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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

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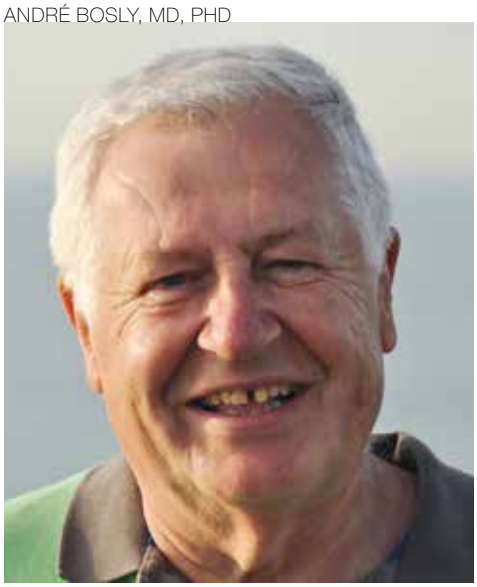
ANDRÉ BOSLY, MD, PHD



DEAR COLLEAGUES,

S. Van Hecke (UZ, KULeuven) reviewed congenital and acquired neutropenia. This comprehensive review detailed causes of neutropenias in adults: congenital (severe and cyclic) and acquired. A practical management of neutropenia with a step-wise approach is proposed with data on prevention of infections and treatment.

M.C. Vekemans (UCLouvain, St Luc, Brussels) presented an update of the BHS guidelines for first-line treatment in multiple myeloma. For young patients (transplant-eligible), VTD or VRD are the most effective induction regimens (Revlimid is not reimbursed in this setting) followed by high-dose Melphalan and autologous stem cells transplantation. Consolidation for patients not achieving at least a VGPR is recommended. The prognostic impact of minimal residual disease is underlined.

L. Heireman (AZ Maria Middelares, Ghent) presented a hematocase of toxoplasmosis infection mimicking a mononucleosis infection-like illness in a patient with B-CLL.

D. Bron (ULB, Bordet Institute, Brussels) summarised an EHA meeting on "Ageing and Haematology" held in Lisbon. Several topics were discussed such as vaccination and mild cognitive impairment acting as prognostic factor. Management of elderly patients in AML/APL, follicular lymphoma (frail), Hodgkin lymphoma, and CLL were also discussed. Decision in older patients must integrate disease status, geriatric assessment, social environment and patient's expectation.

T. Feys (Ariez, Ghent) overviewed two new indications reimbursed in Belgium: Epoietin alfa (Eprex) in MDS with low level of seric erythropoietin, and Ruxilotinib (Jakavi) in myelofibrosis with splenomegaly but also broadened in intermediate 2 and high-risk MDS with symptomatic disease even in absence of splenomegaly.

I wish you a fruitful lecture,

André Bosly, MD, PhD
Editor-in-Chief

Causes, diagnosis and management of congenital or acquired neutropaenia

S. Van Hecke, MD, P. Vandenberghe, MD, PhD, A. Janssens, MD, PhD

SUMMARY

Neutropaenia is a common incidental finding on routine blood studies. This manuscript will focus on the possible causes, challenging differential diagnosis and appropriate management of neutropaenia. Different mechanisms may explain a decreased production, impaired development or increased destruction of neutrophilic granulocytes. We distinguish between congenital and acquired causes. The former includes benign ethnic neutropaenia, severe congenital neutropaenia and cyclic neutropaenia. For the latter, infections, drugs, auto-immune reactions, nutritional deficiencies as well as haematological malignancies are all possible reasons of neutropaenia. The risk of infection in those with non-chemotherapy-induced neutropaenia mainly depends on the bone marrow reserve. Asymptomatic patients with mild or moderate neutropaenia can be observed with serial blood counts at increasing intervals. Infections should always be treated according to the severity of neutropaenia. Therapy with growth factors, drug discontinuation and immunosuppressive therapy can be considered depending on the underlying cause.

(BELG J HEMATOL 2019;10(3):103-12)

INTRODUCTION

Questions about acute and chronic neutropaenia are one of the more common haematological consultations for both hospitalised and non-hospitalised patients. The diagnostic approach, follow-up and treatment plans of neutropaenia remain a challenge for the general practitioner, hospital doctor and also for the haematologist. The finding of neutropaenia covers a broad range of possible causes that are mainly categorised into four basic mechanisms: pseudoneutropaenia, extravascular shift, decreased production and increased destruction. Patients may be asymptomatic at the time neutropaenia is discovered or may present with life-threatening complications. In this manuscript, we discuss a stepwise approach for the management of neutropaenia. Appropriate preventive actions should be taken in all patients with neutropaenia. Possible treatment options include antibiotics, growth factors, drug discontinuation in case of drug-induced neutropaenia, immunosuppressive therapy and allogeneic stem cell transplantation. The specific treatment of chemotherapy-related neutropaenia falls outside the scope of this review.

THE NEUTROPHIL AND NEUTROPAENIA

Neutrophils are part of the polymorphonuclear cell family together with basophils and eosinophils. They represent the most abundant type of white blood cells (WBCs) and form a very important part of our innate immune system. Neutrophils are produced in the bone marrow from myeloid precursor cells. After multiple stages of differentiation, they migrate from the bone marrow into the circulation, the spleen and sites of infection (*Figure 1*).[1]

There is some confusion as regards terminology. Neutropaenia is usually defined as an absolute neutrophil count (ANC) below 1.5 x 10^9 cells/L. The ANC is calculated as the product of the WBC count and the percentage of mature neutrophils from the WBC differential, including polymorphonuclear cells and band forms. Leukopenia means a reduced total WBC count including both myeloid and lymphoid cells. Granulocytopaenia defines a reduced number of neutrophils, eosinophils and basophils, while agranulocytosis stands for <0.1 x 10^9 neutrophils/L or a complete absence of these cells in the blood. Neutropaenia is subdivided into three categories: mild neutropaenia with an ANC between 1 x 10^9/L

Hematology Department, University Hospitals Leuven, Leuven, Belgium.

Please send all correspondence to: S. Van Hecke, MD, Hematology Department, University Hospitals Leuven, Herestraat 49, 3000 Leuven, tel: +32 16346880, email: sam.vanhecke@uzleuven.be.

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Keywords: neutropaenia, neutrophil, severe congenital neutropaenia.

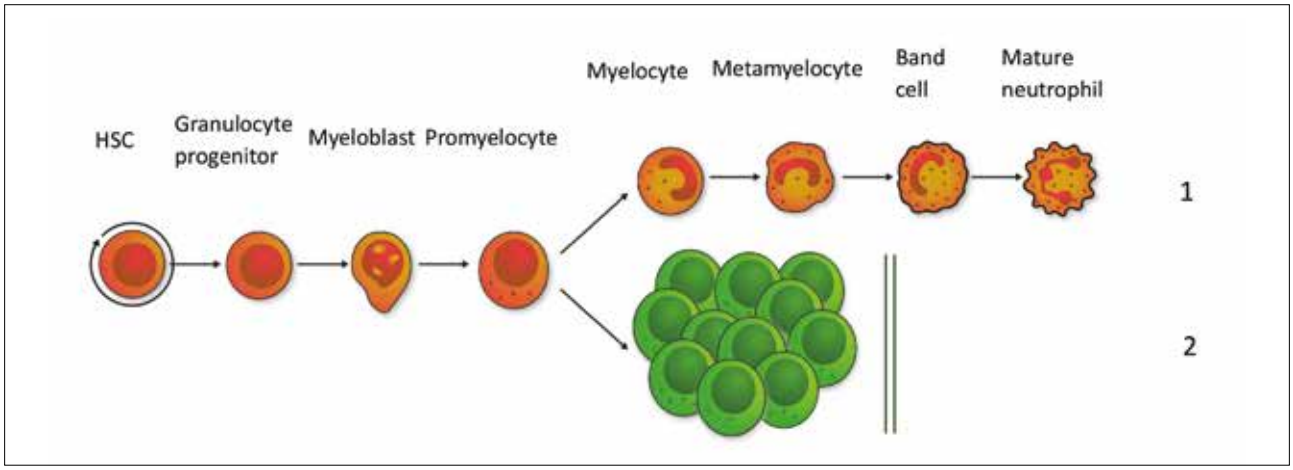

FIGURE 1. Pathway 1: normal proliferation of neutrophil precursors. Pathway 2: maturation arrest at the promyelocyte/myelocyte stage with abundant promyelocytes but a selective reduction in myelocytes, metamyelocytes and mature neutrophils. *HSC: hematopoietic stem cell.*

and 1.5 x 10^9/L, moderate neutropaenia with an ANC between 0.5 x 10^9/L and 1 x 10^9/L and severe neutropaenia when the ANC falls below 0.5 x 10^9/L. Chronic neutropaenia means that the neutropaenia persists longer than three months.

The prevalence of neutropaenia varies by age, ethnic background and presence of an underlying autoimmune disorder like systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA). Moreover, females and smokers have a higher neutrophil mean than males and non-smokers. The lower limit of the normal range is applicable for the global population with the exception of lower values seen in some ethnic groups in Africa or the Middle East and new-born infants who usually have an elevated ANC for the first days of their life (12-15 x 10^9/L).[2]

The most common presentation of neutropaenia is the incidental finding of a lower ANC on a routine blood sample in an asymptomatic patient. If the bone marrow neutrophil reserve pool is significantly depleted, there is a relationship between the absolute neutrophil count and the risk of infection. Only a small percentage of total body neutrophils are circulating in the peripheral blood (approximately 3%). Therefore, a low ANC indicates, in particular, that the circulating neutrophil pool, rather than total body neutrophil stores, is diminished. Another factor that can increase infectious risk is the co-existence of an underlying immuno-deficiency state or autoimmune disorder. Common sites of infection include the skin and the mucous membranes of the oral cavity, perirectal or genital areas. With persistent severe neutropaenia, profound infection with bacteraemia, pneumonia and infections of the gastrointestinal tract occur.[1] In case of chronic neutropaenia, there is an increased risk of fungal infections, especially in case of treatment with corticosteroids.

If the lab results show neutropaenia, we always have to answer two important questions. First: is the patient at increased risk for infection because of the reduced number of WBCs? Second: is there a serious underlying disorder that is the primary cause of the low neutrophil count?

CAUSES OF NEUTROPAENIA

The classification of the causes can be based on whether the neutropaenia is congenital or acquired. Furthermore, all causes can be explained by four important mechanisms: pseudoneutropaenia, extravascular shift, decreased production and increased destruction. Pseudoneutropaenia can occur if blood is left standing for a prolonged period of time and in the presence of paraproteinemia and certain anticoagulants such as ethylenediamine tetra acetic acid (EDTA) that can cause cellular clumping.[3] Rarely, individuals with a congenital condition called myeloperoxidase (MPO) deficiency can be falsely reported to have a low neutrophil count by automated cell counters that use MPO staining to identify the neutrophils.[4] The shift of circulating neutrophils to vascular endothelium or tissues, which can occur with splenomegaly and/or hypersplenism ('margination'), also causes a lower ANC. Congenital defects, chemotherapy or other drugs with direct bone marrow toxicity, nutritional deficiencies and haematological malignancy with bone marrow infiltration all lead to a decreased production or impaired development of neutrophilic granulocytes. Finally, in some cases of neutropaenia, the underlying mechanism consists of an increased destruction due to a drug reaction or an auto-immune disorder. Possible causes of neutropaenia in adults are listed in *Table 1*. Acute neutropaenia in adulthood is most commonly caused by infections and drugs. The most common causes

TABLE 1. Causes of neutropaenia in adults.*

Pseudoneutropaenia	Laboratory error
Congenital disorders	Benign ethnic neutropaenia Severe congenital neutropaenia Cyclic neutropaenia
Infection	Bacterial (e.g., *Salmonella* typhi, *Helicobacter pylori, Mycobacterium tuberculosis,* Borrelia burgdorferi) Viral (e.g., HIV, EBV, CMV, influenza, parvovirus B19, HAV, HBV, HCV, human herpesvirus-6) Parasitic (*Plasmodium* sp.) Fungal
Drug-induced	Most commonly anticonvulsant, antimicrobial, antipsychotic, anti-rheumatic and anti-thyroid drugs
Chronic autoimmune	Primary and secondary autoimmune neutropaenia Idiopathic neutropaenia
Nutritional deficiency	Alcoholism, vitamin B12 or folate deficiency, copper deficiency
Extravascular shift	Hypersplenism, splenomegaly
Metabolic disorders	Gaucher syndrome, Pearson syndrome, acidemias
Complement activation	Haemodialysis, filtration leucapheresis, acute respiratory distress syndrome
Primary haematological disease	Myelodysplastic syndromes Other marrow infiltrative malignancies/disorders

*The most frequent causes are marked grey.
HIV: human immunodeficiency virus, EBV: Epstein-Barr virus, CMV: cytomegalovirus, HAV: Hepatitis A virus, HCV: Hepatitis C virus, HBV: Hepatitis B virus.

of mild chronic neutropaenia are constitutional neutropaenia and dose-related drug-induced neutropaenia. Primary haematological diseases are not discussed separately in the overview below.

