thrombosis in the authors' study is especially striking since some reports point out that a high altitude may magnify the risk of thrombosis in patients with PV.[40] None of the patients experienced transformation to leukaemia or MF. Several reports have indicated the probable leukaemogenicity of HU in PV. The reported range is from non-existent to 11.5% after 10.0 years of exposure.[51-53] A leukaemic transformation rate of 0.4% after 12.4 years of exposure was recently reported,[54] which supports the results obtained in this study.

It is also relevant to evaluate features such as the length of experience, cost efficiency, and safety of these drugs to assess their potential as reliable, accessible resources in settings where there is a need to reconcile economic sustainability with the right to a better quality of health and life.[54] In Latin American, including Bolivia, the treatment for PV that employs ATV, ASA, and HU requires a 30 USD monthly investment, whereas treatment with interferons or ruxolitinib may imply an investment of around 600 USD and 2,500 USD monthly, respectively. It is, therefore, noteworthy that the treatment combination applied in the authors' study was economically feasible, which enabled a good adherence to the regimen.

Future studies are needed to measure *JAK2*^{V617F} before and during therapy in order to determine the effectiveness of HU in reducing the burden of this allele. This is necessary as part of the studied combination of drugs at high altitude, since previous studies in other populations have provided conflicting results.[55] Likewise, ATV could play a beneficial role in other clinical situations of PV, especially in patients with resistance to HU,[56] and patients with contraindication to phlebotomy.[57]

CONCLUSION

In conclusion, the combination of HU, ASA, and ATV has effects of cytoreduction, inhibition of erythroid proliferation, and prophylaxis of thrombosis in patients with PV. This combination potentially provides patients from low- and middle-income countries with an accessible, low cost, and effective treatment for high-risk PV.

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Digital Necrosis as Initial Manifestation of Multiple Myeloma: An Unusual Case Report

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Abstract

Clinical manifestations of multiple myeloma are variable. The authors report a 68-year-old female who presented to the hospital with bilateral digital necrosis and dry gangrenous toes in both left and right feet. She was diagnosed with IgA-λ multiple myeloma associated with Type I cryoglobulinaemia. Emergency management consisted in hyperhydration (plasmapheresis was not available) and thromboprophylaxis. Necrotic digits were amputated. Chemotherapy (bortezomib, lenalidomide, and dexamethasone) was started with good initial evolution. This uncommon presentation can easily be missed, and clinicians should be aware of a possible underlying malignancy.

Key Points

1. This is a rare and atypical case of a patient with multiple myeloma associated with Type 1 globulinaemia, presenting with bilateral digital necrosis and dry gangrenous toes.

2. The emergency management of the patient included hyperhydration and thromboprophylaxis; necrotic digits were amputated. The initiation of a course of chemotherapy (bortezomib, lenalidomide, and dexamethasone) demonstrated good initial results.

3. Clinical manifestations of multiple myeloma can vary widely. Rare manifestations of the disease may lead to misdiagnosis and delayed treatment.

INTRODUCTION

Multiple myeloma (MM) is a B cell malignancy characterised by abnormal proliferation of plasma cells that expand in the bone marrow and produce a monoclonal Ig, also known as M-protein.[1] Several signs and symptoms of the condition are related to the excess amounts of the monoclonal Ig such as hyperviscosity syndrome, amyloidosis,

renal failure, or autoimmune phenomenon.[1] The monoclonal Ig can clump together and cause cryoglobulinaemia, usually of Type I. Cutaneous manifestations associated with Type I cryoglobulinaemia include Raynaud syndrome, acrocyanosis, livedo, urticaria, and cold-induced necrotic ulcers of the extremities.[2] Only few reports of MM with digital necrosis have been described. The authors report the case of a 68-year-old female with MM revealed by gangrene of almost all fingers and toes.

