BJH clinic

Belgian Journal of Hematology

VOLUME 12 | ISSUE 7
NOVEMBER 2021

BSTH
Belgian Society on Thrombosis and Haemostasis

BHS
Belgian Hematology Society

7

THE BELGIAN JOURNAL OF HEMATOLOGY IS THE OFFICIAL JOURNAL OF THE BHS, BSTH, BSPHO AND BSAC

COLOPHON

The Belgian Journal of Hematology (BJH) is the official journal of the Belgian Hematology Society (BHS), the Belgian Society on Thrombosis and Haemostasis (BSTH), the Belgian Society of Paediatric Haematology and Oncology (BSPHO) and the Belgian Society for Advancement of Cytometry (BSAC). The BJH aims to be a peer-reviewed hematology journal covering all aspects of the diagnostic and clinical management of hematology patients, reflecting a multidisciplinary approach to therapy. It aims informing clinicians active in the field of hematology in Belgium and Luxembourg, thereby giving clinicians a solid support for daily practice.

PUBLISHER AND EDITORIAL OFFICE
Ariez International B.V.
Ms. E. van Zanten, MSc
c/o Oude Houtlei 118-120
9000 Gent, Belgium
Tel: 0031 75 642 94 20
E-mail: editor@bjh.be

SUBSCRIPTIONS
For paid subscriptions, please refer to the publisher: abon@ariez.com.

Publication Frequency: 8 issues per year.
Edition: 800 copies.

COVER ILLUSTRATION
Getty Images

ISSN-NUMMER
2033-3749

BELGIAN JOURNAL OF HEMATOLOGY

Editorial on the contribution of V. Labarque, entitled

"New and emergent treatment options in sickle cell disease"

(BELG J HEMATOL 2021;(7):209-5)

P. Zachée, MD, PhD

(BELG J HEMATOL 2021;(7):288-9)

Sickle cell disease (SCD) is a group of inherited monogenic red blood cell disorders. The following are the most common types of SCD: HbSS, HbSC (usually a milder form of the disease), HbS beta-thalassemia (those with HbS beta 0-thalassemia usually have a severe form of SCD. People with HbS beta +-thalassemia tend to have a milder form of SCD), HbSD, HbSE, HbSO (the severity of these rarer types of SCD varies), as well as sickle cell trait: HbAS. SCD affects millions of people throughout the world. The prevalence of the disease is high throughout large areas in sub-Saharan Africa, the Mediterranean Basin, the Middle East, and India because of the remarkable level of protection that the sickle cell trait provides against severe malaria. The "malaria hypothesis" formulated by Haldane in 1949 and by Allison in 1954, is a textbook example of natural selection and balanced polymorphism, an ongoing process. Because of slave trading and contemporary population movements, the distribution of sickle cell disease has spread far beyond its origins. Especially Spanish-speaking regions in the Western Hemisphere (South America, the Caribbean, and Central America). But also in Belgium, in 2013: 1/2,329 new-borns with SCD.[1] The number of patients with sickle cell disease is expected to increase, both in high-income and lower-income countries. In high-income countries, this increase largely reflects gains in life expectancy among affected persons because of interventions such as newborn screening, penicillin prophylaxis, primary stroke prevention, and hydroxyurea treatment. Also by migration from ex-colonial territories. In low-income countries, the vast majority of births with sickle cell genotype occur in three countries: Nigeria (150,000 affected children born every year), the Democratic Republic of the Congo, and India.[2] People with SCD start to show signs of the disease during the first year of life, usually around five months of age. Symptoms and complications of SCD are different for each person and can range from mild to severe.

The reason that infants do not show symptoms at birth is because baby or foetal haemoglobin protects the red blood cells from sickling. When the infant is around four to five months of age, the baby or foetal haemoglobin is replaced by sickle haemoglobin and the cells begin to sickle. Sickle cell patients are affected by a scale of complications: Hand-Foot Syndrome, pain "Episodic" or in "Crisis", anaemia, and aplastic and haemolytic crisis, infection (especially those due to bacteria with capsules because of damage to the spleen), acute chest syndrome, splenic sequestration, vision loss, leg ulcers, stroke, deep vein thrombosis (DVT) and pulmonary embolism (PE).[3] Other complications are damage to body organs (like the liver, heart, or kidneys), tissues, or bones because not enough blood is flowing to the affected area(s). Malnutrition and growth retardation among adolescents can cause delayed onset of puberty and, in males, infertility, gallstones and priapism. Life expectancy has improved significantly in high-income countries over the past 40 years, with childhood mortality now close to that in the general population and an

Department of Haematology, ZNA, Antwerp, Belgium.