CONGENITAL CAUSES

Benign ethnic neutropaenia (BEN), also called benign familial neutropaenia or constitutional neutropaenia, is frequently seen in Africans, Yemenite Jews, West Indians and Bedouins. The neutropaenia is often mild (most commonly >1.2 x 10^9/L) and involves no increased risk of infection because of the normal bone marrow reserve. BEN is not associated with evolution to myeloid malignancies, and it is important to recognise this benign condition. The genetic explanation for BEN is a single nucleotide polymorphism in the *Duffy antigen receptor chemokine (DARC)* gene, which encodes the Duffy antigen, a chemokine receptor expressed on the red blood cell surface. People with this genetic variation should have an evolutionary advantage against malaria. The mechanism of neutropaenia in patients with BEN is not well understood, and BEN without *DARC* polymorphisms also occurs.[5-7]

Severe congenital neutropaenia (SCN) was first described in 1956 by Rolf Kostmann as infantile genetic agranulocytosis. SCN compromises a heterogeneous group of rare inherited disorders that are characterised by a maturation arrest of granulopoiesis at the promyelocyte/myelocyte stage and increased apoptosis of neutrophils and neutrophil precursors (*Figure 1*), peripheral blood ANC <0.5 x 10^9/L and early onset of severe or life-threatening infections. The prevalence is estimated to be 3-8,5 cases per million individuals.[8-9] The diagnosis is usually made at birth or during the first months of life. SCN can be caused by several gene mutations and is sometimes part of a syndrome. The list of monogenic neutropaenia disorders is growing. Single-gene disorders can be classified as being sporadic, autosomal dominant (AD), autosomal recessive (AR) or X-linked. Autosomal dominant inherited *ELANE* mutations are the most common cause of SCN and can be found in about half of the patients. *ELANE*,

previously known as *ELA-2*, encodes for neutrophil elastase, which has a very important role in neutrophil activation. However, the molecular mechanisms by which *ELANE* mutations disrupt granulopoiesis are not well understood. More than 70 different mutations of the *ELANE* gene have been linked to patients with SCN and cyclic neutropaenia. Some of these genetic defects are present in both SCN and cyclic neutropaenia patients, but some are restricted to SCN patients without a clear explanation of how a specific mutation may be associated with completely different phenotypes. *GATA2, GFI1* and *CXCR4* are other examples of genes with autosomal dominant inheritance. The most frequent autosomal recessive pathogenic defects are mutations in *HAX1*, whose product contributes to the activation of the granulocyte colony-stimulating factor (G-CSF) signalling pathway. SCNs due to mutations in *G6PC3, JAGN1, SBDS* (which cause Shwachman-Diamond syndrome) and *SLC37A4* are also disorders that are inherited in a recessive manner. Those diseases are usually diagnosed in consanguineous populations, and these patients are usually the first to receive the diagnosis of SCN. X-linked inheritance of gain-of-function mutations in the Wiskott-Aldrich syndrome gene was first described in a Belgian report containing five cases.[10] An exhaustive list with all forms of congenital neutropaenia can be found in a review about congenital neutropaenias.[1] SCN predisposes to myelodysplastic syndromes (MDS) or acute myeloid leukaemia (AML) with an increased risk of 10^3 to 10^4. In these diseases, sepsis mortality was stable at 0.9% per year, but the risk of MDS/AML increased significantly over time. Ten-year follow-up showed a cumulative incidence of 8% for sepsis mortality and 21% for MDS/AML. By twelve years, the cumulative incidence of MDS/AML had reached 36%. All patients with SCN have a significant risk of developing MDS/AML, but patients who are less responsive to treatment with G-CSF appear to be at a remarkably high risk. The contribution of filgrastim to the process is controversial.[11] The availability of recombinant G-CSF for clinical use dramatically changed both the prognosis and the quality of life for patients with SCN. Overall survival is now estimated to exceed 80%, including patients developing malignancies, compared to 10-20% before the G-CSF era.[12-14]

Cyclic neutropaenia (CyN) is a rare neutrophil disorder in which the neutrophil count drops to a very low level at approximately 21-day intervals. The disease can arise spontaneously, or it can be inherited by germline mutations of *ELANE* in an autosomal dominant pattern. Therefore, it can be present in several members of the same family. The central pathophysiological mechanism of CyN is failure of the bone marrow, which results in failing to maintain a consistent production of mature neutrophils.[15] The symptoms include fever, recurrent mouth infections and oral ulcerations, lymphadenopathy, malaise and sometimes severe infections. In between neutropenic periods, affected individuals are generally healthy. CyN has a lower risk of evolution to MDS and AML and a milder morbidity compared to SCN.[16] Usually, the disease is diagnosed at childhood, but there is a subset of patients with a later onset.

INFECTIONS

Infectious diseases are the most common cause of an acute low ANC in paediatric and adult patients. Neutropaenia can occur during or following a variety of bacterial, parasitic, fungal and viral infections, including hepatitis and human immunodeficiency virus infection. It is important to note that neutropaenia may be both the cause and the consequence of infection. Less commonly, neutropaenia is seen in case of an overwhelming sepsis, which is associated with a poor prognosis due to depletion of the bone marrow storage pool.[17-18]

DRUGS

Non-chemotherapy idiosyncratic drug-induced neutropaenia (IDIN) is a frequent cause of iatrogenic neutropaenia. The actual annual incidence varies across different sources and ranges from 3-16 cases per million inhabitants per year. Although IDIN is not the major cause of all neutropaenias, it is reportedly the cause in as many as two thirds to three quarters of severe cases of neutropaenia.[19] The pathogenesis of IDIN has not been fully elucidated and seems multifactorial including direct damage to the myeloid cell line and immune-mediated destruction.[20] The idiosyncratic nature of IDIN, the lack of animal models and diagnostic testing and its low overall incidence make rigorous studies to explain possible mechanisms exceptionally difficult. Also, drug-induced neutropaenia is a serious concern for the development of new drugs because it can be missed in clinical trials as the incidence is very low. Neutropaenia from non-chemotherapy medications typically occurs within the first few months of starting a new drug. The important variations among the population in front of the same drug can be explained by genetic susceptibility. Almost all classes of medications and hundreds of herbals and supplements have been associated with drug-induced neutropaenia. Moreover, over 125 drugs have been linked to causing drug-induced agranulocytosis.[21] The drugs most frequently associated with IDIN include drugs of the thioamide group (metamizole, thiamazole, carbimazole), antibiotics (beta-lactams, trimethoprim-sulfamethoxazole, vancomycin), psychotropic agents (clozapine, olanzapine, quetiapine, risperidone), anticonvulsants (carbamazepine, valproic acid), sulfasalazine, azathioprine, quinine, ticlopidine and valganciclovir. Some anti-cancer agents not

typically considered to be myelosuppressive may also cause neutropaenia (e.g., rituximab, tyrosine kinase inhibitors). Levamisole is an anti-helminthic and immunosuppressant drug that was withdrawn in 2000 because of side effects such as agranulocytosis and systemic vasculitis. For the last years, an increased incidence of levamisole-induced neutropaenia has been reported in chronic cocaine and heroin users because of adulteration of hard drugs with levamisole.[22] Mortality associated with IDIN is currently estimated at 5%, which is significantly lower than estimates 20 years ago, which was as high as 20%. The main reason is increased awareness among both physicians and patients and the early initiation of an accurate approach.[21,23] The mortality rate increases with age (>65 years), lower ANC, development of sepsis or septic shock and pre-existing comorbidities such as renal, cardiac or pulmonary impairment. Early detection and treatment is critical because 60% of untreated patients develop severe infections.[24]

IMMUNE-MEDIATED CAUSES

Transient neonatal neutropaenia is caused by passive transfer of maternal antibodies directed to paternal antigens on foetal neutrophils. The neutropaenia can last from several weeks to (rarely) several months.

Chronic autoimmune neutropaenia (AIN) is classified as primary or secondary depending on the underlying disease. Primary AIN does not have an apparent cause. The syndrome typically occurs in infants and young children under the age of five, but the range extends from one month to adulthood. The occurrence of infections is very low and the neutropaenia usually resolves spontaneously.[25] On the other hand, secondary AIN has been associated with a variety of underlying diseases including autoimmune diseases (RA, systemic lupus erythematosus, Sjögren syndrome), immunological deficiency syndromes (common variable immune deficiency, autoimmune lymphoproliferative syndrome), solid tumours (pure white cell aplasia associated with thymoma) and haematological conditions. AIN related to haematological conditions can be divided into three categories: Large granular lymphocyte (LGL) leukaemia, Evans syndrome and other haematological malignancies.[26] The overall age-standardised incidence of LGL leukaemia in The Netherlands has been reported as 0.72 per 1,000,000 persons per year.[27] Chronic neutropaenia is the most common presenting symptom of LGL leukaemia and anaemia the second most common. Approximately 10-40% of patients will have a history of autoimmune disorders, most frequently RA. Historically, the triad consisting of RA, splenomegaly and neutropaenia defines Felty's syndrome (FS). LGL leukaemia patients with RA may also have splenomegaly and neutropaenia, and may be clinically indistinguishable from FS patients.[28] Evans syndrome is a combination of at least two autoimmune cytopaenias such as haemolytic autoimmune anaemia, autoimmune thrombocytopaenia and autoimmune neutropaenia. Finally, immune neutropaenia can appear in the context of chronic lymphocytic leukaemia, Waldenström's macroglobulinaemia and Hodgkin lymphoma. Secondary AIN is more common in adults, most often occurring between the ages 40 and 60. The neutropaenia is often mild or moderate, and the risk of infection is unpredictable.[26]

Chronic idiopathic neutropaenia (CIN) describes a heterogeneous group of disorders associated with a reduced number of circulating neutrophils. CIN is a diagnosis of exclusion in neutropenic patients without an apparent cause or mechanism. It can be difficult to distinguish between primary AIN and CIN. Both disorders have neutropaenia with an ANC count between 0.5 x 10^9/L and 1 x 10^9/L and often have a benign course. Unlike primary AIN, CIN is characterised by older age at presentation (late childhood or adulthood), female predominance and the absence of spontaneous remission.[29]

NUTRITIONAL DEFICIENCIES

Deficiencies of vitamins and minerals typically cause neutropaenia along with other cytopaenias, but isolated neutropaenia is also possible. Common causes include alcohol use, inadequate dietary intake, intestinal disorders and a history of bariatric surgery.[17]

UNCOMMON CAUSES

Hypersplenism, metabolic disorders and complement activation are rare causes of isolated neutropaenia. For the latter cause, the exposure of blood to artificial membranes such as in dialysis may result in neutropaenia due to neutrophil destruction via complement activation *in vivo*.[30]

DIAGNOSIS, MANAGEMENT AND FOLLOW-UP

New onset neutropaenia, even in the presence of physical findings or symptoms, requires further evaluation. Longstanding neutropaenia without a history of infection suggests a more benign cause such as constitutional neutropaenia. Most causes of neutropaenia are benign, especially if the ANC is above 1 x 10^9/L. We suggest the following stepwise approach for managing neutropaenia (*Figure 2*).

First, it is essential to repeat the differential WBC count manually to exclude a pseudoneutropaenia by laboratory error. Secondly, the physician must assess the severity of the neutropaenia. Despite the advances in modern diagnostic tests, the medical history and physical examination are still crucial to achieve an accurate diagnosis. The medical record must

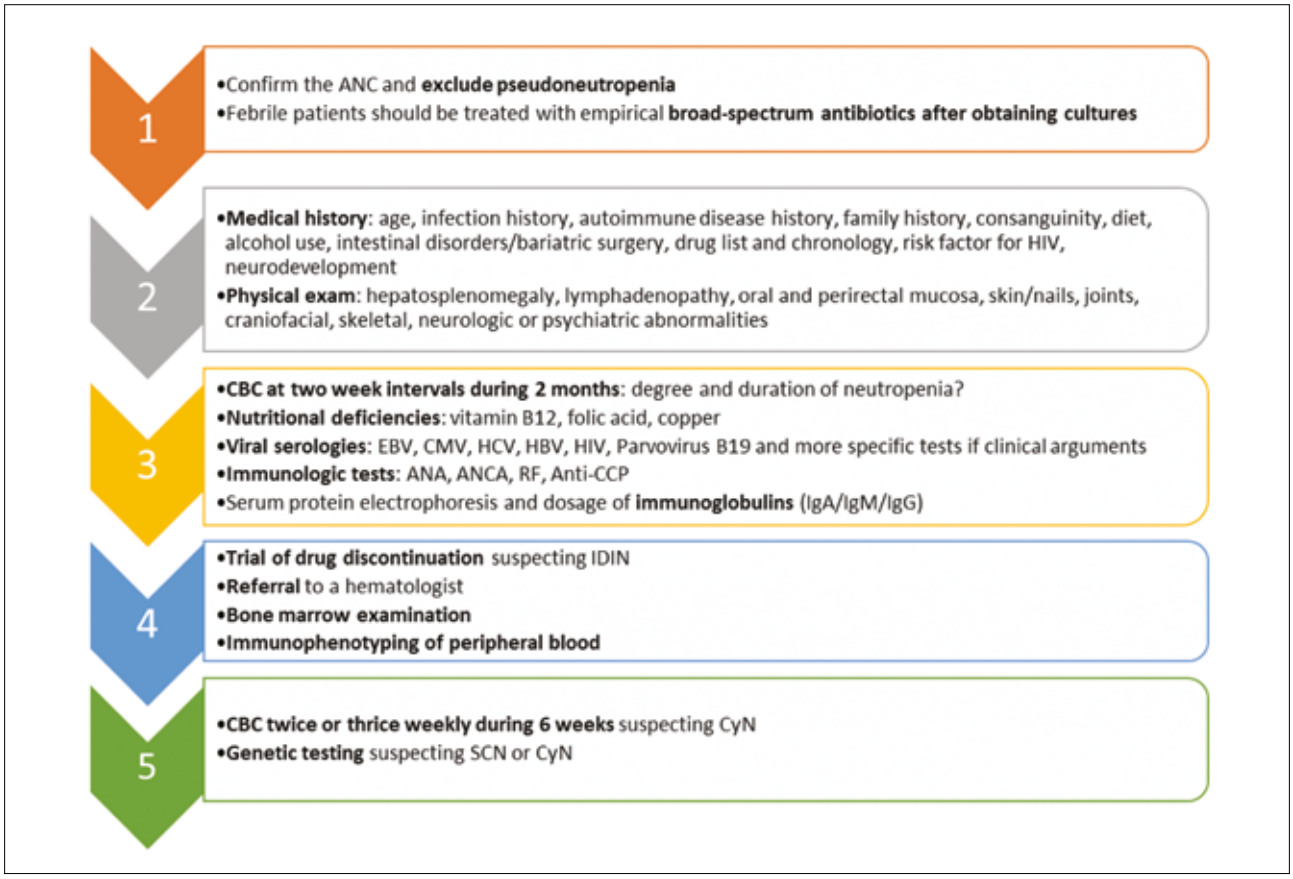

FIGURE 2. Management of neutropaenia.