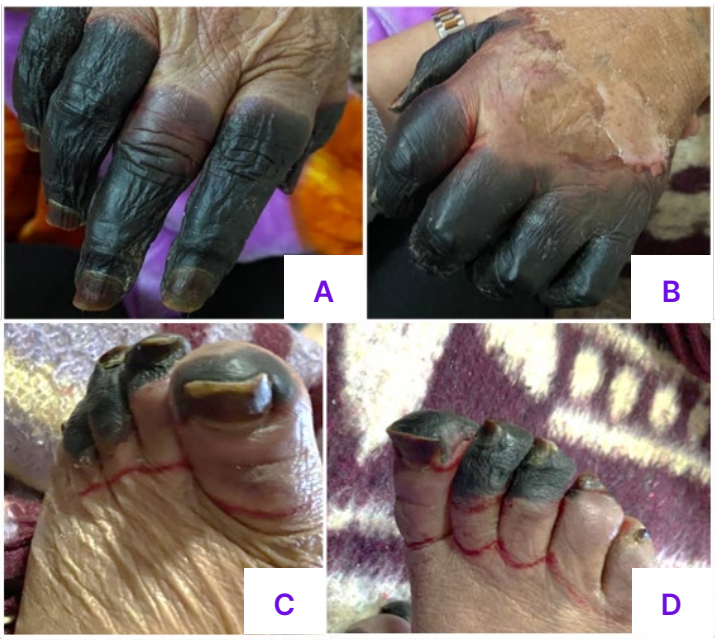
CASE DESCRIPTION

A 68-year-old female, with medical history of neglected non-toxic multinodular goitre but no history of diabetes, venous thromboembolism, ischaemic heart disease, intravenous drug abuse, cigarette smoking, or alcohol dependence, presented to the hospital with a 3-week history of bilateral fingers and toes pain with blackish discoloration.

On admission, she was febrile (temperature: 38.7 °C), tachypnoeic (respiratory rate: 42 cycle/min), and tachycardic (pulse rate: 120 /min). Blood pressure and oxygen saturation were normal, as well as her Glasgow coma score (GCS). Her BMI was 23.4 (normal). Physical examination revealed bilateral digital necrosis and dry gangrenous toes (1st, 2nd, 3rd, and 4th) in both left and right feet (Figure 1) with normal peripheral pulses. Neck exam showed hard painless and nodular goitre. There were no palpable lymph nodes, hepatosplenomegaly, or bone pain. Cardiopulmonary auscultation showed lower-right lung dullness with crackling rales.

The admitting laboratory results were as follows: haemoglobin: 9.9 g/dL; leukocyte count: 16 giga/L with 80% neutrophils; platelet count: 201 giga/L. Erythrocyte sedimentation rate: 90 mm/1st hour; total serum protein: 82 g/L (reference range: 62–87); albumin: 18.9 g/L (reference range: 35–50); calcium: 85 mg/L (reference range: 85–100); albumin-corrected calcium: 106.14 mg/L; C-reactive protein: 172.00 mg/L (reference range: 0.0–5.0); creatinine: 205.0 mmol/L (reference range: 53–115); fasting blood sugar: 4.2 mmol/L (reference range 3.9–6.1). Serum protein electrophoresis showed a monoclonal spike of 40.9 g/L in the β region and immunofixation electrophoresis confirmed that it involves IgAλ.

Figure 1: Gangrene in almost all of fingers and toes of the authors' patient, seen on the right hand (A), left hand (B), left foot (C), and right foot (D).

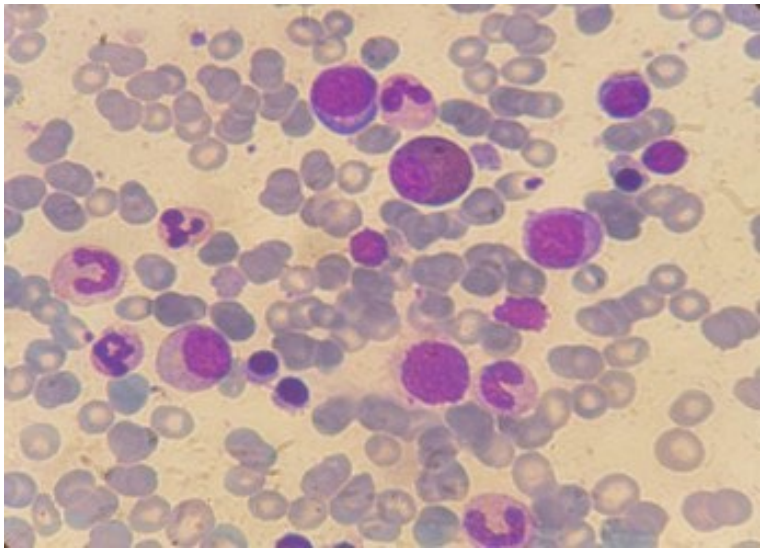


The serum-free κ was 19 mg/L, serum-free λ was 125 mg/L, and κ/λ ratio was 0.125 mg/L. Urine Bence Jones protein was positive. Cryoglobulin test was positive (qualitative research with cryoprecipitation method). Electrophoresis-immunofixation showed a monoclonal peak and typed the cryoprecipitate as IgA-L. β2 microglobulin was 6.2 mg/L (reference range: 0.97–2.64 mg/L), and lactate dehydrogenase 984 units/L (reference range: 120–300). Thyroid function was normal. Serological exams for HIV, hepatitis B virus, and hepatitis C virus were negative.