Please send all correspondence to: P. Zachée, MD, PhD, Department of Haematology, ZNA Lange Beeldekenstraat 267, 2060 Antwerp, Belgium, tel: +32 495 20 22 91, email: pierre.zachee@zna.be.

Conflict of interest: The author has nothing to disclose and indicates no potential conflict of interest.

New and emergent treatment options in sickle cell disease

V. Labarque, MD, PhD

SUMMARY

Sickle cell disease (SCD) is one of the most frequently inherited diseases but it no longer only affects children. More and more patients survive well into adulthood. They experience repeated acute complications and inevitably develop chronic organ damage. For years, hydroxyurea and chronic transfusions were the only disease-modifying options in the treatment of SCD patients. Thanks to a better understanding of the pathophysiology, new components have been and are now being tested. Three of these are already used in clinical practice, namely L-glutamine, crizanlizumab and voxelotor. On the other hand, progress has also been made in the field of haematopoietic stem cell transplantation, through the introduction of alternative donors as well as the use of less toxic conditioning regimens. Finally, hopeful results are being achieved in the first studies of gene therapy in patients with SCD but it has yet to be proven that genetically manipulated stem cells maintain the long-term repopulation potential.

(BELG J HEMATOL 2021;12(7):290-5)

INTRODUCTION

Sickle cell disease (SCD) is the most prevalent haemoglobinopathy worldwide, which affects millions of people.[1] In Belgium, it has become one of the most frequently inherited diseases.[2] A mutation in the β-globin gene causes an amino acid substitution (p.E7V or p.E6V according to the previous nomenclature) and results in the β^S allele. Most individuals with SCD are homozygous for the β^S allele (HbSS or sickle cell anaemia (SCA)), while others are compound heterozygous with another mutation in the β-globin gene (HbSC, HbSβ^+ and HbSβ^0). A switch from γ-globin to β-globin expression is completed by the time a baby reaches 6 months of age.[3] After this time, over 95% of the haemoglobin (Hb) is adult HbA ($\alpha2\beta2$) and symptoms start to occur in children with SCD. However, over the years, SCD has changed from a fatal disease during childhood into a chronic disorder in adulthood featuring ongoing haemolytic anaemia and recurrent vaso-occlusive events, with unavoidable organ damage. Thanks to advancement in diagnosis, comprehensive care and therapeutic strategies, longevity of individuals with SCD has indeed improved in the Western world. Nevertheless, acute events persist and chronic complications are significant contributors to morbidity and mortality, shortening the lifespan of these patients by 25-30 years.[4] The pathophysiology of SCD is complex. It has long been known that the mutant adult Hb, called "sickled shape haemoglobin (HbS)", can easily polymerise under hypoxic conditions leading to vaso-occlusion and haemolysis, the main hallmarks of the disease. However, oxidative stress, endothelial dysfunction, inflammation, platelet activation and hypercoagulability also play a role.[1,5]

Current standard-of-care therapy consists of hydroxyurea and chronic transfusions. A haematopoietic stem cell transplantation (HSCT) from a matched sibling donor (MSD) should be considered in patients with a severe phenotype. More than 20 years ago, hydroxyurea (HU) was first shown to significantly reduce the rates of vaso-occlusive crises (VOCs) and acute chest syndrome (ACS), as well as the need for transfusions among patients ≥18 years.[6] Not much later, the first study demonstrating the clinical efficacy in

Department of Paediatric Haemato-Oncology, University Hospitals Leuven, Leuven, Belgium.

Please send all correspondence to: V. Labarque, MD, PhD, Department of Paediatric Haemato-Oncology, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium, tel: +32 (0)16 34 38 34, email: veerle.labarque@uzleuven.be.