ANC: absolute neutrophil count, HIV: human immunodeficiency virus, CBC: complete blood count, EBV: Epstein-Barr virus, CMV: cytomegalovirus, HCV: Hepatitis C virus, HBV: Hepatitis B virus, ANA: antinuclear antibodies, ANCA: anti-neutrophil cytoplasmic antibodies, RF: rheumatoid factor, Anti-CCP: anti-cyclic citrullinated peptide, IgA: immunoglobulin A, IgM: immunoglobulin M, IgG: immunoglobulin G, IDIN: idiosyncratic drug-induced neutropaenia, CyN: cyclic neutropaenia, SCN: severe congenital neutropaenia.

always include a family history. This is extremely important to determine whether there are multiple individuals in the same family with similar medical problems and if the patient's parents are consanguineous. Moreover, the simultaneous presence of multiple clinical clues can point in the direction of an underlying syndrome. For instance, short stature, failure to thrive, exocrine pancreatic insufficiency and the presence of neutropaenia are common manifestations of Shwachman-Diamond syndrome.[1] The actual bone marrow reserve and ability to produce neutrophils can be estimated indirectly from some clinical findings. The presence of mucosal ulcerations or severe stomatitis suggests an inability to deliver neutrophils. However, a neutropenic patient with a frank abscess or purulent exudate succeeds in delivering neutrophils to the inflamed tissue and seems to have an adequate bone marrow reserve.

The obligated blood test requires a complete blood count (CBC), inflammatory parameters and a screening for nutritional deficiencies, infectious diseases and auto-immune causes. Obtaining previous CBCs with differential counts can be very useful to assess the natural course. Neutropaenia accompanied by anaemia and/or thrombocytopaenia suggests a nutritional deficiency, an autoimmune disorder or a primary bone marrow disorder. Increased (or normal) absolute monocyte counts are seen in many patients with chronic forms of neutropaenia. Autoimmune neutropaenia is characterised by the presence of autoantibodies – usually immunoglobulin G – directed against neutrophils. Seven antigens have been described in the human neutrophil alloantigen (HNA) system, and they have been classed into five groups: HNA-1, HNA-2, HNA-3, HNA-4 and HNA-5.[26] While scientifically interesting, the presence or absence of detectable antibodies in the serum is not helpful in the diagnosis or management of immune neutropaenia. There are many technical difficulties with neutrophil antibody testing, and very few laboratories are able to carry out all of the possible tests. Moreover,

there is a significant false negative rate unless several different detection methods are used, and neutrophil-antibodies can be present in the absence of neutropaenia too.[31] We also recommend a peripheral blood smear and flow cytometry on peripheral blood to detect diseases such as LGL leukaemia. The diagnosis of LGL leukaemia should always be considered in the appropriate clinical context of presenting features such as cytopaenias and autoimmune diseases. An increased blood count of large granular lymphocytes (>0.5 x 10^9/L) is supportive, but the diagnosis of LGL leukaemia needs to be confirmed by detection of clonality in the LGL population, which distinguishes the LGL expansion from a polyclonal, reactive lymphocytosis that may accompany a viral infection, post-splenectomy status or bone marrow/organ transplantation. The T-cell form will usually show an immunophenotyping pattern characterised by CD3+/CD8+/CD57+, whereas the NK-cell form will usually show CD3-/CD8+/CD16+/CD56+.[28]

The most reasonable approach for isolated mild or moderate neutropaenia in the absence of infections or any abnormal clinical finding consists of a period of observation and obtaining serial blood counts at increasing intervals. We recommend to check the blood counts and re-evaluate the patient at two week intervals for the first two months. If the neutropaenia persists, the interval can be prolonged to approximately every three months. After the first year, follow-up can be discontinued, but the patient has to be informed about alarm symptoms of infectious complications. As a general rule, the frequency of visits can be decreased if a greater time without infections elapses and the neutropaenia is not evolving to a more severe condition.

A referral to a haematologist is recommended in case of an ANC <0.5 x 10^9/L, longstanding neutropaenia >4 weeks, more than 1 affected blood cell lineage, splenomegaly, B-symptoms and serious infections.

The ability of the bone marrow to produce adequate neutrophils can be demonstrated by an elevation of the ANC in response to a corticosteroid stimulation test or G-CSF, but it is only determined with certainty from a bone marrow examination. The presence of more than one affected blood lineage, chronicity or severity of neutropaenia and/or stigmata of an inherited bone marrow failure syndrome requires further examination. A bone marrow aspirate and biopsy will be the next step of our approach to exclude (or confirm) haematological diseases such as leukaemia, aplastic anaemia and myelodysplasia. It is important to perform the bone marrow examination in a reasonably stable condition (after treatment is given for an acute infection). Reduced bone marrow cellularity or late myeloid arrest at the myelocyte or metamyelocyte stage is seen in some cases of idiopathic or autoimmune neutropaenia, some drug-induced neutropaenias and chronic infection. Myeloid hypoplasia and early myeloid arrest characterise toxic drug-induced neutropaenias, pure white cell aplasia, LGL syndrome, SCN and MDS. Furthermore, patients with BEN, AIN, drug-induced mild to moderate neutropaenia that is dose-related and stable, splenic sequestration of neutrophils or chronic idiopathic neutropaenia without frequent infections have an adequate bone marrow reserve of neutrophils and do not require extensive monitoring for infection.[1,5,19,26]

Genetic testing should be performed when SCN is suspected. Germline mutations can be identified by DNA sequencing of blood, saliva or another tissue sample. When using genetic sequencing to confirm a diagnosis of SCN, analysis of the most commonly affected *ELANE* gene should be considered first, unless the family history of the patient, clinical clues from the physical examination or general laboratory testing suggest otherwise. If *ELANE* mutations are not detected, sequencing of a panel of neutropaenia-associated genes (mostly in association with a primary immunodeficiency gene panel) or whole-exome sequencing can be performed. Additional benefits to greater use of next-generation sequencing (NGS) include earlier identification of cancer/leukaemia predisposition syndromes, better selection of related stem cell donors and more accurate family planning and genetic counselling. However, NGS is not going to solve everything because bone marrow failure NGS panels may miss if mutations occur in regulatory regions. Despite the improvement of sequencing technologies, a genetic diagnosis could not be found so far in about one third of registered European SCN patients.[1,12] A diagnosis of cyclic neutropaenia doesn't always require genetic testing and may be confirmed by monitoring an individual's neutrophil count twice or thrice weekly for six weeks.

The SCN International Registry recommends a CBC with differential every three months, and a yearly surveillance marrow should be performed to detect *CSF3R* mutations and chromosomal abnormalities.

If a previously asymptomatic patient develops new symptoms or physical findings (e.g., B-symptoms, splenomegaly, new abnormalities on the CBC), a re-evaluation of the cause of neutropaenia is appropriate.

TREATMENT

PREVENTION, ANTIBIOTICS AND GRANULOCYTE INFUSIONS

Regular dental care and mouthwashes, proper patient hand hygiene, updated age-appropriate immunisations, good nutritional status and healthy living patterns are preventive measures that are recommended in all neutropenic patients.

Vitamin deficiencies should be thoroughly supplemented.
The treatment of fever mainly depends on the bone marrow reserve. Fever in a patient with neutropaenia due to chemotherapy, hematopoietic cell transplant or bone marrow suppression from any cause is a medical emergency because such patients are at risk of sepsis and death from overwhelming infections. Treatment with empiric intravenous broad-spectrum antibiotics should be initiated rapidly and must cover for gram-negative organisms including *Pseudomonas* species. In general, antibiotics should not be discontinued until resolution of fever and ANC increase above 0.5 x 10^9/L. The treatment of an infection in those known to have an adequate bone marrow neutrophil reserve can be similar to the general population. If a patient presents with fever and neutropaenia of unknown cause, one must assume that the patient has an inadequate marrow reserve and is at high risk of infection. Granulocyte infusions are controversial and have been given to patients with gram-negative sepsis who have not shown a clinical response to antibiotics within 24-48 hours. Patients with chronic neutropaenia should be monitored for fungal infections. Both prophylactic antibiotics and routine reverse isolation procedures are of no value.[32]
For all patients with neutropaenia, it is important to inform the patient and family about the risk of infection and when they should seek medical advice. We must also reassure patients with isolated chronic asymptomatic neutropaenia that they don't have an increased risk of developing leukaemia.

DRUG DISCONTINUATION

The most important treatment of IDIN is discontinuation of the offending drug. Infection and malignancy have to be excluded before a diagnosis of IDIN is considered. In the case of mild or moderate neutropaenia, the drugs can be reduced or discontinued (temporarily). On the other hand, severe neutropaenia or agranulocytosis require immediately and permanently discontinuation of the implicated drug. It can be difficult to determine the causative agent if the patient is taking multiple medications, but those drugs frequently associated with IDIN should be suspected initially. After drug removal, most cases of neutropaenia resolve over time, and only symptomatic therapy such as antibiotics for treatment of infections are necessary. Serial ANCs following discontinuation of the suspected drugs should show an improvement over two or three weeks, unless the drug has a longer half-life. The average time for full recovery of the neutrophil count is nine days (range: 9-24 days). Clozapine-induced neutropaenia may have a variable time of recovery.[19] It is also important to mention the implicated drug(s) as a contraindication in the patient's medical record.

GROWTH FACTORS

Myeloid differentiation and proliferation is highly sensitive to G-CSF stimulation. The subcutaneous administration of exogenous G-CSF amplifies neutrophil production and shortens maturation time from 5 days to 1 day, leading to the rapid release of mature neutrophils from the bone marrow into the circulation.
The use of G-CSF is controversial and there are no strict criteria. Growth factors should be given to patients with an ANC <0.5 x 10^9/L, decreased marrow reserve or neutropaenia associated with early myeloid arrest and recurrent aphthous ulcers, a single life-threatening unprovoked infection or two or more serious infections over the course of a year. Treatment with G-CSF is indicated in most cases of SCN, human immunodeficiency virus (HIV) infections, aplastic anaemia and CIN with recurrent infections. The use of G-CSF prior to confirmation of a correct diagnosis may impair diagnostic efforts. G-CSF can be classified as short-acting agents (filgrastim, lenograstim) or long-acting preparations (pegfilgrastim, lipegfilgrastim). Possible side effects are bone pain, headache and splenomegaly. We prefer short-acting preparations, rather than long-acting PEGylated G-CSF, to treat non-chemotherapy induced neutropaenia because of reimbursement restrictions and increased side effects with the latter in SCN patients. The Belgian reimbursement criteria of filgrastim include primary and secondary prevention and treatment of febrile neutropaenia due to cytotoxic therapies, hematopoietic stem cell transplantation settings, SCN, HIV-related neutropaenia and CIN. On the other hand, lenograstim is only reimbursed for oncology and hematopoietic stem cell transplantation settings.
The starting dose of filgrastim is 5 μg/kg/day in case of myelosuppressive chemotherapy, idiopathic neutropaenia and cyclic neutropaenia. Patients experiencing prolonged neutropaenia in case of IDIN may also require additional treatment with hematopoietic growth factors after discontinuation of the drug. However, G-CSFs are currently not approved for the use in IDIN. A commonly reported dosage for treatment of adult patients is a daily subcutaneous injection of 300 μg.[33]
The initial recommended dose for patients with SCN is 6 μg/kg/day as a twice daily injection, but the dose needs to be adjusted based on the neutrophil count and clinical status. The patient is considered a 'non-responder' at G-CSF dosages of >50 μg/kg/day and ANCs of <0.5 x 10^9/L, but some experts use a lower threshold (25 μg/kg/day) for defining a poor or non-responder.[1,12] We recommend titering the dose of filgrastim to achieve an ANC of 0.5 x 10^9/L to 0.75 x 10^9/L. Patients who don't respond to filgrastim need to be evaluated for CSF3R mutations in the external domain.

KEY MESSAGES FOR CLINICAL PRACTICE

1. Neutropaenia can be categorised as mild (absolute neutrophil count [ANC] between 1 x 10^9/L and 1.5 x 10^9/L), moderate (ANC between 0.5 x 10^9/L and 1 x 10^9/L) and severe (ANC below 0.5 x 10^9/L). Chronic neutropaenia means that the neutropaenia persists longer than three months.
2. The peripheral blood neutrophil count represents only a small percentage of total body neutrophils. The risk of infection in those with non-chemotherapy-induced neutropaenia can be quite variable and mainly depends on the bone marrow reserve.
3. Acute neutropaenia in adulthood is usually caused by drugs and infections. The most common causes of mild chronic neutropaenia are benign ethnic neutropaenia and drug-induced neutropaenia.
4. We suggest a stepwise approach for the management of neutropaenia with a profound medical history, complete physical examination and blood study including screening for nutritional deficiency, infectious diseases and autoimmune causes.
5. Neutropaenia is a side effect of most classes of medications, but trimethoprim-sulfamethoxazole, clozapine and anti-thyroid medications have been the most frequently associated with agranulocytosis. Severe neutropaenia requires immediately discontinuation of the implicated drug.
6. Asymptomatic patients with mild or moderate neutropaenia can be observed with serial blood counts at increasing intervals. A referral to a haematologist is recommended in the event of an ANC <0.5 x 10^9/L, longstanding neutropaenia >4 weeks, more than one affected cell lineage, splenomegaly, B-symptoms and serious infections.
7. Growth factors should be given to patients with an ANC <0.5 x 10^9/L, a decreased marrow reserve or neutropaenia associated with early myeloid arrest and recurrent aphthous ulcers, a single life-threatening unprovoked infection or two or more serious infections over the course of one year. Treatment with G-CSF is indicated in most cases of SCN, HIV infections, aplastic anaemia and chronic idiopathic neutropaenia with recurrent infections.