Under the suspicion of a connective tissue disease, a set of analyses were performed, including rheumatoid factor, anti-nuclear, anti-double-stranded DNA, anti-Sjögren's-syndrome-related antigen A autoantibodies, anti-Sjögren syndrome antigen B, anti-nucleosome, anti-histone, anti-Smith antigen, anti-U3-ribonucleoprotein, anti-Jo-1, and anti-Scl-70 antibodies, which were all negative. Serum complement titrations were within normal values. Bone marrow aspirate revealed 30% infiltration by plasma cells including atypical forms, with no marked reduction in granulopoiesis or erythropoiesis (Figure 2). Conventional karyotype and fluorescent *in situ* hybridisation were normal.

Chest X-ray showed lower-right lobar shadow. Whole body MRI showed no bone lesions. The diagnosis of MM with Type I cryoglobulinaemia was made. The patient was staged by the Revised International Staging System (R-ISS) as Injury Severity Score (ISS) III. Emergency management consisted in hyperhydration (plasmapheresis was not available), intravenous antibiotics, and thromboprophylaxis with low-molecular-weight heparin. All the necrotic digits were amputated (the decision was made in co-ordination with vascular surgery staff, the patient, and her family). The patient was started on bortezomib, lenalidomide, and dexamethasone. Initial evolution was good, with normalisation of fever and respiratory symptoms, and no further extension of the acrocyanosis. However, at Day 15 of the second chemotherapy session, she presented to the emergency room with 24 hours history of chest pain and dyspnoea. The diagnosis of massive pulmonary embolism was made, and the patient received curative anti-thrombotic treatment with low-molecular-weight heparin. Unfortunately, the patient died 48 hours later in the intensive care unit.

Figure 2: Bone marrow aspirate of our patient showing dystrophic plasma cells.



DISCUSSION

MM is a plasma cell dyscrasias afflicting mostly the elderly, over the age of 70.[3] The International Myeloma Working Group (IMWG) consensus updated the diagnostic criteria for MM to include laboratory biomarkers, radiological, and histological findings in addition to hypercalcaemia, renal failure, anaemia, and bone lesions (CRAB) criteria.[4] General symptoms such as fatigue, fever, night sweats, weight loss, and bone pain are classic manifestations of MM. Although, this malignancy exhibits a wide range of uncommon presentations, including ocular symptoms (proptosis, optic neuropathy, retinal haemorrhage, and detachment), neurological presentations (cranial nerve palsies, vertigo, and diabetes insipidus related to pituitary involvement), and gastrointestinal manifestations (acute and chronic pancreatitis, mesenteric ischaemia, and hepatosplenomegaly).[5] In this case, MM was revealed by digital necrosis related to capillary lumen obstruction by Type I cryoglobulin precipitates. Cryoglobulins are abnormal plasma Igs that precipitate at low temperatures and dissolve upon rewarming. According to Brouet et al.,[6] they are classified into three types:

1) Type I cryoglobulins are monoclonal (IgM > IgG > IgA), usually associated with B cell malignancies, most often MM, monoclonal gammopathy of undetermined significance (MGUS), or Waldenström macroglobulinaemia;

2) Type II cryoglobulins are polyclonal Igs associated with monoclonal Igs; and

3) Type III cryoglobulins involve only polyclonal Igs.

Type II and III cryoglobulins are usually IgM (κ > λ) and are referred as 'mixed cryoglobulins'.[7] They happen along with hepatitis C virus infection (70–90%), autoimmune diseases (Sjögren's syndrome, followed by lupus and scleroderma), or B cell lymphoid malignancies. This patient's cryoglobulinaemia was typed as IgA-L which is an extremely rare form. Rheumatoid factor activity is often found in mixed cryoglobulinaemia, unlike Type I cryoglobulinaemia, where it is rarely identified.[8] Clinical manifestations associated

Table 1: Characteristics of patients presented with multiple myeloma presented as cryoglobulin Type I-related digital necrosis.

