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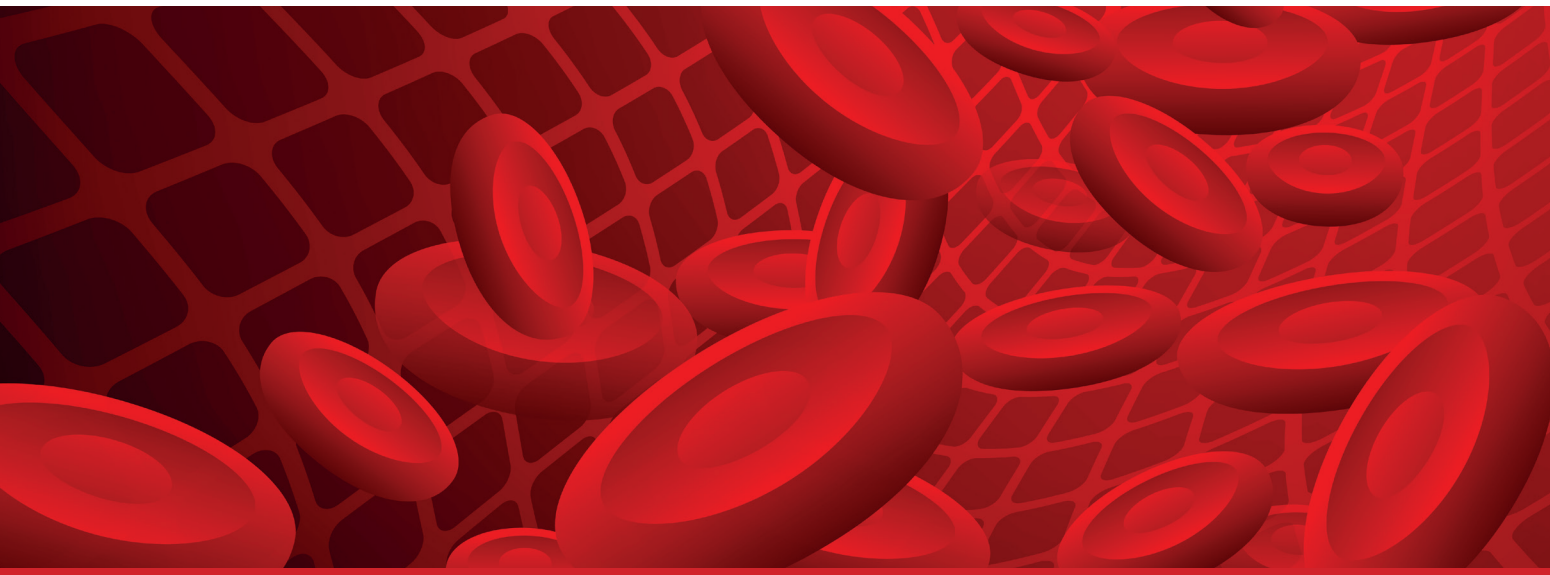

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EDITORIAL

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New leadership, old direction

Bartosz Puła

Department of Hematology, Institute of Hematology and Transfusion Medicine, Warsaw, Poland

As the new Editor-in-Chief, it gives me great pleasure to invite our dear readers and esteemed authors to share their achievements in the pages of 'Acta Haematologica Polonica' (AHP). Although our Journal is not indexed in the PubMed database, nor does it possess an Impact Factor, AHP has built a considerable reputation for itself since its launch back in 1970. The journal showcases the work of the Polish Society of of Haematologists and Transfusiologists.

The first change regarding the Journal has involved the planned introduction of the Journal to new databases. This will bring us closer to elevating AHP into a recognizable 'brand'. For this to be possible, the cooperation of our society and intensified publication input is necessary. Therefore, I heartily encourage you to publish in the pages of the journal as well as to cite the articles published in AHP.

The long-awaited expert guidelines for diagnosing and treating chronic lymphocytic leukemia were published at the end of 2023 [1]. Drawing upon these guidelines, two review articles address such important topics as emergencies in patients undergoing hematopoietic stem cell transplantation, and the identification of frailty in older patients with large B-cell lymphoma [2, 3]. The last review focuses explicitly on the pathophysiological aspects of hematological parameters in the pathogenesis of hypertension [4].

In this issue, readers will also find two original studies addressing the incidence of cardiac complications among transfusion-dependent thalassemia patients, plus a single-center analysis of the health issues related to multiple myeloma [5, 6]. Lastly, a case of acquired hemophilia in the course of myeloproliferative syndrome is described [7].