Conflict of interest: The author has nothing to disclose and indicates no potential conflict of interest.

Keywords: crizanlizumab, gene therapy, haploidentical, L-glutamine, reduced intensity, sickle cell disease, voxelotor.

How to treat classical Hodgkin's lymphoma in older patients: Belgian expert opinion

S. Snauwaert, MD, PhD[1]*, V. Van Hende, MD[2]*, A. Janssens, MD, PhD[3], M. André, MD[4], S. Van Hecke, MD[5], E. Van Den Neste, MD, PhD[6]

On behalf of the lymphoproliferative disease committee BHS

SUMMARY

Classical Hodgkin's lymphoma (cHL) is a rather rare disease with an incidence of 2-3/100,000 per year and typically presents in patients at the age of 20-30. It is however well known that a second peak occurs at the age of 60-65 years.[1] Nowadays Hodgkin is a curable disease for most of the younger patients but treatment is more difficult and less successful in the older patient population. In this review, we want to summarise the possibilities for the treatment of cHL patients above 60 years, with a focus on evidence from the rather rarely available clinical trials. We also look at future treatments. In this article we will use the term 'older patients' for patients of 60 years and older at diagnosis. We will make a distinction between fit patients older than 60 years and frail or vulnerable patients (so called elderly).

(BELG J HEMATOL 2021;12(7):296-304)

BACKGROUND

There is a bimodal age distribution in Hodgkin lymphoma with two incidence peaks, one in young adulthood and one around 60-70 years. However, with the aging of the population we see an increased incidence of cHL in the older patients. In this article we will use the term 'older patients' for patients of 60 years and older at diagnosis. We will make a distinction between older than 60 years fit and frail patients. In 2018, 311 new cases of cHL were registered by the Belgian Cancer Registry, 170 male patients and 141 women. Of those 82 (26%) were older than 60 years (*Figure 1*).

Treatment of Hodgkin's lymphoma has changed rapidly in the last decade and the disease has become curable for most of the younger patients. It is well described that the disease behaves differently in older patients. Besides the comorbidities and polypharmacy that have to be taken into account, patients often present with more aggressive disease with B symptoms and advanced stage at diagnosis. The mixed cellularity subtype is seen more often, as is EBV positivity. cHL in older patients might be a biologically more aggressive disease. Presence of a large mediastinal mass is less common.[2]

When treating patients above 60 years we encounter more comorbidity, more toxicity of standard treatments and unfortunately also a higher mortality rate. Moreover, those patients are underrepresented in clinical trials: in most studies, only 5-10% of patients are aged above 60. In clinical trials from the German Hodgkin's Study Group (GHSG), the 5-year progression-free survival (PS) and overall survival

[1]Clinical Haematology, AZ Sint-Jan, Bruges, Belgium, [2]Clinical Haematology, AZ Nikolaas-AZ Lokeren, Sint-Niklaas, Lokeren, Belgium, [3]Clinical Haematology, UZ Leuven, Leuven, Belgium, [4]Clinical Haematology, CHU Dinant Godinne, UCL Namur, Yvoir, Belgium, [5]Clinical Haematology, AZ Damiaan, Oostende, Belgium, [6]Clinical Haematology, Université Catholique de Louvain, Brussels, Belgium.

*Equal contribution

Please send all correspondence to: V. Van Hende, MD, AZ Nikolaas, Lodewijk De Meesterstraat 5, 9100 Sint Niklaas, Belgium, tel: +32 3 760 26 82, email: vanessa.vanhende@aznikolaas.be.

Conflicts of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Keywords: frail, Hodgkin's lymphoma, older patients, treatment options.

PARTNER-project: A model and tools to support shared decision making in relapsed/refractory multiple myeloma (RRMM) treatment

L. Sillis, PharmD[1], A. Van Hecke, PhD[2,3], V. Foulon, PharmD, PhD[1]

SUMMARY

Introduction

Treatment options for multiple myeloma have increased substantially. To find the best therapy for each individual patient, patient preferences should be taken into account whenever a decision regarding relapsed/refractory multiple myeloma (RRMM) treatment has to be made. Shared decision-making (SDM) is one of the keys to person-centred care. Previous research, using semi-structured interviews, investigated the experiences and preferences of Belgian RRMM patients and their carers regarding involvement in decisions related to treatments. The aim of this part of the PARTNER-project was to develop a model and tools to support the implementation of SDM in RRMM treatment.