Case report	Age (years); sex	Bone marrow	MM type	ISS	Chemotherapy	Outcome
Narayanan et al.,[11] 2016	45; female	Increase in plasma cells	IgG-κ	III	Bortezomib, lenalidomide, and dexamethasone	Complete remission
Ninomiya et al.,[12] 2010	61; male	31% plasma cells	IgG-λ	II	Vincristine, adriamycin, and dexamethasone	Died
Solimando et al.,[13] 2018	71; male	>90% plasma cells	IgG-κ	I	Bortezomib, melphalan, and prednisone	Partial remission
Abdulla et al.,[14] 2014	54; female	63% plasma cells	IgG-λ	-	Dexamethasone, cyclophosphamide, and bortezomib	Died
Vacula et al.,[15] 2010	68; male	Diffuse infiltration by matured plasma cells	IgG-λ	-	Vincristine, idarubicin, and dexamethasone	Died
The authors' case	68; female	30% plasma cells	IgA-λ	III	Bortezomib, lenalidomide, and dexamethasone	Died

ISS: Injury Severity Score; MM: multiple myeloma.

with Type I cryoglobulinaemia are mainly cutaneous (purpura, Raynaud's phenomenon, distal ulcers and necrosis, cold urticaria, and livedo). Rheumatologic, neurological, renal, gastrointestinal, and cardiopulmonary involvements are rare.[9]

According to a cohort study, 13.3% of patients with digital ischaemia associated with cancer had cryoglobulinaemia.[9] The largest series of MM that presented as cryoglobulin-related symptoms was reported by Payet et al.[10] Most of the patients had skin lesions (71 [4%]) among which only one patient presented with digital necrosis and gangrene. Treatment strategies for Type I cryoglobulinaemia with extensive necrosis involve plasmapheresis to quickly manage necrotising lesions and help their resolution. Specific chemotherapy prevents cryoglobulinaemia relapse and targets the underlying malignancy. In MM, bortezomib and lenalidomide are one of the most effective first line therapeutic agents.[2,8,10]

Unfortunately, despite an adequate initial management, MM associated with Type I cryoglobulinaemia has a poor prognosis. Most of the cases reported in the literature had fatal evolution (Table 1). In a retrospective study of 1,228 patients with MM, patients with skin involvement had significantly decreased overall survival compared to those without skin involvement (median: 28 versus 57 months).[16]

CONCLUSION

Digital necrosis is a rare and atypical presentation of MM. Most often, it is related to Type I cryoglobulinaemia, a condition that requires specific management. It may lead to misdiagnosis and delayed treatment. Clinicians should be aware of this rare manifestation and consider MM diagnosis even in the absence of classical CRAB criteria.

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IMRT/IGRT Helical Tomotherapy: A Successful Treatment of Lung Parenchyma Compression Due to Extramedullary Haematopoiesis in β-Thalassaemia - A Case Report

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Abstract

Thalassaemia is a chronic haemolytic anaemia that is endemic in the Mediterranean Basin. Extramedullary haematopoiesis (EMH) is a natural compensatory reaction involving several organs or tissues. This report outlines a case of dyspnoea due to bilateral dorsal paravertebral EMH, which was treated successfully with helical tomotherapy, a technique that combines intensity-modulate radiation therapy with image-guided radiation therapy. By the end of the first week of treatment, an increase in the haemoglobin value (up to 7.8 g/dL) and a remarkable reduction of dyspnoea were obtained, with haemoglobin values maintained at 7.8–7.3 g/dL without further blood transfusions. At 1-year follow-up, the patient was totally asymptomatic, with a complete resolution of dyspnoea and asthenia. The therapeutic approach to EMH remains controversial because there are no pre-established protocols, with current treatments including serial blood transfusions, hydroxyurea, radiation therapy, and surgical decompression. This clinical case description reports how helical tomotherapy may be used as a valid and effective treatment for compressive atelectasis due to EMH. In fact, radiation therapy improved the general clinical condition and self-reported symptoms of the patient and reduced the size of EMH masses visible in the chest CT scan.