IMMUNOSUPPRESSIVE THERAPY

Specific treatment of AIN is usually not required. Primary AIN does not justify curative therapy as the disease is characterised by a spontaneous remission. Immunosuppressive therapy should only be proposed for symptomatic patients with CIN or AIN who fail to respond to G-CSF.[29] In case of secondary AIN, the underlying disease must be treated.[26] Immunosuppressive regimens are the mainstay of treatment of LGL leukaemia because its pathogenesis is attributed to sustained activation of cytotoxic cells. Guidelines for front-line therapy have not been established. Current first-line therapeutic options include methotrexate, cyclophosphamide and cyclosporin A. They should be continued if tolerated for at least four months to determine response. In certain circumstances, prednisone can be added if a faster response is needed (e.g., severe neutropaenia <0.1 x 10^9/L). Overall response rates for any of these first-line therapies are approximately 50-60% in retrospective studies without evidence of cross-resistance among the different treatments.[28]

TRANSPLANTATION

Indications for an (early) allogeneic hematopoietic stem cell transplantation include SCN patients who are less responsive to G-CSF or require high doses of filgrastim, the presence of a mutated *CSF3R* or the appearance of frank myelodysplasia or increased bone marrow or peripheral blasts. Deciding the optimal time point for hematopoietic stem cell transplantation in patients who do not respond to G-CSF treatment remains very difficult.[34,35]

CONCLUSION

Neutropaenia is a common finding on routine blood studies. The most frequent causes in adulthood include BEN, infections, drug-induced neutropaenia, nutritional deficiency, autoimmune disorders and primary haematological disease. Also, younger patients should be screened for a congenital cause such as severe congenital neutropaenia or cyclic neutropaenia. The risk of infection in those with non-chemotherapy-induced neutropaenia can be quite variable and mainly depends

on the bone marrow reserve. After exclusion of pseudoneutropaenia, we suggest a stepwise approach with a profound medical history, complete physical examination and orienting blood test in the first place. Afterwards, a bone marrow examination, trial of drug discontinuation or genetic testing may be considered. Asymptomatic patients with mild or moderate neutropaenia can be observed with serial blood counts at increasing intervals. A referral to a haematologist is generally recommended in the event of an ANC of $<0.5 \times 10^9$/L, longstanding neutropaenia, more than one affected cell lineage, splenomegaly, B symptoms and serious infections. Fever in a patient with mild or moderate neutropaenia should be managed according to age and vitals. In contrast, patients with infection and severe neutropaenia will require hospital admission and administration of intravenous broad-spectrum antibiotics. Growth factors should be given to patients with an ANC of $<0.5 \times 10^9$/L, decreased marrow reserve or neutropaenia associated with early myeloid arrest and recurrent infections. However, the use of G-CSF is still influenced by clinical experience and the Belgian reimbursement rules. Tailored NGS may help to find a genetic cause in the SCN patients without detectable mutations at this time. Future objectives of acquired neutropaenia include elucidating the mechanisms of IDIN, better selection of patients at high risk of infection and finding variables to distinguish infectious, autoimmune or drug-related causes of neutropaenia.

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Practical management of newly-diagnosed multiple myeloma: 2018 update for transplant eligible patients

M.C. Vekemans[1], N. Meuleman[2], C. Doyen[3], K.L. Wu[4], P. Mineur[5], G. Bries[6], A. Kentos[7], L. Michaux[8], M. Delforge[9]
On behalf of the Multiple Myeloma Study Group of the Belgian Hematology Society

SUMMARY

With the introduction of immunomodulatory agents and proteasome inhibitors, major improvements have been achieved in the treatment and outcome of multiple myeloma. Different treatment combinations are now in use and newer therapies are being developed. Nevertheless, autologous stem cell transplantation remains the corner stone of therapy for fit, newly-diagnosed multiple myeloma patients. Based on an extensive review of the recent literature, we propose recommendations on myeloma care, to be used by haematologists as a reference for daily practice.

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INTRODUCTION

The treatment landscape for multiple myeloma (MM) is rapidly changing. Based on an extensive review of the recent literature, we propose an update of our recommendations on myeloma care for transplant-eligible patients in first-line therapy.[1] Levels of evidence and grades of recommendations are based on previously published methods.[2] We recommend participation in clinical trials to gain knowledge in the fast evolving field of MM treatment.

INITIAL THERAPY IN SYMPTOMATIC MULTIPLE MYELOMA

Treatment has to be initiated in all patients with a diagnosis of MM as defined by the IMWG 2014 criteria.[3] The recommended investigations to be performed at diagnosis are reported elsewhere in this issue (*Fostier et al*). All patients should undergo risk stratification using ISS and cytogenetic evaluation (FISH), even if risk-adapted therapy is not available in most cases at the moment. The goal of therapy in MM is to achieve the maximal response since MRD negativity is associated with better long-term outcome.[4]

Autologous stem cell transplantation (ASCT) remains the standard of care for fit, newly diagnosed MM (NDMM) patients, although remarkable results have been obtained in the non-transplant setting with novel agents.[5,6] Selection criteria for high-dose therapy (HDT) include age, performance status and comorbidities. As there is no definite age cut-off in the context of transplantation, specific risk-assessment models can be used to better evaluate the risk-benefit ratio of the procedure for each patient.[7,8]

[1]Department of Hematology, Cliniques universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium; [2]Department of Hematology, Institut Bordet, Université Libre de Bruxelles, Brussels, Belgium; [3]Department of Hematology, Cliniques universitaires Mont-Godinne, Université catholique de Louvain, Yvoir, Belgium; [4]Department of Hematology, Ziekenhuis Netwerk Antwerpen Middelheim, Antwerpen, Belgium; [5]Department of Hematology, Grand Hopital de Charleroi, Charleroi, Belgium; [6]Department of Hematology, AZ Turnhout, Turnhout, Belgium; [7]Department of Hematology, Hopitalde Jolimont, Haine Saint-Paul, Belgium; [8]Department of Human Genetics, Universitair Ziekenhuis Gasthuisberg, Katholieke Universiteit Leuven, Leuven, Belgium; [9]Department of Hematology, Universitair Ziekenhuis Gasthuisberg, Katholieke Universiteit Leuven, Leuven, Belgium. Please send all correspondence to: M.C. Vekemans, MD, Department of Hematology, Cliniques universitaires Saint-Luc, Université catholique de Louvain, 10 avenue Hippocrate, 1200 Brussels, Belgium; tel: +32 (0)2 764 1800, email: marie-christiane.vekemans@uclouvain.be.

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THERAPY FOR TRANSPLANT-ELIGIBLE PATIENTS

The current treatment paradigm for NDMM patient eligible for ASCT consists of 4 phases: induction, transplantation, post-transplant consolidation and maintenance.

INDUCTION

Induction therapy usually consists of 4-6 cycles of therapy with the aim to achieve rapid disease control, improve symptoms and allow for subsequent stem cell collection.

Bortezomib-dexamethasone (VD) is the standard backbone of induction therapy.[9,10] The addition of a **third agent**, thalidomide (VTD)[11], cyclophosphamide (VCD)[12], doxorubicine (PAD)[13] or lenalidomide (VRD)[14] provides higher response rates. In prospective trials, induction with **VTD** is superior to VCD in terms of response rate, at the cost of a higher incidence of peripheral polyneuropathy (PN) but lower incidence of haematological toxicities. Of note, progression-free (PFS) and overall survival (OS) were not assessed in this study.[15] To reduce the PN incidence, the IFM proposed the **vtD** regimen with reduced doses of bortezomib and thalidomide, which is associated with a lower incidence grade 3/4 PN (14% *vs.* 34%), but at the expense of lower response rates.[16] **VCD** was also shown to be as effective as PAD in terms of response, but less toxic.[17] Replacement of thalidomide by lenalidomide in the **VRD** regimen induces higher CR rates before and after ASCT (47% and 88% of patients with a very good partial response [VGPR] or better, respectively).[14] Current regimens used in front-line are listed in *Table 1*. Other highly effective combinations such as carfilzomib-lenalidomide-dexamethasone (KRd) or ixazomib-lenalidomide-dexamethasone (IRd) are currently under evaluation in phase 3 trials.

Four-drug regimens combining cyclophosphamide with VRD or KTD do not provide substantial advantage over 3-drug combinations, due to a higher incidence of adverse events.[18,19] However, the introduction of monoclonal antibodies will change the landscape of induction therapy in the near future. Ongoing prospective trials combining daratumumab with VTD (Cassiopeia) or VRD (Perseus), or elotuzumab with VRD are exploring the role of induction with antibody-based quadruplets.

Besides expected efficacy of the regimen chosen for induction, it is also important to take into account its expected toxicity. Patients should be evaluated for risks of infection, PN and thromboembolic disease. Vaccination and bisphosphonate therapy should be systematically recommended.

STEM CELL COLLECTION

Peripheral blood progenitor cells are usually collected for more than one ASCT (at least 2.5 x10^6 CD34+ cells/kg per transplantation). Since the use of lenalidomide can impair stem cell collection, apheresis in this situation should be performed after 3-4 cycles, and may require the use of cyclophosphamide or plerixafor.

HDM-ASCT

High-dose melphalan (melphalan 200 mg/m^2, MEL200) remains the standard conditioning regimen prior to ASCT. A dose reduction (100 to 140 mg/m^2) is recommended in case of renal impairment (estimated GFR <60ml/min). In this group of patients, including those requiring dialysis, ASCT is feasible but exposes the patient to severe mucositis, prolonged hospitalisation and an increased risk of transplant-related mortality (4% *vs.* <1%).[20]

Despite encouraging results from phase 2 studies, the addition of bortezomib (1 mg/m^2 on days -6, -3, +1, +4) to HDM fails to show any additional benefit in a prospective randomised trial.[21,22]

UPFRONT OR DELAYED ASCT

Based on the efficacy and safety profile of novel agents in the non-transplant setting, the question to delay ASCT at the time of first relapse has been raised in 2 phase 3 trials. In the IFM 2009 trial, VRD induction plus ASCT was associated with a significantly longer PFS than VRD alone (50 *vs.* 36 months), without an effect on OS.[14] ASCT could not be performed in 21% of the patients in the VRD arm, mainly because of disease refractoriness at relapse. In the EMN02-HOVON95 trial, upfront ASCT resulted in a significantly longer PFS compared with non-transplant (not reached *vs.* 46 months) but in the setting of PI-based induction (VCD) and consolidation (VMP). There was no impact on OS (immature follow-up), except in high-risk patients defined by the presence of del(17p) and/or t(4;14) and/or t(14;16) or a stage III R-ISS).[23]

A second, Italian phase 3 trial confirmed a significant PFS advantage with upfront ASCT compared to conventional treatment with cyclophosphamide-lenalidomide-dexamethasone (43.3 *vs.* 28.6 months).[24] In the absence of an OS benefit, the decision to proceed to ASCT upfront can be evaluated in perspective of patient preferences or risk of toxic effects, particularly in case of co-morbidities. In the near future, these decisions will probably be guided by the MRD status achieved after induction therapy, although this needs to be explored prospectively.

POST-TRANSPLANT STRATEGIES

The concept of consolidation and/or maintenance is a commonly adopted approach after transplantation. The objective

TABLE 1. Currently used first-line regimens in transplant-eligible newly-diagnosed MM.

Front-line regimens	Schedule	≥PR	≥VGPR	Median PFS	3-year OS rate
VTD [11]	Bortezomib: 1.3 mg/m² sq days 1, 8, 15, 22 Thalidomide: 100 mg orally days 1-21 Dexamethasone: 40 mg orally days 1, 8, 15, 22 28-day cycles	93%	63%	NR	90%
vTD [16]	Bortezomib: 1 mg/m² sq days 1, 8, 15, 22 Thalidomide: 100 mg, J1-28 Dexamethasone: 40 mg orally days 1-4, 9-11 on cycles 1-2, days 1-4 on cycles 3-4 21-day cycles	89%	51%	26 months	NA
VCD [12]	Bortezomib: 1.3 mg/m² IV or sq days 1, 8, 15, 22 Cyclophosphamide: 300 mg/m2 orally days 1, 8, 15 Dexamethasone: 40 mg orally days 1, 8, 15, 22 28-day cycles	88%	71%	NA	NA
PAD [13]	Bortezomib: 1.3 mg/m² sq days 1, 8, 15, 22 Adriamycine: 9 mg/m² days 1-4 Dexamethasone: 40 mg orally days 1-4,9-12,17-20 28-day cycles	90%	42%	35 months	61%
VRD [14]	Bortezomib: 1.3 mg/m² sq, days 1,4,8,11 Lenalidomide: 25 mg orally, days 1-14 Dexamethasone: 20 mg orally, days 1, 2, 4, 5, 8, 9, 11, 12 28 days cycles		CR, 49%	50 months	81% at 4 years

A: doxorubicin; C: cyclophosphamide; D: dexamethasone; M: melphalan; P: prednisone; NA: not available; NR: not reached; OS: overall survival; PAD: bortezomib, doxorubicin, dexamethasone; PFS: progression-free survival; PR: partial response; R: lenalidomide; t: low-dose thalidomide; T: thalidomide; v: low dose bortezomib; V: bortezomib; VGPR: very good partial response.

of such an approach is to improve the depth of response (consolidation) and extend the duration of response (maintenance) to ultimately prolong the PFS and eventually also the OS. Consolidation relates to the administration of a short-term intensive therapy aimed at improving the quality of response after transplant. Maintenance, on the other hand, consists of the administration of a therapy for a prolonged period in order to maintain the response achieved after ASCT and prevent progression.

Consolidation with second ASCT

Before the era of novel agents, the main approach was to propose a second ASCT. However, tandem ASCT did not provide any OS or PFS advantage, except in patients not achieving VGPR after the first transplant.[25,26] With the introduction of novel agents, this concept has been revisited. With tandem ASCT, the HOVON-65/GMMG-HD4 trial showed a benefit in OS, particularly in patients with a del(17p),[27] when using bortezomib in induction and maintenance, but the study was not powered for a comparison between single and double ASCT.[13] The EMN02/H095 trial compared single *vs.* tandem ASCT, the second transplant being conducted according to the transplant policy of each centre. Tandem ASCT was associated with a significant improvement in PFS and OS (3-year PFS rate: 73% *vs.* 64%; 3-year OS rate: 89% *vs.* 81%), with a more pronounced benefit in patients with high-risk cytogenetics (3-year PFS: 69% *vs.* 44%). Double transplant emerged as an independent prognostic factor predicting PFS.[28] Contradictory results were reported by the StaMINA trial in which a second ASCT offered no PFS or OS advantage over single ASCT in the context of lenalidomide maintenance.[29] Nevertheless, tandem ASCT with HDM as conditioning can currently be recommended for transplant-eligible patients with high-risk cytogenetic features at diagnosis.