Methodology

The practice model for SDM and the proof of concepts of the tools were developed using a 2-phase co-design approach. First, results from the interviews were combined with data from the literature to draft the model and tools. In the second phase, meetings with expert panels were set up to discuss the model and tools and to adapt them according to the feedback.

Results

The PARTNER model for SDM in RRMM that has been developed as part of this project is a conceptual framework, describing essential elements in the decision-making process. Four tools were designed to convert the model into practice. It concerns 1) a question prompt list, to be used by patients to prepare for consultations with clinicians; 2) knowledge clips for patients and healthcare professionals (HCPs) to enhance the understanding of the SDM concept; 3) a conversation starter, aimed to open the dialogue among HCPs about organising and implementing SDM; and 4) a conversation tool, which is a hands-on step-by-step guide for conversations about treatment options between HCPs and RRMM patients. Additionally, suggestions on dissemination strategies were formulated.

Conclusion

Efforts were made to enhance a fit of the PARTNER model and tools into the Belgian RRMM setting. For some of the tools, evidence was provided on the improvement of the decision-making process, but none of the tools were yet tested. Further research should focus on pilot testing and evaluating the tools regarding their impact and feasibility to support SDM.

(BELG J HEMATOL 2021;12(7):305-17)

[1]KU Leuven, Department of Pharmaceutical and Pharmacological Sciences, Leuven, Belgium, [2]Ghent University, University Center for Nursing and Midwifery, Ghent, Belgium, [3]Ghent University Hospital, Nursing director department, Ghent, Belgium.

Please send all correspondence to: V. Foulon, PharmD, PhD, KU Leuven, Department of Pharmaceutical and Pharmacological Sciences – Clinical Pharmacology and Pharmacotherapy, Herestraat 49, bus 521, 3000 Leuven, Belgium, tel: + 32 (0)16 32 34 64, email: veerle.foulon@kuleuven.be.

Conflict of interest: Takeda funded this work. The research team of KU Leuven/UGent conducted this study independently, according to an agreement. There was no interference of Takeda in the course of the study.

Keywords: communication, patient-centred care, relapsed/refractory multiple myeloma, shared decision-making, tools.

Clinical case: High grade "triple hit" lymphoma

G. Sqalli, MD[1], T. Connerotte, MD[2], B. Lambert, MD[3], L. Dierge, PhamD[4], T. Roy[4], J. Simar, MD[4]

SUMMARY

We report the case of a 64-year-old patient, known for follicular lymphoma, admitted with facial paralysis accompanied by acute cervicobrachialgia. A lumbar puncture revealed the presence of centroblastic lymphoma cells whose clonal nature was confirmed by immunophenotyping. The histological examination of a lymph node biopsy was consistent with Burkitt-like high-grade lymphoma. Cytogenetic analysis showed the concomitant presence of a rearrangement of MYC as well as of BCL2 and BCL6. A final diagnosis of "triple-hit" high-grade B cell lymphoma (HGBL) was thus made. This entity belongs to the HGBL category of the WHO 2016 classification and shares characteristics with diffuse large B-cell lymphoma and Burkitt lymphoma. The diagnosis of this entity can be complex, in particular in view of a significant morphological variability. The cytogenetic work-up is thus essential for the differential diagnosis.

(BELG J HEMATOL 2021;12(7):318-22)

CASE PRESENTATION

A 64-year-old patient presented with facial paralysis accompanied by cervicobrachialgia that had suddenly appeared two weeks earlier. The patient had also lost four kg in two weeks and was experiencing night sweats.

In his history, there was mention of jugulocarotid and supraclavicular lymphadenopathy known for six years, the aetiology of which had been attributed to follicular lymphoma. This diagnosis was made based on a tru-cut biopsy examination but had not been confirmed by a surgical biopsy.

The biology on admission was unremarkable except for the presence of a few reactive lymphocytes and a slight increase of LDH at 385 U/L (VN: 125-243 U/l).