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Diagnostic and therapeutic recommendations of the Polish Society of Haematologists and Transfusiologists, and Polish Adult Leukemia Group-CLL for chronic lymphocytic leukemia in 2023

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Abstract

Chronic lymphocytic leukemia (CLL) is a disease of the elderly, with a median age at diagnosis of c.70 years. The natural course of the disease varies greatly, and patients with non-progressive and asymptomatic leukemia do not require treatment. But advanced and progressive CLL do require treatment. The results of CLL treatment have improved significantly in recent years, mainly due to the introduction of new and more effective drugs, including B-cell receptor inhibitors and B-cell lymphoma 2 (BCL2) inhibitors. These new drugs are used continuously as monotherapy, or in combination schemes for specified periods. Venetoclax in combination with anti-CD20 antibodies is used for 24 (rituximab) or 12 (obinutuzumab) months, while treatment with ibrutinib and venetoclax lasts 15 months. The choice of treatment protocol should largely depend on the assessment of 17p deletion/*TP53* mutation, and in second treatment line immunoglobulin variable heavy chain (IGVH) mutation status, which correlate with a response to immunochemotherapy. The role played by immunochemotherapy has recently significantly decreased. It is still an option for first line treatment in patients without 17p deletion/*TP53* mutation, with mutated gene encoding IGVH and in good performance status. However, the results of recent studies have shown that these patients may also obtain major benefit from chemotherapy-free regimens. The remaining patients, both in the first and subsequent treatment lines, should receive new targeted therapies, which are currently available in Poland under the drug program. In this article, we present an update of the guidelines for the diagnosis and treatment of CLL, including the treatment of autoimmune complications, as well as the

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prophylaxis and treatment of infections, developed by the Polish Society of Haematologists and Transfusiologists and the Polish Adult Leukemia Group-CLL working group.

Key words: chronic lymphocytic leukemia, 17p deletion/*TP53* mutation, Bruton's kinase inhibitors, ibrutinib, acalabrutinib, zanubrutinib, BCL2 inhibitor, venetoclax, rituximab, obinutuzumab, fludarabine, bendamustine

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Introduction

Chronic lymphocytic leukemia (CLL) is a disease of the elderly, with a median age at diagnosis of 70–72 [1–3]. Apart from age, the only risk factor for developing CLL is family history [4, 5]. In CLL patients, the risk of secondary cancers is around three times greater than in the general population [6]. The advanced age of CLL patients was previously associated with a poor prognosis, mainly due to comorbidities and poor tolerance of more aggressive therapies [3]. In recent years, the treatment options for CLL have significantly expanded with the introduction of new groups of drugs i.e. B-cell receptor (BCR) signal transduction inhibitors including Bruton's kinase inhibitors (BTK), and B-cell lymphoma 2 (BCL2) inhibitors. These drugs are well tolerated by the elderly and highly effective also in patients with unfavorable prognostic factors such as 17p deletion (del17p)/*TP53* mutation and unmutated immunoglobulin heavy-chain variable region gene (IGVH) [7, 8].

Selecting the most appropriate treatment requires an assessment of the patient's clinical condition, age and comorbidities. Before treatment commences, it is recommended to assess factors of prognostic and predictive importance, primarily del17p/*TP53* mutation, and in cases of the first line of treatment also the *IGVH* mutation status, because lack of mutation correlates with a worse response to immunochemotherapy [7, 8]. The role played by immunochemotherapy has significantly decreased in recent years, and it is currently recommended in the first line only in patients without del17p/*TP53* mutation and mutated *IGVH,* although the results of recent studies show that these patients may also obtain a major benefit from chemotherapy-free regimens. The remaining patients should receive novel targeted therapies, which are currently available in Poland under the B.79 drug program.

In this article, we present an update of management standards in the diagnosis and treatment of CLL, including the treatment of autoimmune complications, as well as the prevention and treatment of infections, developed by the Polish Society of Haematologists and Transfusiologists and the PALG-CLL (the Polish Adult Leukemia Group — Chronic Lymphocytic Leukemia working group). The guidelines proposed in this paper were developed based on the results of clinical trials with different strengths of evidence and the authors' clinical experience.