Consolidation with new drugs

Initially, bortezomib or VT(D) consolidation were shown to increase the quality of response by 30% and were considered at least in patients who failed to achieve a VGPR or a complete

TABLE 2. Selected maintenance regimens used after ASCT.

Maintenance	Schedule	PFS/EFS	OS	Discontinuation and SE
IFM 2005-02 R consolidation 2 cycles, then R maintenance *vs.* placebo[38]	R, 10-15mg, 21/28 d until progression (stopped after 2y)	PFS, 41m *vs.* 23m 5y-PFS2, 60%	5y-OS, 68% *vs.* 67%	21% 2.4x higher risk of SPM
CALGB R maintenance *vs.* placebo[39]	R, 10-15mg, 21/28 d until progression	mTTP, 53m *vs.* 23m 3y-PFS, 66%	NR *vs.* 76m	12% 3x higher risk of SPM
MM XI R maintenance *vs.* placebo[41]	R, 10 mg 21/28 d until progression	mPFS, 60 m	3y-OS, 88% *vs.* 80%	-
HOVON VAD-ASCT-T *vs.* PAD-ASCT-V[13]	T, 50mg/d or V, 1.3mg/m2 qw, for 2 years	28m *vs.* 35m CR/nCR, 34% *vs.* 49%	5y-OS, 55% *vs.* 61%	5% *vs.* 3% at 5y

ASCT: autologous stem cell transplantation; CR: complete response; d: day; EFS: event-free survival; m: months; NA: not available; nCR: near complete response; NR: not reached; OS: overall survival; PAD: bortezomib, adriamycin, dexamethasone; PFS: progression-free survival; R: lenalidomide; SE: side effects; SPM: secondary primary malignancies; T: thalidomide; V: bortezomib; VAD: vincristine, adriamycin, dexamethasone.

response (CR)/near CR (nCR) after ASCT.[9,30] Nowadays, the role of consolidation remains unclear. In the EMN02-HO95 trial, consolidation with VRD was associated with a significant prolongation of PFS compared to no consolidation,[28] while in the StaMINA-BMT CTN 0702 trial, no significant benefit in terms of PFS was demonstrated using either a second transplant or 3 cycles of VRD as consolidation.[29] Of note, both studies were different in terms of design, and the lack of OS benefit may be influenced by the follow-up as well as the maintenance given to all patients. Trials using either carfilzomib or ixazomib in this setting are currently ongoing. Overall, consolidation remains a reasonable practice in patients who failed to achieve a VGPR or nCR/CR after transplantation.

Maintenance

The positive role of **IMiDs** given in maintenance has been demonstrated in several phase 3 trials. Variable doses and duration of **thalidomide** significantly improved the quality of response and PFS (6 to 12 months) with a variable effect on OS,[31-37] except in patients with adverse cytogenetics where it has a negative impact on OS.[33] However, prolonged use of thalidomide is associated with adverse side effects like irreversible PN, which significantly impact the quality of life of patients. **Lenalidomide** is more suitable in this setting. Given daily in monotherapy at the dosage of 10-15 mg until progression, lenalidomide maintenance was associated with a doubling of the median PFS, compared to placebo or observation.[38,39] In a meta-analysis, it was also associated with an overall OS benefit of more than 2 years (median OS not reached with lenalidomide *vs.* 86 months with observation/placebo), leading to its approval in maintenance therapy of NDMM after ASCT. This OS benefit was less convincing in patients with high-risk cytogenetics or with ISS stage 3.[40] Conversely, continuous maintenance with lenalidomide given in the Myeloma XI trial was associated with an improved PFS, irrespective of cytogenetic risk.[41] The optimal duration of maintenance is still a matter of debate but an average duration of 2 years with a 3-week on/1-week off treatment schedule has become widely adopted. Concerns were raised about a potential rise in secondary primary malignancies (SPM), but this incidence was not subsequently increased after long-term follow-up.[42] As such, the OS benefit with lenalidomide maintenance largely outweigh the risk of developing a SPM. There is no evidence of increased mutational instability or significant toxicity with lenalidomide maintenance.[41]

Bortezomib maintenance has also been studied. Given at the dose of 1.3 mg/m^2 every other week for 2 years after a tandem ASCT, it was the first to demonstrate a survival advantage compared to thalidomide. However, in this trial the induction regimen was different in the 2 arms, the survival effect might be related to the use of bortezomib in the induction phase. Bortezomib was also able to overcome

TABLE 3. 2011 response assessment.[54]

CR	Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and < 5% plasma cells in bone marrow. In patients for whom only measurable disease is by serum FLC level, normal FLC ratio of 0.26 to 1.65 in addition to CR criteria is required; two consecutive assessments are needed.
sCR	CR as defined plus normal FLC ratio and absence of clonal plasma cells by immunohistochemistry or two- to four-color flow cytometry; two consecutive assessments of laboratory parameters are needed.
Immuno-phenotypic CR	sCR as defined plus absence of phenotypically aberrant plasma cells (clonal) in bone marrow with minimum of 1 million total bone marrow cells analyzed by multiparametric flow cytometry (with > four colors).
Molecular CR	CR as defined plus negative allele-specific oligonucleotide polymerase chain reaction (sensitivity 10^{-5}).
VGPR	Serum and urine M component detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M component plus urine M component < 100 mg/24 h. In patients for whom only measurable disease is by serum FLC level, > 90% decrease in difference between involved and uninvolved FLC levels, in addition to VGPR criteria, is required; two consecutive assessments are needed.
PR	≥ 50% reduction of serum M protein and reduction in 24-hour urinary M protein by ≥ 90% or to < 200 mg/24 h. If serum and urine M protein are not measurable, ≥ 50% decrease in difference between involved and uninvolved FLC levels is required in place of M protein criteria. If serum and urine M protein and serum FLC assay are not measurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M protein, provided baseline percentage was ≥ 30%. In addition, if present at baseline, ≥ 50% reduction in size of soft tissue plasmacytomas is required. Two consecutive assessments are needed; no known evidence of progressive or new bone lesions if radiographic studies were performed.
MR for relapsed refractory myeloma only	≥ 25% but ≤ 49% reduction of serum M protein and reduction in 24-hour urine M protein by 50% to 89%. In addition, if present at baseline, 25% to 49% reduction in size of soft tissue plasmacytomas is also required. No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).
SD	Not meeting criteria for CR, VGPR, PR, or PD; no known evidence of progressive or new bone lesions if radiographic studies were performed.
PD	*Increase of 25% from lowest response value in any of following:* Serum M component with absolute increase ≥ 0.5 g/dL; serum M component increases ≥ 1 g/dL are sufficient to define relapse if starting M component is ≥ 5 g/dL and/or; Urine M component (absolute increase must be ≥ 200 mg/24 h) and/or; Only in pâtients without measurable serum and urine M protein levels: difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL); Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC level, bone marrow plasma cell percentage (absolute percentage must be ≥ 10%). Development of new or definite increase in size of existing bone lesions or soft tissue plasmacytomas. Development of hypercalcemia that can be attributed solely to plasma cell proliferative disorder. Two consecutive assessments before new therapy are needed.

ASCT: autologous stem cell transplantation; CR: complete response; d: day; EFS: event-free survival; m: months; NA: not available; nCR: near complete response; NR: not reached; OS: overall survival; PAD: bortezomib, adriamycin, dexamethasone; PFS: progression-free survival; R: lenalidomide; SE: side effects; SPM: secondary primary malignancies; T: thalidomide; V: bortezomib; VAD: vincristine, adriamycin, dexamethasone.

TABLE 4. 2016 response assessment: MRD negativity criteria.[55]

Types of response	Response criteria
	Based on flow cytometry or NGF (such as Euroflow operation procedure for MRD detection in MM or validated equivalent method) or NGS (LymphoSIGHT or other validated equivalent method)
MRD-negativity	Absence of aberrant clonal PC in BM, ruled out by an assay with minimum sensitivity of 1 in 10^{-5} nucleated cells of higher
Imaging and MRD-negativity	MRD-negativity as defined by flow or NGS, plus disappearence of every area of increased tracer uptake found at baseline or preceding PET/CT, or decrease to < mediastinal blood pool SUV, or decrease to less than that of surrounding normal tissue
Sustained MRD-negativity	MRD negativity in BM (as defined by flow or NGS or both) and by imaging (as defined), confirmed minimum 1 year apart ; subsequent evaluations can be used to further specify the duration of negativity

BM: bone marrow; MM: multiple myeloma; MRD: minimal residual disease; NGF: next-generation flow cytometry; NGS: next-generation sequencing; PC: plasma cells; PET-CT: positron-emitting tomography-computed tomography.

the adverse prognosis linked to the presence of a del(17p),[13] making it an interesting approach for this subcategory.
Trials incorporating ixazomib, pomalidomide, carfilzomib and monoclonal antibodies as maintenance are currently ongoing. Bortezomib and thalidomide are not approved as maintenance treatment post-ASCT. Selected maintenance regimens used in this setting are listed in *Table 2*.

Allogeneic stem cell transplantation

Allogeneic stem cell transplantation (allo-SCT) remains a curative option for MM, but its role is still controversial due to a 10-20% treatment-related mortality (TRM), the risk of graft-versus-host disease (GvHD), even with reduced intensity conditioning (RIC), and the occurrence of long-term post-transplant relapses.[43,44] Consequently, there is no routine indication for allo-SCT in frontline therapy.

SPECIAL CONDITIONS

PLASMA CELL LEUKAEMIA

Plasma cell leukaemia (PCL) is the most aggressive form of PC dyscrasia, with a median OS of around 1 year. It is defined by the presence of PC consisting of more than 20% of the differential white cell count in the peripheral blood, or an absolute plasma cell peripheral blood count of greater than 2.0×10^9 cells/l. Primary PCL (pPCL) refers to PCL detected *de novo* at diagnosis in patients with no prior history of MM, while secondary PCL (sPCL) arises in patients with a known history of MM. Primary PCL is associated with more immature or 'plasmablastic' PC clones, and more high-risk cytogenetic features.[45,46]
Upfront therapy should include a triplet regimen with novel agents (VRd or KRd). The IFM proposed as induction, 4 alternating cycles of PAD and VCD.[44] In patients with extensive disease burden or who are non-responsive to initial therapy, VTD-PACE or VRD-PACE should be considered since drugs such as doxorubicin and cyclophosphamide are particularly active in lymphoproliferative diseases. ASCT upfront, if possible in tandem, is recommended to achieve a deeper response and likely a longer disease control. Allo-SCT should not be considered except in the setting of a clinical trial, since this procedure has been associated with a higher relapse mortality compared with tandem ASCT.[48] Consolidation should be proposed in patients not achieving a CR, followed by maintenance with either bortezomib or lenalidomide.[49] In frail patients, induction with VCD or PAD can be used as a milder alternative, given for up to 8-10 cycles, followed by indefinite maintenance therapy to keep the disease under control.[49]

RENAL IMPAIRMENT

Renal failure (creatinine >2mg/dl) is seen in around 20% of NDMM patients at diagnosis. It requires prompt rehydration and treatment of precipitating events such as hypercalcaemia, acidosis, infection and discontinuation of nephrotoxic drugs. **Bortezomib** can safely be used without dose modification, even in patients under dialysis, and acts rapidly (responses in 0.7-1.6 months). It can be used in association with **dexamethasone** (40 mg, days 1-4) ± **thalidomide, doxorubicine or cyclophosphamide**.[50,51] Thalidomide does not require dose reduction, but may induce severe hyperkalemia, particularly in patients under dialysis. **Lenalidomide** requires appropriate dose reductions. **Bendamustine** can

be an option, particularly in combination with bortezomib and prednisone.[52]

Mechanical methods of removing FLC from the blood should only be considered within the context of a clinical trial. Plasma exchange is theoretically useful in cast nephropathy, but removes FLC only from the intravascular compartment (17% of total body FLC). Compared to conventional haemodialysis, use of extended high-cut off haemodialysis in combination with bortezomib-based chemotherapy does not offer any significant advantage in terms of haemodialysis independence at 3 months.[53]

RESPONSE ASSESSMENT AND FOLLOW-UP

Responses to therapy should be assessed using the 2011 IMWG response criteria (*Table 3*), updated in 2016 (*Table 4*).[54,55] The M-protein level should be evaluated by serum and urine protein electrophoresis every month while on therapy, and every 3-4 months when off-therapy. The FLC assay is used to monitor patients who lack a measurable M-protein, particularly in oligo- or non-secretory and light-chain MM, provided the FLC ratio is abnormal and the involved FLC level is ≥100mg/l.

SUPPORTIVE CARE

Recommendations on supportive care, already described in the previous update, have been updated in this special issue of the BJH (*Meuleman et al*).

BELGIAN ACCESS TO DRUGS – REIMBURSEMENT

In *Table 5*, the reimbursement criteria for the different drugs discussed above are listed.

TABLE 5.

Drugs	Terms of reimbursement in first-line for transplant-eligible NDMM patients
Velcade	Reimbursed for induction (6 cycles)
Carfilzomib	No access
Ixazomib	No access
Thalidomide	Reimbursed
Lenalidomide	Reimbursed as maintenance therapy
Bendamustine	No access
Daratumumab	No access
Elotuzumab	No access

CONCLUSIONS

The changes in the treatment paradigm of MM patients in the last 2 decades dramatically improved survival, with most patients expecting a long-term disease control. In the era of novel agents, ASCT remains the standard of care for NDMM eligible for transplant. In the near future, new classes of drugs (such as monoclonal antibodies) and second-generation PIs and IMiDs will probably move to the upfront setting, and clinical research will also focus on quality of life, optimal sequencing of therapy, appropriate tools for patients selection, optimal strategies for high-risk diseases and costs of prolonged novel-agents strategies.

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RECOMMENDATIONS FOR UPFRONT THERAPY IN TRANSPLANT-ELIGIBLE NDMM

1 **Diagnosis and risk assessment:** Diagnosis of MM requires the fulfilment of the 2014 IMWG criteria (IV, C). All patients should undergo risk stratification using ISS (I, A) and cytogenetics (FISH)(II, B), even if risk-adapted therapy is not available in most cases at the moment.

2 **Goal of therapy:** The goal of therapy is to achieve CR, the most important surrogate marker of OS. However, in the elderly population, increased PFS is a worthwhile goal if QoL is maintained and can delay the onset of disease side effects.