The CT-scan revealed multifocal axillary and mediastinal lymphadenopathy, which did not appear hypermetabolic on the FDG-PET SCAN. However, as the patient was already under corticosteroid treatment, these results must be interpreted with caution.

Borrelia serology was also performed and was positive for IgG but negative for IgM. The Western blot confirmed the positivity of the serology. Treatment with ceftriaxone 2 g/day was initiated, but the patient deteriorated further with the onset of diplopia and paresis of the lower limbs.

A lumbar puncture was therefore performed and revealed the presence of centroblastic lymphoma cells (*Figure 1A*). A phenotypically immature B lymphocyte clone was characterised by immunophenotyping as CD19+, CD10+, CD20, CD22-, CD5-, CD23- with weak expression of surface immunoglobulin light chains.

A lymph node biopsy performed a few days later showed a monomorphic population of lymphoma cells. The morphotype was similar to that found in the cerebrospinal fluid (CSF) with both small cells and numerous blastoid cells, which may suggest lymphoblastic lymphoma (*Figures 2A, B*). Two different B lymphoid populations were actually distinguished. The smaller population had a similar phenotype as that found in CSF. The larger population had a

[1]Clinical biology, University of Liège, Liège, Belgium, [2]Haematology, Clinique Saint-Pierre Ottignies, Ottignies, Belgium, [3]Institute of pathology and genetics, Gosselies, Belgium, [4]Clinical biology, Clinique Saint-Pierre Ottignies, Ottignies, Belgium.

Please send all correspondence to: G. Sqalli, MD, Clinical biology, Av. de l'Hôpital, 1 CHU de Liège Sart-Tilman, 4000 Liège, Belgium, tel: +32 4 284 28 55, email: gsqalli@chuliege.be.

Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Keywords: Burkitt lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, lymphoblastic lymphoma, triple-hit.

Recurrent deep venous thrombo-embolism in an obese anticoagulated patient

N. Ghorra, S. Eeckhoudt, PhD, L. Rozen, PhD

SUMMARY

Deep venous thrombosis (DVT) is a medical emergency requiring immediate anticoagulant treatment to prevent further clot formation and pulmonary thrombo-embolism. We present here the case of a patient affected by class I obesity who suffered from recurrent DVT despite anticoagulation with rivaroxaban.[1] After a switch to VKA, it appeared that the patient also presented resistance to vitamin K antagonists (VKA). Through this case, we would like to highlight the factors that must be taken into account when initiating and monitoring an anticoagulation therapy, including obesity and VKA resistance.

(BELG J HEMATOL 2021;12(7):323-6)

HIGHLIGHTS

1. DOACs are not contraindicated in patients with obesity but distribution volume and half-life are impacted and it could lead to under-dosage. In this case, monitoring of the anti-Xa activity is recommended to determine the appropriate DOAC dose.
2. Greater doses of VKA and longer lead-in periods for achieving INR therapeutic values are required in obese patients.
3. The presence of polymorphisms of the VKORC1 and CYP2C9 genes has to be considered when facing a resistance to VKA treatment, characterised by a low INR, despite increased dosage.
4. VKA are not contraindicated in patients carrying polymorphisms of the VKORC1 or CYP2C9 genes, however, a closer monitoring regimen is recommended.

INTRODUCTION

Deep venous thrombosis (DVT) is the most common clinical manifestation of venous thromboembolism (VTE). The management of DVT has to be quick and efficient in order to avoid complications and lower the mortality rate. The quick start of anticoagulant therapy constitutes the therapeutic keystone of DVT.[2] We describe here a case of recurrent DVT despite anticoagulation with rivaroxaban.

CASE REPORT AND RESULTS

A 66-year-old man was referred to the Emergency Room (ER) for deterioration of his general condition and bilateral swelling of his legs. The patient reported acute chest pain, pain when walking and asthenia. The patient was known for ischemic cardiopathy, hypertension, type II diabetes mellitus and hypercholesterolemia.

He had already suffered from previous DVT episodes. The patient recollects a first bilateral DVT episode occurred few years earlier but unfortunately, no medical documentation concerning the treatment received at that time was found. Seven years later, after a second DVT episode, a

Department of Haematology, LHUB-ULB (Laboratoire Hospitalier Universitaire de Bruxelles), Brussels, Belgium.