Definition and epidemiology

Chronic lymphocytic leukemia is a lymphoid cancer which is characterized by clonal proliferation of B-cells, presenting on their surface CD5 antigen typical for the T line, and their accumulation in the peripheral blood, bone marrow, lymphoid organs, and, less frequently, in extralymphatic organs. According to the 5th edition of 2022 World Health Organization (WHO) classification [1] CLL is a type of neoplasm derived from mature B-cells. It is the most common leukemia in the western world, with just over five new cases per 100,000 population annually (SEER, Surveillance, Epidemiology, and End Results) [2]. The etiology of the disease is unknown, and there is no association between its occurrence and exposure to environmental or occupational factors. The incidence is 6.8/100,000 in males and 3.5/100,000 in females [2]. The disease is most common in the elderly between 65 to 74 years of age, 70% of patients are aged over 65, and only 10% are under 55. The median age at diagnosis is 72 [3]. CLL patients account for 1.3% of all cancer patients in the United States. Annual mortality from CLL is 1.1/100,000. Apart from age, the only risk factor for developing CLL is a family history. In first-degree relatives of CLL patients, the relative risk of developing CLL is up to 8.5 times higher than in the general population [4, 5]. In patients with CLL, the risk of secondary cancers is approximately three times that of the general population. The most common secondary neoplasms are skin cancer (an 8-times greater risk), lung cancer, gastrointestinal neoplasms, and hematological malignancies [6].

Diagnostic criteria

The main criterion for the diagnosis of CLL is the presence of at least 5 G/L clonal B lymphocytes in the peripheral blood, confirmed by immunophenotypic examination of light chains [kappa (κ), lambda (λ)] [7, 8]. Leukemic CLL cells are mostly small, mature lymphocytes, with a narrow border of cytoplasm and dense nuclear chromatin. This population also includes larger, atypical, nuclear-indented cells or prolymphocytes, the percentage of which should not exceed 55% of all peripheral blood lymphocytes. The presence of a higher percentage of prolymphocytes supports the diagnosis of chronic B-cell prolymphocytic leukemia (B-cell PLL) [7]. However, B-PLL as a separate disease entity was not included

in the WHO classification published in 2022 (5th ed.). Cases meeting WHO's previously used criteria should be diagnosed as other lymphoproliferative syndromes, especially mantle cell lymphoma or a disease newly defined by this classification called 'splenic lymphoma/splenic B-cell lymphoma/leukemia with prominent nucleoli'. B-PLL as a separate disease entity remained in the International Consensus Classification (ICC) published in 2022 [9].

CLL cells show typical co-expression of B-cell antigens (CD19, CD20) with T-cell antigen CD5 as well as CD23, CD43, and CD200 antigens [8]. Expression level of CD20, CD79a, and surface immunoglobulin antigens is lower than in normal B-cells. In 50% of cases, B-cell prolymphocytic leukemia cells do not express CD5, while CD20 and surface immunoglobulin are expressed [7]. According to the European Research Initiative on CLL (ERIC) and the European Society for Clinical Cell Analysis (ESCCA) expert panel recommendations, testing of CD19, CD5, CD20, CD23 antigens and κ and λ chains on peripheral blood lymphocytes is necessary and sufficient to establish the diagnosis in typical cases. The expert panel also recommends additional testing of CD43, CD79b, CD81, CD200, CD10 and ROR1, which may be helpful in establishing the diagnosis in more difficult cases [10].

Patients with lymphadenopathy and/or splenomegaly, with B-cells with typical CLL immunophenotype in the peripheral blood, but less than 5 G/L, meet the diagnostic criteria of small lymphocytic lymphoma (SLL) [7]. A final diagnosis of SLL requires histopathological examination of the affected tissue. According to the WHO classification, CLL and SLL are separate clinical manifestations of the same disease [1].

The presence of less than 5 G/L of clonal B cells in the peripheral blood, without accompanying lymphadenopathy or organomegaly, cytopenia or systemic symptoms, allows the diagnosis of monoclonal B-cell lymphocytosis (MBL). Annually, 1–2% of MBL cases progress to CLL [11].

A simplified diagram showing the cytometric differential diagnosis of CLL with leukemic forms of other B-cell lymphomas is presented in Figure 1.

Bone marrow examination is not needed to diagnose CLL. However, it should be performed in patients with cytopenia to diagnose its cause (e.g. displacement of normal hematopoietic cells by leukemic cells, drug toxicity or immunocytopenia), as well as in the case of inconclusive results of immunophenotyping [7, 8]. Typically, the bone marrow of CLL patients shows a diffuse or nodular infiltration of more than 30% of lymphoid cells. In patients with concomitant lymphadenopathy and an inconclusive immunophenotyping result, an open biopsy of the lymph node should be performed.