3 **Indication for therapy:** Treatment should be considered in all patients with a diagnosis of symptomatic MM as defined by the IMWG 2014 criteria (IV, C). Treatment choice depends on patient's eligibility for ASCT based on biological age, performance status and co-morbidities (I, B). Objective risk-assessment scores can be used (I, B).

4 **Transplant-eligible NDMM patients:** Induction followed by HDM with ASCT remains the standard of care in patients in good clinical condition (I, A). Based on response rates, depth of response and PFS, 3-drug combination including at least bortezomib and dexamethasone are considered the standard of care before ASCT (I, A). VTD is superior to VCD but at the cost of more peripheral polyneuropathy (II, B). Three to four cycles are recommended before stem cell collection. Switching therapy is recommended in case of progressive disease (PD) after 2 cycles or less than partial response (PR) after 4 cycles. The role of consolidation remains not clear while maintenance has been proven to improve OS.

5 **Allo-SCT** is still considered investigational for MM. Because of the risk of severe TRM and GvHD, it should only be performed in patients with high-risk disease in good response, within clinical trials (IV, C).

6 **Plasma-cell leukaemia:** Upfront therapy should include a 3-drug bortezomib-based regimen (VCD, VTD, PAD, VRD or VDT-PACE) followed by HDM and ASCT, consolidation with 2-4 cycles (VTD or RVD), and maintenance with bortezomib until progression. Consolidation with allo-SCT can be considered in young patients (<50), in the setting of a clinical trial.

7 **Renal failure:** Renal failure requires prompt rehydration and treatment of precipitating events (IV, C). High-dose dexamethasone should be started immediately (IV, C). Bortezomib is safely used without dose modification, even in patients under dialysis (IV, C). Lenalidomide requires appropriate dose reductions (IV, C).

8 Physical methods to remove FLC from the blood should be performed within clinical trials (IV, C). ASCT can be proposed for patients with GFR <30ml/min, using melphalan 100-140mg/m2 (II, B).

Supportive care – Recommendations should follow the Belgian guidelines published in 2014.

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An unusual mononucleosis infectiosa-like illness caused by toxoplasmosis in a B-cell chronic lymphocytic leukaemia patient

L. Heireman, PharmD[1], J. Dierick, MD[1], S. Debussche, MD[2], S. Steyaert, MD[1], H. Vanhouteghem, PharmD[1], R. Joos, MD[3], A. Luyckx, MD, PhD[1]

SUMMARY

The differential diagnosis of mononucleosis infectiosa (MI)-like illness can be challenging since several infectious causes have been identified to date. The most common associated pathogen is Epstein-Barr virus, followed by cytomegalovirus, human immunodeficiency virus type 1 and human herpesvirus-6. MI-like illness is rather rarely caused by *Toxoplasma gondii*, a parasite that is transmitted through consumption of undercooked food or contact with faeces from infected cats. In this case report, we discuss a B-cell chronic lymphocytic leukaemia patient with a MI-like illness caused by toxoplasmosis.

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INTRODUCTION

About one third of the population worldwide is infected with *Toxoplasma gondii*.[1] Toxoplasmosis may cause severe disease in the developing foetus and in immunocompromised patients, for example patients with lymphatic cancers, acquired immunodeficiency syndrome or treated with immunosuppresives.[1,2] Only a few cases about toxoplasmosis-induced mononucleosis infectiosa (MI)-like illness have been documented in literature so far. In this case report, we discuss a B-cell chronic lymphocytic leukaemia (B-CLL) patient with MI-like illness caused by *Toxoplasma gondii* infection.

CASE PRESENTATION

A 62-year-old male patient presented at our hospital with malaise, severe fever, occipital pain, sore throat and night sweats. Further, the patient was complaining of diffuse myalgia and proximal muscle weakness, initially suggestive for a flu-like illness. Six years earlier, he was diagnosed with monoclonal B-cell lymphocytosis (lambda type) that evolved to a CLL (Rai stage I, Binet stage A) four years later. His medical history further includes hypogammaglobinaemia with severely decreased immunoglobulin (Ig)M, atrial fibrillation and spondyloarthritis. The patient was taking bisoprolol, omeprazole and atorvastatin medications on a daily basis and paracetamol or ibuprofen on occasion. Physical examination revealed a palpable spleen and liver. Additionally, various palpable and painful cervical, axillary, occipital and inguinal lymph nodes were noticed. Echography showed hepatosplenomegaly, fatty liver parenchyma and swollen occipital lymph nodes. Further investigation by PET-CT was performed to exclude Richter's transformation. Multiple cervical, axillar, mediastinal, bilateral hilar, hepatic hilar, retroperitoneal and parailiacal adenopathies were noticed

[1]Department of Laboratory Medicine, AZ Maria Middelares, Ghent, Belgium, [2]Haematology Department, AZ Maria Middelares, Ghent, Belgium, [3]Department of Rheumatology, Ziekenhuis Netwerk Antwerpen, Antwerp, Belgium.

Please send all correspondence to: J. Dierick, MD, AZ Maria Middelares, Buitenring Sint-Denijs 30, 9000 Ghent, Belgium, tel: +32 92469205, email: jan.dierick@azmmsj.be.

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

Keywords: chronic lymphocytic leukaemia, mononucleosis-like illness, reactive lymphocytes, Toxoplasma gondii.

TABLE 1. Results of haematology parameters at time of admission and during follow-up with corresponding reference values.

Haematology parameters	January, 2018	February, 2018	March, 2018	April, 2018	Reference values
Haemoglobin (g/dL)	14.5	13.6	14.6	14.8	13.7-17.5
WBC count (×10³/mm³)	**11**	**16.6**	**12.7**	**14.3**	4.2-9.1
Lymphocytes (×10³/mm³)	**8.97**	**14.18**	**9.21**	**10.37**	1.50-3.50
Microscopic review	Reactive lymphocytes and Gumprecht shadows				–
T lymphocytes (/µL)	**4144**	–	**3398**	–	700-2100
B lymphocytes (/µL)	**3705**	–	**5139**	–	100-500
T helper cells (/µL)	**2027**	–	**1704**	–	300-1400
T cytotoxic cells (/µL)	789	–	801	–	200-1200
CD4/CD8 (–)	2.6	–	2.12	–	1.00-3.60
NK cells (/µL)	**987**	–	562	–	90-600

Results in bold denote an abnormal patient result.
WBC: white blood cell, NK: natural killer.

and seemed to be only moderate metabolic active and not suspicious for Richter's transformation. Therefore, the patient underwent no further lymph node biopsy.

Laboratory results for haematology and chemistry parameters at the time of admission and during follow-up are shown in *Table 1* and *2* respectively. The strongly increased lymphocyte count and presence of Gumprecht shadows were typical for B-CLL (*Figure 1*). Flow cytometric analysis revealed an increased concentration of both B and T lymphocytes (with normal CD4/CD8 ratio) as well as natural killer (NK) cells. The patient was known with an elevated B lymphocyte count for several years, corresponding with B-CLL. However, the strong increase in T lymphocytes and NK cells may indicate an infection. Laboratory analysis showed increased beta-2-microglobulin and C-reactive protein concentrations. Serum electrophoresis showed elevated alpha-1 and alpha-2 fractions and a lowered gamma fraction with a small monoclonal peak, conform previous results. Evolving muscle problems incited us to perform a muscle enzyme test, showing elevated creatine kinase up to 4000 U/L. Myositis-specific anti-Mi-2 antibodies on extractable nuclear antigen blot test were positive, indicating an autoimmune myositis.

Infectious serology tests were performed since the presence of reactive lymphocytes were specifically suggestive for an Epstein-Barr virus (EBV) or cytomegalovirus (CMV) infection. However, CMV serology tested negative, and for EBV only a past infection could be detected (EBV IgG index 1.67). The absence of a CMV infection was confirmed by a negative CMV serology during follow-up. EBV polymerase chain reaction was also performed nine days after the serology tests and was slightly positive (616 copies/µL, reference value <300 copies/µL). An EBV early antigen test was negative, thereby excluding acute EBV infection. Infections with hepatitis virus A, B and C, *Chlamydia trachomatis* and *psittaci*, *Mycoplasma pneumoniae*, Coxsackie B1, B2, B3, B4 and B5 were excluded through negative serology test results. For *Chlamydia pneumoniae* and parvovirus B19, only a past infection was detected (*Chlamydia pneumoniae* IgG titer 1/60). Nine days after admission, *Toxoplasma* serology tests were performed since further anamnestic investigation revealed the patient was owning a cat. Test results for *Toxoplasma* IgM and IgG were positive. In a convalescent sample collected 18 days later, the diagnosis was confirmed by a significant increase in *Toxoplasma* IgM (despite nearly absent total IgM concentration) as well as *Toxoplasma* IgG concentration com-

TABLE 2. Results of chemistry parameters at time of admission and during follow-up with corresponding reference values.

Chemistry parameters	January, 2018	February (1st half), 2018	February (2nd half), 2018	March, 2018	April, 2018	Reference values
ALP (U/L)	**161**	**131**	88	–	–	40-129
AST (U/L)	**42**	**55**	**223**	**81**	34	<38
ALT (U/L)	**76**	**60**	**146**	**103**	32	<41
LDH (U/L)	**764**	**952**	**1160**	**874**	**487**	240-480
CK (U/L)	**223**	–	**3925**	**1189**	**506**	<190
CRP (mg/L)	**29.96**	**23.05**	**6.44**	3.31	1.88	<5.00
Beta-2-microglobulin (mg/L)	**5.07**	**7.00**	**7.73**	**5.55**	–	1.09-2.53
IgG (g/L)	–	–	**6.50**	–	–	7.00-16.00
IgM (g/L)	–	–	**0.25**	–	–	0.40-2.30
Toxoplasma IgM (-)	–	**Pos (index 57.37)**	**Pos (index 100.6)**	**Pos (index 61.02)**	**Pos (index 10.99)**	Negative
Toxoplasma IgG (IU/mL)	–	**1.4**	**21.6**	**101.8**	**581.1**	–

Results in bold denote an abnormal patient result.
ALP: alkaline phosphatase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, CK: creatine kinase, CRP: C-reactive protein, IgG: immunoglobulin G, IgM: immunoglobulin M.

pared to the first collected sample. Results of *Toxoplasma* IgM (index) and IgG (IU/mL) at time of diagnosis and during follow-up are graphically displayed in *Figure 2*. Interference with performed serological tests was excluded. Therapy with sulfamethoxazole 800 mg/trimethoprim 160 mg was started for two months, and the patient responded well.

DISCUSSION

EBV, the well-known causative pathogen of MI, has infected more than 90% of the population worldwide.[3,4] EBV infection may promote the evolution of B-CLL cells to a high-grade non-Hodgkin lymphoma (Richter's transformation).[4,5] These patients present with a sudden clinical deterioration, fever in the absence of infection, rapidly enlarging lymphoid mass and usually elevated levels of lactate dehydrogenase and beta-2-microglobulin.[5] Diagnosis is confirmed by lymph node or bone marrow biopsy.[5] In the patient described here, serology tests and the normal CD4/CD8 ratio excluded an acute EBV infection as the cause of the MI-like illness. Since our patient was known with CLL, clinical signs and laboratory findings were also indicative for a Richter's transformation. However, progression of CLL to Richter's transformation was excluded by a PET-CT scan. Further investigation of infectious causes other than EBV was necessary to provide this patient with a diagnosis. Other frequent causes of mononucleosis include CMV, human immunodeficiency virus type 1 and human herpes virus type 6 and less often herpes simplex virus type 1, parvovirus B19, adenovirus and *Toxoplasma gondii* infection.[3,6] CMV and human herpesvirus-6 are the most frequent non-EBV causes of MI-like illnesses.[3] In the case presented here, CMV and parvovirus B19 infections were excluded by serologic testing and the normal CD4/CD8 ratio. In only ≤3% of patients presenting with MI-like illness, the causative pathogen is *Toxoplasma gondii*.[3]

Patients are often asymptomatic, but cervical or occipital lymphadenopathy, maculopapular rashes, pharyngitis and hepatosplenomegaly may occur.[3] Toxoplasmosis shares many characteristics with EBV and CMV infections, for example the presence of hepatosplenomegaly, lymphocytosis and reactive lymphocytes.[7] Anti-*Toxoplasma* IgM production generally starts at the beginning of primary infection and can persist for several years after infection.[3] Anti-*Toxoplasma* IgG appears within two weeks of primary infection and remains lifelong detectable.[3] In the patient described here, *Toxoplasma* IgM and IgG were measured only nine days after admission and both tested positive. In a convalescent sample 18 days later, *Toxoplasma* IgM and IgG were further increased, confirming the diagnosis of toxoplasmosis. Moreover, the patient showed a period of myositis. Presumably, this myositis was *Toxoplasma* induced since remission occurred after prolonged therapy with sulfamethoxazole. Our case shows that a thorough anamnesis of patients is important in revealing rather rare causes of MI-like illness.

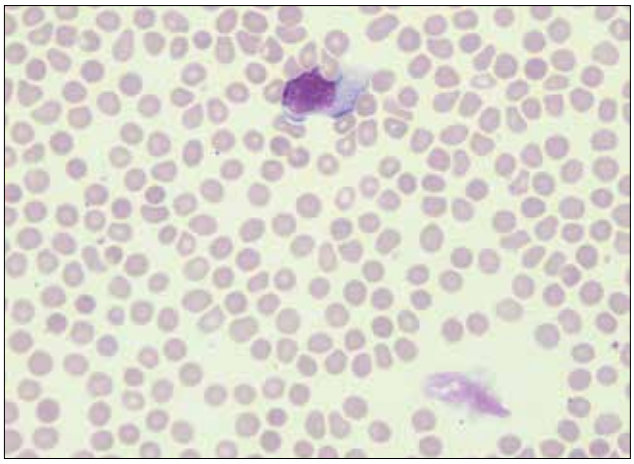

FIGURE 1. Microscopic review showing one Gumprecht shadow and one reactive lymphocyte with low nucleus/cytoplasm ratio and abundant dark blue cytoplasm.