Key Points

1. Extramedullary haematopoiesis (EMH) occurs as a compensatory reaction in chronic haemolytic anaemias, including thalassaemia, in a variety of locations and can lead to the compression of neighbouring structures.

2. Therapeutic management of EMH is controversial due to the absence of pre-established protocols, with current treatments including serial blood transfusions, hydroxyurea, radiation therapy, and surgical decompression.

3. Helical tomotherapy, which combines intensity-modulated radiation therapy with image-guided radiation therapy, was an effective treatment for compressive atelectasis due to EMH in this case, leading to a reduction in dyspnoea, reduction in the size of EMH masses, and an increased haemoglobin value at 1-year follow-up.

INTRODUCTION

Thalassaemia is an autosomal recessive haematological disorder that is characterised by defective synthesis of the globin moiety in haemoglobin (Hb), leading to chronic haemolytic anaemia. This condition is endemic in the Mediterranean Basin.[1,2]

Extramedullary haematopoiesis (EMH) usually occurs in almost all of the chronic haemolytic anaemias, as well as in myelofibrosis, polycythaemia vera, thalassaemia, sickle cell anaemia, leukaemia, lymphoma, or after bone marrow irradiation.[2-9] EMH is a natural compensatory reaction involving several organs or tissues. The bone marrow of the vertebrae reacts to the increased demand for peripheral red blood cells by proliferating beyond the spongious bone of the vertebrae into the paraspinal regions. The most common involved sites are the spleen, liver, lymph nodes, adrenal glands, pleura, and spinal canal.[1-9] The presence of haematopoiesis in these atypical locations can lead to the compression of neighbouring structures.[1-3]

The therapeutic management of EMH remains controversial, with treatments including blood transfusions, splenectomy, hydroxyurea, surgical decompression, radiation therapy (RT), or a combination of these.[1-8] This case report describes a case of dyspnoea due to bilateral dorsal paravertebral EMH. The aim of this study is to demonstrate the efficacy of RT, in terms of local control and the improvement of symptoms, in cases of compressive atelectasis due to EMH.

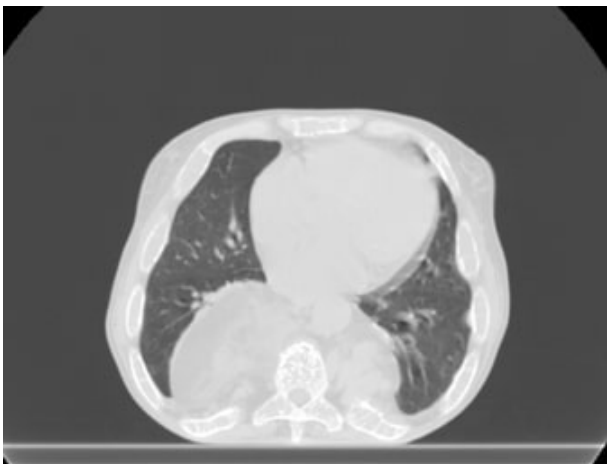
CASE PRESENTATION

A 53-year-old female was diagnosed with non-transfusion-dependent β-thalassaemia (caused by a nonsense mutation at codon 39) when they were 2 years old, had received a splenectomy when they were 17-years-old, and was treated with blood transfusions until 2009. In 2009, hydroxyurea was started due to the occurrence of allogenic immunisation and self-immunisation. The first time the patient presented to the Radiotherapy Department of ARNAS Civico Hospital, Palermo, Italy, was in September 2019, where they were examined for anaemia (Hb: 6.3 g/dL) and dyspnoea, which was suggestive of compression of the lung parenchyma. A chest CT scan revealed several bilateral dorsal paravertebral masses with lung compression due to EMH (Figure 1). As a result, the decision was made to treat the patient with a total radiation dose of 2,000 cGy in 10 fractions (200 cGy/fraction) delivered over 2 weeks, after contouring T4–T12, the paravertebral haematopoietic masses, and the organs at risk.

Treatment planning was performed using the tomotherapy planning system. RT was delivered using helical tomotherapy (HT), a technique that combines intensity-modulated radiation therapy (IMRT) with image-guided radiation therapy (IGRT). This image-guided system (IMRT/IGRT HT) was based on the daily execution of a megavoltage CT scan prior to each fraction, in order to verify the accuracy of the setup. HT was used so that the effective dose could be delivered with a greater precision for the target, thereby saving the organs at risk as much as possible.