Please send all correspondence to: N. Ghorra, rue Haute 322, 1000 Brussels, Belgium, tel: +32 477 22 99, email: Nathalie.ghorra@lhub-ulb.be.

Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Keywords: deep venous thrombosis, direct oral anticoagulant, LMWH, obesity, rivaroxaban, venous thrombo-embolism, VKORC1, vitamin K antagonists, vitamin K antagonist resistance.

New haematology reimbursements in Belgium

P. Specenier, MD, PhD

OVERVIEW OF BELGIAN REIMBURSEMENT NEWS

(BELG J HEMATOL 2021;12(7):327)

TEPADINA®

Thiotepa is reimbursed when administered according to an appropriate paediatric schedule as preparatory treatment for allogeneic haematopoietic stem cell transplantation in neonates, children and adolescents with acute lymphoblastic leukaemia under eighteen years of age, or for the treatment of adult patients primary central nervous system lymphoma, or as preparatory treatment for a haploidentical stem cell transplant or umbilical cord blood transplant in adult patients with a blood disorder.

CALQUENCE

As of November 1st, 2021, the next-generation Bruton Tyrosine Kinase (BTK) inhibitor Calquence® will be reimbursed in Belgium. The drug will be reimbursed as monotherapy for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are not candidates for a fludarabine-based treatment. This reimbursement is based on the results of the phase III ELEVATE-TN trial, in which acalabrutinib with or without obinutuzumab was shown to significantly improve the progression-free survival (PFS) compared to first-line treatment with obinutuzumab-chlorambucil chemoimmunotherapy.[1] This trial randomised a total of 535 untreated CLL patients, aged 65 years or older, or aged 18-65 years with a creatinine clearance of 30-69 mL/min or a Cumulative Illness Rating Scale for Geriatrics score greater than six. Additional inclusion criteria included an Eastern Cooperative Oncology Group performance status score of two or less and an adequate haematologic, hepatic, and renal function. At median follow-up of 28.3 months, median progression-free survival was longer with acalabrutinib-obinutuzumab and acalabrutinib monotherapy, compared with obinutuzumab-chlorambucil (median not reached with acalabrutinib and obinutuzumab *vs.* 22.6 months with obinutuzumab, hazard ratio [HR] 0.1; 95% CI 0.06-0.17, p< 0.0001; and not reached with acalabrutinib monotherapy *vs.* 22.6 months with obinutuzumab, 0.20; 0.13-0.3, p< 0.0001).[1] In addition to being reimbursed in first-line, Calquence® will also be eligible for reimbursement as monotherapy for the treatment of patients with relapsed/refractory CLL.

REFERENCE

1. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. Lancet. 2020;395(10232):1278-91.

Department of Oncology, University Hospital Antwerp, Edegem, Belgium.

Please send all correspondence to: P. Specenier, MD, PhD, Antwerp University Hospital, Department of Oncology, Wilrijkstraat 10, 2650 Edegem, Belgium, tel: +32 3 8214014, email: pol.specenier@uza.be.

Conflict of interest: The author has nothing to disclose and indicates no potential conflict of interest.

Keywords: Acalabrutinib, Calquence®, Tepadina®, thiotepa.

CONGRESS CALENDAR HEMATOLOGY

32nd ISBT Regional Congress
13-16 November 2021, Brisbane, Australia

BSPHO Symposium
19 November 2021, Provinciehuis, Leuven, Belgium

63rd ASH Annual Meeting and Exposition
11-14 December 2021, Atlanta, GA, United States

CONGRESS CALENDAR HEMATOLOGY 2022

24th Post-ASH meeting 2022
14 January 2022, Sheraton Brussels Airport, Belgium

Seminar 4: Supportive Care in Hematology
15 January 2022, Brussels, Belgium

Dutch Hematology Congress
19-21 January 2022, Papendal, Arnhem, The Netherlands

International Conference on Cellular Therapy (ICCT)
21-22 January 2022, Amsterdam, Netherlands

19th Annual Mayo Clinic Hematology Review
29 January 2022, Bloomington, MN, United States