CONCLUSION

In the described case, a huge *Toxoplasma* IgM response was demonstrated in a CLL patient despite a low total IgM concentration. A *Toxoplasma gondii* infection should be considered as a cause of MI-like illness in immunocompromised patients with negative EBV and CMV serology. In patients with CLL, the diagnosis of toxoplasmosis-induced MI-like illness is further complicated since in addition to infectious causes, malignant causes for example transformation to high-grade lymphoma should be examined. Finally, in this case, *Toxoplasma* infection probably caused a transient autoimmune myositis.

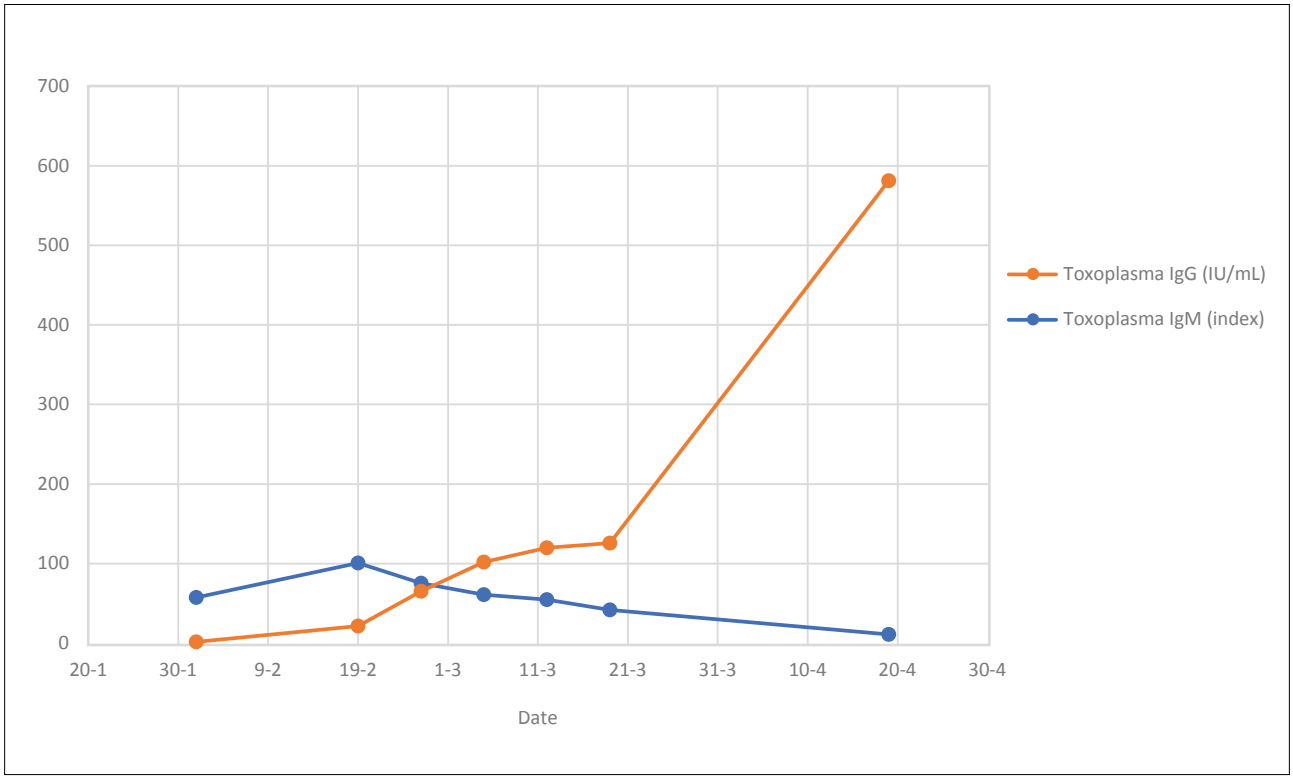

FIGURE 2. Results of *Toxoplasma* IgM (index) and IgG (IU/mL) at time of diagnosis and during follow-up.
IgG: immunoglobulin G, IgM: immunoglobulin M.

KEY MESSAGES FOR CLINICAL PRACTICE

1. *Toxoplasma gondii* infection is a rather uncommon cause of mononucleosis infectiosa (MI)-like illness characterised by fever, pharyngitis, lymphadenopathy and reactive lymphocytes but normal CD4/CD8 ratio.
2. A thorough anamnesis, including pet ownership, is essential in diagnosing less common infectious causes of MI-like illness.
3. Correct differentiation between infectious and malignant causes is important in CLL patients presenting with MI-like illness.
4. Parameters beta-2-microglobulin and lactate dehydrogenase are not specific for malignant proliferation.
5. *Toxoplasma gondii* infection may cause a transient autoimmune myositis.

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EHA Scientific Working Group meeting on ageing and haematology

D. Bron, MD, PhD, V. Thibaud, MD, S. Wittnebel, MD, PhD
*On behalf of the organising committee**

SUMMARY
After a successful first edition in Lisbon, a second edition of this scientific working group meeting was held in Warsaw in October 2018. The objective was to organise roundtables with scientists, clinicians, onconurses and patient's organisations to improve the management of older patients with haematological disorders. Several unsolved issues were debated as outlined below.
(BELG J HEMATOL 2019;10(3):127-9)

VACCINATION IN OLDER PATIENTS

(G. PAWELEC, TUBINGEN, GERMANY)

There are a number of basic prerequisites for adaptive immune responses to pathogens and vaccines:

- Reponses to most vaccines require antigen presentation by dendritic cells.
- The antigen must be recognised by T cells.
- The T cells must be able to differentiate to helper and cytotoxic cells specific for pathogen antigen.
- B cells must be present in the repertoire and able to produce antibodies.

There is evidence for an impaired capacity of immunity in older people in all of the above steps. Differences between young and old individuals is due to differences both at the level of the hematopoietic stem cells (HSCs) and the stromal microenvironment, resulting in a different distribution of the major immune cell types. In addition, memory cell production and function may be compromised, and suppressive feedback by regulatory T cells and myeloid-derived suppressor cells (MDSCs) may be enhanced in older individuals. For example, older people vaccinated with a genuine neoantigen (attenuated yellow fever virus) show poorer antibody responses than younger people due to a paucity of CD4+ naïve T cells and impaired dendritic cell function. Recent data implicating intrinsic changes at the level of the HSC in mice appear paralleled by similar phenomena in humans.

MILD COGNITIVE IMPAIRMENTS: UNSUSPECTED PROGNOSTIC FACTORS

(D. BRON, BRUSSELS, BELGIUM)

The G8 screening tool is too sensitive and overestimates vulnerability in clinically fit older patients with haematological malignancies. Indeed, three items of the G8 score are related to nutritional status, which is often disease-related and easily reversible with optimal treatment. Regarding overall survival, a multivariate analysis showed that cognitive status (Mini Mental State Examination [MMSE] <27 or Montreal Cognitive Assessment [MOCA] <26) in the global cortical atrophy scale had a strong predictive value for one-year overall survival.

More recently, we also found that mild cognitive impairment (MCI) has an impact on two-year overall survival among older cancer patients. MCI detected by the MMSE (<27) was not a significant predictor of survival. Only, MCI detected by the MOCA (<26) has an impact on overall survival among this specific population. There are two possible reasons for this discrepancy. First, the MOCA is more sensitive to detect vulnerable patients in terms of MCI compared to MMSE (only 13%). Second, MOCA is more reliable in terms of reproducibility. To further explain that a MCI can affect survival, we found a significant correlation with other prognostic factors such as comorbidities, psychological and social vulnerabilities.

Department of Hematology, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium.
**L. Ades, R. Cordoba, T. Fulop, V. Goede, P. Soubeyran, R. Stauder, G. Storti, S. Zweegman.*
Please send all correspondence to: D. Bron, MD, PhD, Institut Jules Bordet, Rue Heger Bordet 1, 1000 Brussels, Belgium, tel: + 32 25413232, email: dominique.bron@bordet.be.
Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.
Keywords: aging, elderly, immunosenescence, older patients.

Proper management of cognitive impairments should thus be considered to increase compliance among patients with MCI. Information of primary caregivers and family doctors should be included in these supportive interventions in order to maximise the efficacy of the treatment and minimise its toxicity for the patient.

Future prospective studies should include an assessment of MCI before a cancer treatment and primarily when an oral treatment is proposed.

AML AND APL IN OLDER PATIENTS

(A. AMALMEIDA, LISBON, PORTUGAL)

Acute myeloid leukaemia

Even though age is significantly associated with poor survival, older age is not a reason to withhold a treatment. Indeed, older patients with good prognostic acute myeloid leukaemias (AMLs; i.e., acute promyelocytic leukaemia (APL), core binding factor (CBF) leukaemia and isolated *NPM1* mutated AML) can be cured with intensive chemotherapy (ICT). Thus, the issue is to identify the elderly AML patients who could benefit from ICT.

It should be noted that delaying treatment until the cytogenetic status is known does not modify overall survival (OS) in older leukaemia patients, suggesting that we could wait for the results of cytogenetic and molecular tests before making a treatment decision.

In AML patients without favourable cytogenetics, a trial comparing azacitidine to conventional care regime (low dose cytarabine, ICT or best supportive care) showed that azacitidine was associated with clinically meaningful improvement in median OS (10.4 *vs* 6.5 months) and one-year survival (46.5% *vs* 34.2%) versus conventional care regime. This suggests that azacitidine could be the reference treatment for unfit AML patients without favourable cytogenetics.

Nevertheless, the survival remains poor and it is hoped that combination treatment regimens may further improve the outcome. Results of early trials of azacitidine in combination with venetoclax, APR-246 or new approaches evaluating single agent targeted therapies are very promising.

Other concerns such as loss of quality of life and loss of autonomy require further evaluation. Thus, the key message is that we have to identify those older patients likely to benefit from ICT or hypomethylating agents and discuss the final therapy decision with them.

Acute promyelocytic leukaemia

Contrary to other types of AML, APL is not frequent in the elderly. Only 1-6% of APL patients are older than 70 years. Treatment of APL in the elderly with conventional *all-trans* retinoic acid (ATRA) plus chemotherapy (CT) regimens is associated, like in younger patients, with very few relapses, but relatively high death rates during induction treatment or in complete response (CR). Indeed, the CR rate in patients older than 60 was 98.1%, but among these older patients, 5 of 51 patients (10%) died in CR.

Recent results obtained in adult APL with ATRA plus arsenic trioxide (ATO; CT free) regimens may cause a decrease in the incidence of deaths in CR, without increasing relapses. However, we should remember that ATRA-ATO (CT free) regimens might also be associated with potentially fatal complications in the elderly, such as early severe activation syndrome and later cardiac or neurological impairment, due to high cumulative doses of ATO.

FRAIL PATIENTS WITH FOLLICULAR LYMPHOMA

(G. ROSSI, BRESCIA, ITALY)

Among lymphoproliferative disorders, follicular lymphoma (FL) is the second most common form of lymphoma and accounts for 20-30% of all newly diagnosed non-Hodgkin lymphomas (NHLs), with an annual incidence of 1.6-3.1/100,000 cases in western countries. FL occurs in the elderly with a median age at diagnosis of 61 years.

While the contribution of geriatric assessment in the clinical management of aggressive lymphoma, such as diffuse large B-cell lymphoma, has been extensively studied and has proven to be essential for an appropriate treatment choice, its usefulness specifically for FL patients has not been established, and clinical judgement is still the current standard to manage individual patients.

The characteristics of FL in patients over 80 show a higher incidence of grade 3 histology and lower responses rates to chemo-immunotherapy. Age by itself (>60 years) has been shown to be one of the most important poor prognostic factors in the Follicular Lymphoma International Prognostic Index.

For the diagnosis of FL, an excisional biopsy, or at least a core biopsy, is required also in aged patients since fine needle aspirations are insufficient. Conventional staging procedures should be performed but further staging procedures should be avoided as they do not have impact on treatment decisions. A PET-CT scan may be useful to confirm localised disease for which local radiotherapy (RT) is the treatment of choice. As underscored by Specht *et al.*, RT is also an excellent palliative treatment for indolent lymphomas in older patients, where doses as low as 4Gy in two fractions offer durable local control with minor if any side-effects.

In asymptomatic patients showing mildly progressive disease, rituximab single agent should be offered in order to prevent major comorbidities, which are frequent in the aged popula-

tion (61% >70 years of age).

For patients with high tumour burden being able to tolerate chemotherapy, a bendamustine/rituximab combination is recommended, with appropriate dose reduction. Of note, while obinutuzumab has proven to be more effective than rituximab, concerns have been raised due to the higher frequency of severe infections and fatal events of patients receiving the combination obinutuzumab/bendamustine.

In the management of elderly FL patients at relapse, treatment such as radio-immunotherapy has a cost/benefit ratio particularly favourable in aged patients.

HODGKIN LYMPHOMA IN THE ELDERLY

(I. AURER, ZAGREB, CROATIA)

Hodgkin lymphoma (HL) is usually regarded as a disease of the young. Outcomes in the elderly lag behind significantly. This is mostly due to increased toxicity of effective regimens, but also to the fact that in the elderly, HL has more frequently unfavourable biological characteristics.

Mixed cellularity is more frequent than nodular sclerosis and advanced stage than localised disease. The incidence of EBV positivity and B symptoms is also significantly higher. Pathological diagnosis can also be problematic since it is frequently difficult to distinguish between HL and EBV-driven NHLs containing so called 'Reed-Sternberg-like cells' or even non-malignant EBV-related conditions.

Due to unacceptable frequent, serious and even fatal pulmonary toxicity with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) x6, fit patients above 70 (some experts would say above 60) should receive no more than two ABVD cycles, followed by AVD.

The combination of AVD with brentuximab vedotin (BV) in patients between 60 and 70 results in slightly better response rates and progression-free survival (PFS; but not overall survival) and in significantly higher haematological, infectious and neurological toxicity. It should be kept noted that late side effects of RT are less important for the elderly and that therefore, in the frail patient group, irradiation has an excellent efficacy/toxicity ratio.