In just 2 weeks, the patient received encouraging results: an increased Hb value (7.8 g/dL versus 6.3 g/dL prior to treatment) and a remarkable reduction of dyspnoea by the end of the first week of treatment. After 1 month, dyspnoea was no longer observed and the Hb value was stabilised at 7.8 g/dL. A new chest CT scan showed a reduction in the size of the

Figure 1: A chest CT scan, taken prior to helical tomotherapy treatment, showing paravertebral masses with lung compression due to extramedullary haematopoiesis.



EMH masses with resolution of compressive atelectasis in the right lower lobe.

After 6 months, the patient had fully improved clinically, and a comparison of chest CT scans pre-IMRT/IGRT and post-IMRT/IGRT revealed a further reduction in the size of the EMH masses. At 1-year follow-up, the patient was totally asymptomatic. They had complete resolution of dyspnoea and asthenia, with Hb values maintained at 7.3–7.8 g/dL without further blood transfusions. The patient continued therapy with hydroxyurea. A chest CT scan revealed a regular bronchovascular distribution and that the size of the EMH masses was stable with no progression (Figure 2).

DISCUSSION

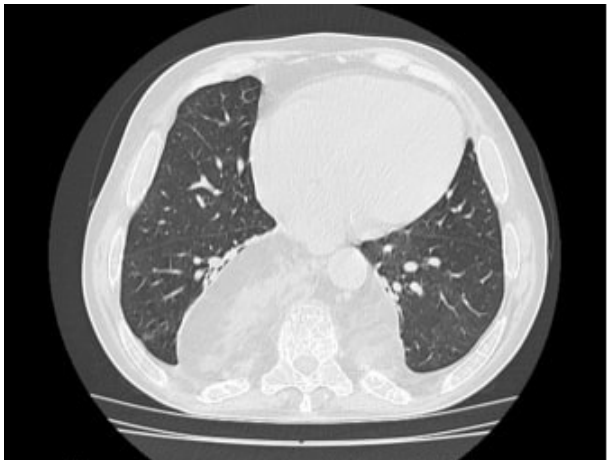
EMH is a common complication of ineffective haematopoiesis that occurs in many chronic haemolytic anaemias, including thalassaemia.[2-9] EMH more frequently affects the liver, spleen, lymph nodes, epidural space, and paravertebral regions;[2-9] while it less frequently affects the adrenal glands, kidneys, breasts, dura mater, adipose tissue, and skin.[6] Moreover, EMH usually has a predilection for impacting the lower thoracic region, but the reasons for this are not yet completely understood.[4,7-9] EMH is almost exclusively asymptomatic, but in rare cases it can compress the affected organ and lead to clinical signs.[2,4,7,9] Spinal cord compression due to EMH in thalassaemia was first reported in 1954 by Gatto et al.[10]

Diagnoses of EMH are typically made based on a background of chronic haemolytic anaemia; MRI scans are the gold standard for showing EMH masses, especially the spinal cord compression related to these. In the absence of availability or if there is a contraindication to MRI use, a CT scan may be utilised.[2,4,6,7] The treatment options available for EMH include blood transfusions, hydroxyurea, surgery, RT, or a combination of these.[1-8] Due to the extreme rarity of this condition, direct comparisons between various treatment modalities are not possible.

Salehi et al.[1] reviewed 56 cases of spinal cord compression due to EMH, of which some cases were treated with RT.[1] Haemopoietic tissue is extremely sensitive to radiation and low doses can cause rapid shrinkage, so the advantages of this technique include its immediate availability and rapid clinical benefits. A few authors reported patients with spinal cord compression who underwent combined surgical decompression and RT with good results.[2,7,11-13] In the cases reviewed, the radiation dosage used most frequently in different treatment protocols ranged from 1,000 cGY to 3,000 cGy.[1,2]

This case report presents a patient with respiratory symptoms due to the presence of

Figure 2: A chest CT scan, taken at 1-year follow-up from helical tomotherapy treatment, showing no progression in the size of the extramedullary haematopoiesis masses.



paravertebral EMH masses. After RT, the patient showed a rapid and remarkable reduction of dyspnoea. There was a progressive reduction in the size of the EMH masses, and at 1-year follow-up, the patient was totally asymptomatic with no side effects occurring. Therefore, it was concluded that RT may be an optimal and safe therapeutic approach in such cases.