Elderly fit patients tolerate bendamustine that has a response rate in the relapsed/refractory (R/R) setting of around 50% and PFS around six months. Combinations with other drugs (including BV) are hampered by increased toxicity, mostly infectious, due to its immunosuppressive effects. Efficacy of BV monotherapy is at least similar in the R/R elderly as in younger patients, with response rates of about 75% and a PFS of 15 months. Unfortunately, BV-related neuropathy is especially problematic in the elderly.

PD-1 blockers are very effective for R/R HL. Response rates in patients failing two to three lines of treatment vary between 70 and 90% with PFS in the vicinity of two years and mostly mild immune-related side-effects, making them very attractive drugs for elderly patients.

CHRONIC LYMPHOCYTIC LEUKAEMIA

(V. GOEDE, COLOGNE, GERMANY)

Diagnosis and staging procedures in older patients should follow general guidelines and are not different in older compared with younger patients. Data on geriatric assessment in chronic lymphocytic leukaemia (CLL) are still sparse. Anti-leukemic therapy of CLL should be tailored towards the disease-related risk (mutation of *TP53*) and patient-related risks (fitness). Older patients with previously untreated standard-risk CLL (no *TP53* alteration) can be treated with CD20 antibody-based chemo-immunotherapy or the tyrosine kinase inhibitor ibrutinib.

Older patients with otherwise good health (no comorbidity, no geriatric impairment) may benefit from bendamustine/rituximab. Elderly patients with increased comorbidity or geriatric impairments may benefit from chlorambucil/obinutuzumab. Older patients with previously untreated high-risk CLL (*TP53* alteration) should be treated upfront with ibrutinib. Relapsed CLL in an older patient (with or without *TP53* alteration) should be treated with ibrutinib, idelalisib/rituximab or venetoclax/rituximab.

Novel combinations (e.g., obinutuzumab/ibrutinib, obinutuzumab/venetoclax) are currently explored in trials conducted in older patients with CLL and likely will result in further changes of the treatment landscape in this patient population.

CONCLUSION

Decision making in older patients is rather complex, integrating disease status, patient geriatric assessment but also the socio-familial environment and patient's expectations.

New haematology reimbursements in Belgium

T. Feys, MSc, MBA

OVERVIEW OF BELGIAN REIMBURSEMENT NEWS

(BELG J HEMATOL 2019;10(3):130-1)

LIPOSOMAL IRINOTECAN (ONIVYDE®)

Since the 1st of May 2019, liposomal irinotecan is reimbursed in association with 5-fluorouracil (5-FU) and leucovorin (LV) for the treatment of adults patients with metastatic pancreatic cancer who have progressed on gemcitabine-based therapy.

This reimbursement is based on the results of the phase III, randomised, open-label NAPOLI-1 trial. This study randomly assigned patients (from 76 sites in fourteen countries) with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapy to receive either liposomal irinotecan monotherapy (120 mg/m^2 every three weeks, equivalent to 100 mg/m^2 of irinotecan base) or 5-FU/LV. A third arm consisting of liposomal irinotecan (80 mg/m^2, equivalent to 70 mg/m^2 of irinotecan base) with 5-FU/LV every two weeks was added later (1:1:1) in a protocol amendment.[1]

After 313 events, the median overall survival (OS, the primary endpoint) in patients assigned to liposomal irinotecan + 5-FU/LV (N=117) was 6.1 months as compared to 4.2 months with 5-FU/LV (N=149) in the intention-to-treat population analysis (HR[95%CI]: 0.67[0·49–0·92]; p=0.012). The median OS did not differ between patients assigned to liposomal irinotecan monotherapy and those treated with 5-FU/LV. The median progression-free survival (PFS) was 3.1 months in patients in the combination arm *vs.* 1.5 months in those allocated 5-FU/LV (unstratified HR[95%CI]: 0.56[0.41–0.75]; p=0.0001). The objective response rate with liposomal irinotecan + 5FU/LV was 16% as compared to 1% with 5-FU/LV (p<0.0001). The health related quality of life measured through the EORTC QLQ-C30 questionnaire was maintained in the patients treated ONIVYDE + 5-FU/LV over twelve weeks.[2] The most frequent grade 3/4 adverse events (AEs) among the 117 patients treated with liposomal irinotecan + 5-FU/LV were neutropenia (27%), diarrhoea (13%), vomiting (11%), and fatigue (14%).[1] The reimbursement is to be requested through the eHealth platform and specific reimbursement criteria are, among others, patients with ECOG performance score ≤2 who have not yet been treated with irinotecan.[3]

EPOETIN ALFA (EPREX®)

Since April 1st, the reimbursement criteria for Eprex® (epoetin alfa) were extended to include the following indication: the treatment of symptomatic anaemia (haemoglobin concentration of ≤10 g/dL) in adults with IPSS risk category low- or intermediate-1-risk primary myelodysplastic syndromes (MDS) who have low serum erythropoietin (<200 mU/mL). This new indication is based on a randomised, double-blind, placebo-controlled, multicentre study which evaluated the efficacy and safety of epoetin alfa in adult anaemic subjects with IPSS low- or intermediate-1-risk MDS.[4] Subjects were stratified by serum erythropoietin (sEPO) level and prior transfusion status at screening.[4] Erythroid response was defined according to International Working Group (IWG) 2006 criteria as a haemoglobin increase ≥ 1.5 g/dL from baseline or a reduction of RBC units transfused by an absolute number of at least four units every eight weeks compared to the eight weeks prior to baseline, and a response duration of at least eight weeks.[4]

Erythroid response during the first 24 weeks of the study was demonstrated by (31.8%) of the subjects in the epoetin alfa group compared to (4.4%) of the subjects in the placebo group (p<0.001).[4] All of the responding subjects were in the stratum with sEPO <200 mU/mL during screening.[4] In that stratum, 50% subjects without prior transfusions demonstrated erythroid response during the first 24 weeks, compared with 22.6% subjects with prior transfusions.[7]

Ariez International BV, Ghent, Belgium.

Please send all correspondence to: T. Feys, MSc, MBA, Ariez international BV, Oude Houtlei 118, 9000 Ghent, Belgium, tel: +32 479 56 78 90, email: t.feys@ariez.com.

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

The median time from baseline to the first transfusion was significantly longer in the epoetin alfa group compared to what was seen with placebo (7.0 *vs.* 5.3 weeks; p=0.046).[4] After four weeks of treatment the time to first transfusion was further increased in the epoetin alfa group (20.3 *vs.* 7.1 weeks, p=0.007).4 The percentage of subjects who were transfused in the epoetin alfa group decreased from 51.8% in the eight weeks prior to baseline to 24.7% between weeks 16 and 24, while the placebo group had an increase in transfusion rate from 48.9% to 54.1% over the same time periods.[4]

The recommended starting dose in this indication is 450 IU/kg (max. total starting dose is 40,000 IU) administered subcutaneously once every week, with a ≥5-day interval between doses.[4] Appropriate dose adjustments should be made to maintain haemoglobin concentrations within the target range of 10 to 12 g/dL (6.2 to 7.5 mmol/L).[5] It is recommended to assess the initial erythroid response eight to twelve weeks following the start of the treatment.[5] Dose increases and decreases should be done one dosing step at a time. A haemoglobin concentration of greater than 12 g/dL (7.5 mmol/L) should be avoided.[5]

Epoetin alfa needs to be prescribed by a physician specialised in haematology or oncology, or a specialist in internal medicine with a title in clinical haematology. The electronic request needs to be submitted through the eHealth platform and the prescribing physician must keep the supporting documents at the disposal of the advising physician. The maximum dosing that can be reimbursed is 1,050 IU/kg (total dose 80,000 IU) per week.

RUXOLITINIB (JAKAVI®)

As of May 1st 2019, new criteria are in place for the reimbursement of ruxolitinib in patients with myelofibrosis. The main changes include that also patients with intermediate-1 risk disease and palpable splenomegaly of ≥5cm under the left rib cage are eligible for reimbursement. Ruxolitinib is also reimbursed in patients with intermediate-2 or high-risk disease and symptomatic and palpable splenomegaly <5 cm under the left rib cage. The reimbursement is further broadened to intermediate-2 and high-risk MDS with symptomatic disease, but no palpable splenomegaly or with a splenectomy.

The application for reimbursement can now be processed via eHealth instead of an application via the orphan college. Also the stopping rules in patients with intermediate-2 or high-risk MDS have been adapted in a sense that ruxolitinib can be continued in patients for as long as there is symptomatic benefit (even in the presence of a progressive spleen enlargement; up to a 40% increase in palpable spleen size from baseline).

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Congress Calendar 2019

MAY

1-4 MAY
32th Annual Meeting of the American Society of Pediatric Hematology/ Oncology (ASPHO)
New Orleans, LA, United States
http://aspho.org/about/calendar-of-events

2 MAY
6th Annual PBMTC Meeting at ASPHO
Pittsburgh, Pennsylvania, United States
http://www.pbmtc.org/meetings

8-11 MAY
33rd European Immunogenetics and Histocompatibility Conference
Lisbon, Portugal
www.efi2019.org

8-11 MAY
MDS 2019 - 15th International Symposium on Myelodysplastic Syndromes
Copenhagen, Denmark
https://mds.kenes.com

9-11 MAY
International Symposium on Technical Innovations in Laboratory Hematology (ISLH-2019)
Vancouver, Canada
http://www.islh.org

10-11 MAY
MyKE -The 2019 Myeloma Knowledge Exchange
Barcelona, Spain
Website: https://ecancer.org/conference/calendar/1150-myeloma-knowledge-exchange-2019.php

10-12 MAY
The 16th WFH International Musculoskeletal Congress
Madrid, Spain
www.wfh.org/en/msk

16-18 MAY
The 5th World Congress on Controversies in Multiple Myeloma (COMy)
Paris, France
https://www.comy2019.cme-congresses.com/

17-19 MAY
International Conference on Acute Lymphoblastic Leukaemia
Berlin, Germany
http://www.esh.org/conferences/

20-25 MAY
SIOP Europe 2019 Annual Meeting
Prague, Czech Republic.
https://www.siope.eu/

31 MAY-4 JUNE
2019 ASCO Annual Meeting
Chicago, IL, United States
http://am.asco.org/

JUNE

13-16 JUNE
24th EHA Congress
Amsterdam, The Netherlands
www.ehaweb.org

18-22 JUNE
15-ICML International Conference on Malignant Lymphoma
Lugano, Switzerland
http://www.lymphcon.ch/icml/website/index.php

19-22 JUNE
The 26th International Congress on Thrombosis
Athens, Greece
https://www.thrombosiscongress.org/index.php

22-26 JUNE
The 29th Regional congress of the ISBT
Basel, Switzerland
www.isbtweb.org/congresses/isbt-congresses/annual-conference/

JULY

6-10 JULY
ISTH 2019
Melbourne, Australia
https://www.isth2019.org/

9 JULY
The Annual SHOT Symposium 2019
United Kingdom
http://www.shotuk.org/events-2/annual-shot-symposium/

AUGUST

22-25 AUGUST
International Society for Experimental Hematology - ISEH 48th Annual Scientific Meeting
Brisbane, Australia
https://www.iseh.org/page/2019Brisbane

Congress Calendar 2019

SEPTEMBER

5-7 SEPTEMBER
17th World Hematology Congress
Paris, France
https://worldhematology.conference-series.com/

6-7 SEPTEMBER
ASH Meeting on Hematologic Malignancies
Marriott Marquis Chicago, Chicago, IL, United States
http://www.hematology.org/Meetings/

12-15 SEPTEMBER
21th Annual John Goldman Conference on Chronic Myeloid Leukemia: Biology and Therapy
Bordeaux, France
http://www.esh.org/conferences/

14 SEPTEMBER
Post-EHA meeting
Brussels, Belgium
https://bhs.be/meetings

17-20 SEPTEMBER
16th International Congress on Antiphospholipid Antibodies
Manchester, UK
http://icapaconference.com/

20-22 SEPTEMBER
International Conference on Cellular Therapies: Focus on Immune Based Therapeutic Concepts
Mandelieu, France
http://www.esh.org/conferences/

20-23 SEPTEMBER
The 18th International Workshop on Chronic Lymphocytic Leukemia (XVII iwCLL 2019)
Edinburgh, UK
http://www.iwcll2019.org/

OCTOBER

3-5 OCTOBER
5th International Conference on New Concepts in Lymphoid Malignancies
Estoril, Portugal
http://www.esh.org/conferences/

17-18 OCTOBER
8th InterAmerican Oncology Conference
Auditorio UCA - Universidad Católica Argentina, Buenos Aires, Argentina.
www.oncologyconferences.com.ar/

17-18 OCTOBER
2nd Hematologists Global Summit 2019
Osaka, Japan
https://hematology.conferenceseries.com/asiapacific/

19-22 OCTOBER
AABB Annual Meeting 2019 - American Association of Blood Banks
San Antonio, Texas, United States
http://www.aabb.org/annual-meeting/go/Pages/future.aspx

23-24 OCTOBER
13th World Congress on Hematology and Oncology
Tokyo, Japan
https://hematology.global-summit.com/

24-26 OCTOBER
5th International Conference on Acute Myeloid Leukemia 'Molecular and Translational': Advances in Biology and Treatment
Estoril, Portugal
Website: http://www.esh.org/conferences/

NOVEMBER

13-14 NOVEMBER
WFH Global Forum - World Federation of Hemophilia
Montreal, Canada
www.wfh.org/en/globalforum

16-19 NOVEMBER
The 30th Regional congress of the ISBT
Bangkok, Thailand
www.isbtweb.org/events/isbt-congresses/

19-20 NOVEMBER
Belgian Society for the Advancement of Cytometry (BSAC) Annual Meeting
Chassé Theater, Breda, the Netherlands
http://www.cytometry.be

28-29 NOVEMBER
27th BSTH Annual Meeting
Mechelen, Belgium
https://www.bsth.be/about-bsth

29 NOVEMBER
BSPHO – Biannual Meeting 2019
The Provinciehuis, Leuven, Belgium
https://www.bspho.be/

NOVEMBER
Multiple Myeloma Symposium 2019
Hof ter Musschen, Brussel, Belgium
https://bhs.be/meetings

DECEMBER

7-10 DECEMBER
61th ASH Annual Meeting
Orlando, FL, United States
http://www.hematology.org/Annual-Meeting/Archive.aspx