CONCLUSION

The therapeutic approach to EMH remains controversial because there are no pre-established protocols, with current treatments including serial blood transfusions, hydroxyurea, RT, and surgical decompression. This clinical case description reported how IMRT/IGRT HT can be used as a valid and effective treatment for compressive atelectasis due to EMH. The patient presented here showed rapid and remarkable results. They reported no more dyspnoea at 1-year follow-up and an increased Hb value, as well as a reduction in the size of EMH masses.

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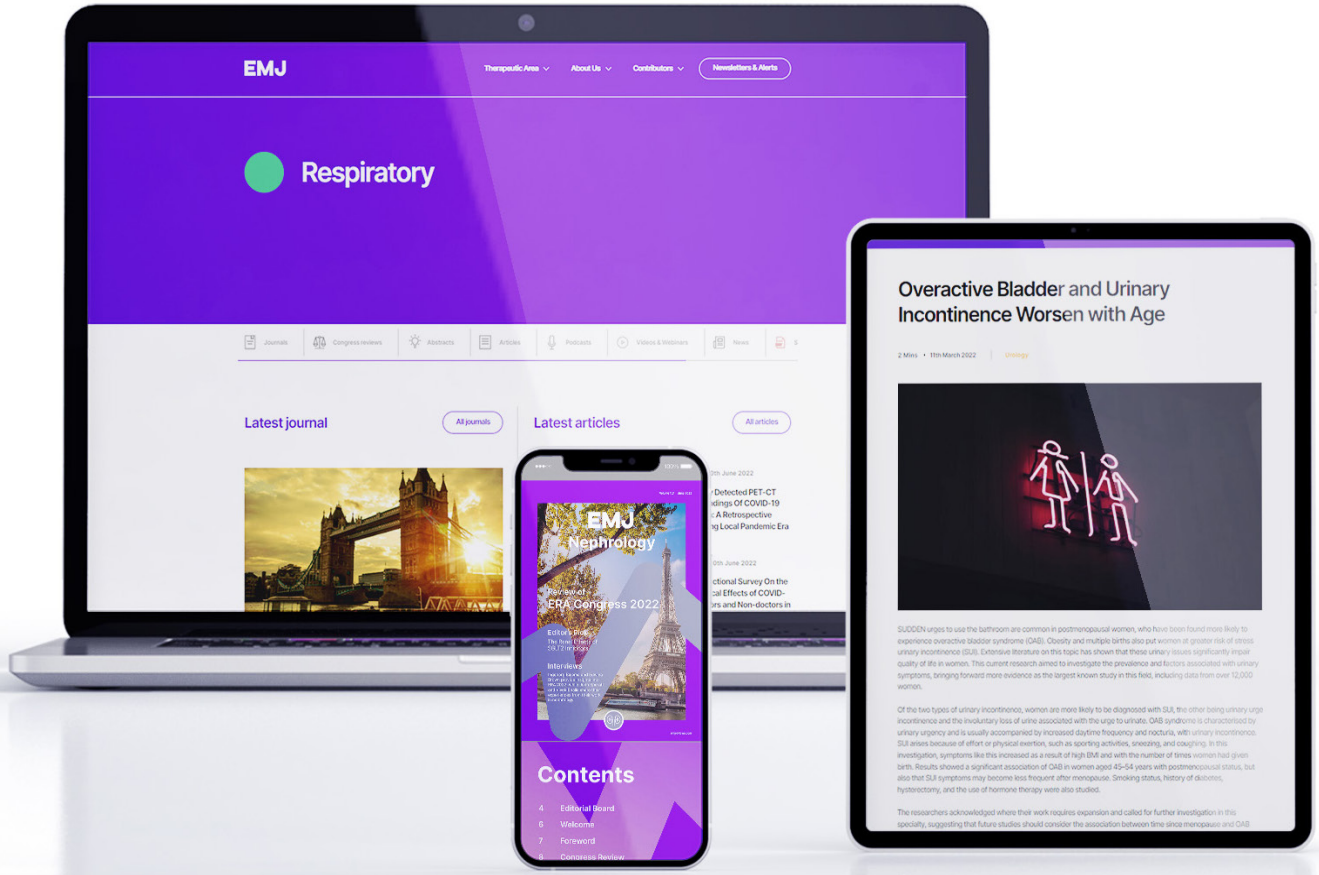

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