Patient evaluation at CLL diagnosis

Initial evaluation of a patient diagnosed with CLL should include a medical history, physical examination including lymph nodes, liver and spleen, laboratory tests, and, if necessary, diagnostic imaging. Attention should be paid to the general symptoms related to the disease (fever of unknown origin >38.0°C for ≥2 weeks, night sweats lasting ≥1 month, weight loss of more than 10% of the initial weight in the last six months, progressive weakness), recurrent infections and comorbidities that may influence therapeutic decisions. Laboratory tests include complete blood count with a manual blood smear review, biochemical tests with the assessment of kidney and liver function, three basic classes of immunoglobulins (IgA, IgG and IgM) blood levels, and a direct antiglobulin test (DAT) [7, 8]. In daily clinical practice, in asymptomatic patients it is not necessary to perform imaging diagnostics such as ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI). However, these tests are required in prospective clinical trials. Positron emission tomography (PET)/CT examination is recommended in patients with suspected Richter's transformation (RT) to determine the optimal biopsy site [7, 8].

During initial diagnostics, it is not necessary to perform cytogenetic and molecular tests, in particular the determination of *TP53* and IGHV mutation status [7, 8]. Cytogenetic tests may be helpful in cases of CLL with an atypical CD23 phenotype, which can accompany trisomy of chromosome 12.

During diagnostics, the clinical stage of CLL should be determined using one of the two equivalent clinical staging systems: Rai or Binet [12, 13]. Both classifications are based on the results of blood count and physical examination. According to the current recommendations, the modified 3-stage Rai staging system should be used rather than the original 5-stage system [7, 14]. The Binet staging system depends on the number of nodal areas involved, including:

1) enlarged lymph nodes in the head and neck, including Waldeyer's ring (counted as one area even if more than one node is enlarged at that location);
2) enlarged axillary lymph nodes (counted as one area even with bilateral involvement);
3) enlarged inguinal lymph nodes (counted as one area even with bilateral involvement);
4) spleen palpable on physical examination;
5) liver enlarged on physical examination.

The Rai and Binet classifications are set out in Table I [12–14].

Prognostic factors

The most important prognostic factors in CLL, the measurement of which before starting therapy is recommended by international guidelines [European Society For Medical Oncology (ESMO), National Cancer Center Network (NCCN), International Workshop on Chronic Lymphocytic Leukemia

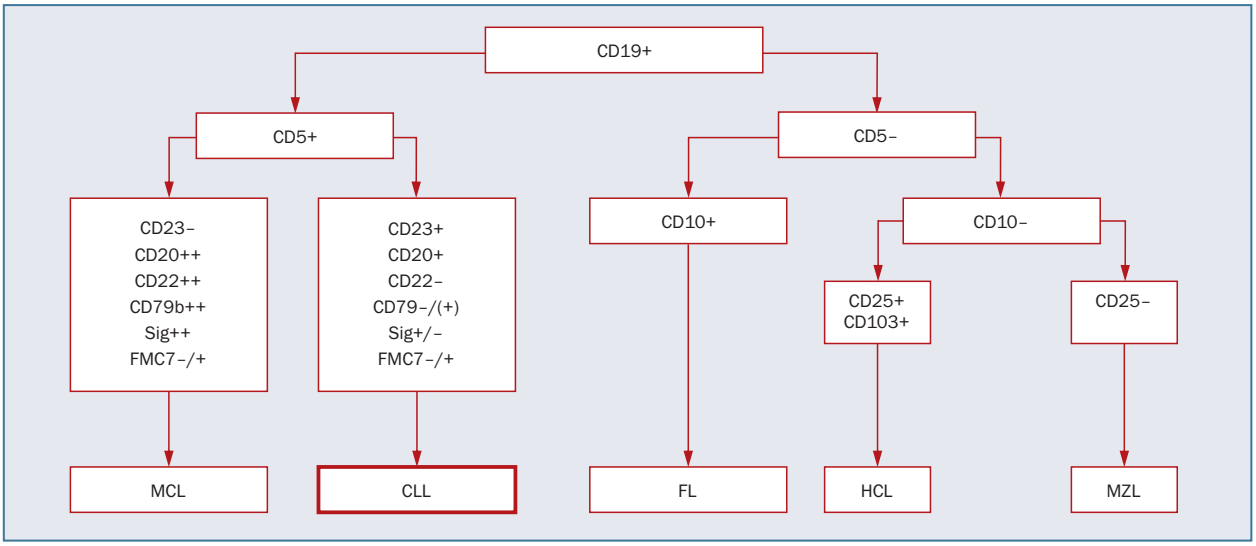

Figure 1. Simplified algorithm for the differential cytometric diagnosis of chronic lymphocytic leukemia (CLL); MCL — mantle cell lymphoma; FL — follicular lymphoma; HCL — hairy cell leukemia; MZL — marginal zone lymphoma

Table I. Clinical staging of chronic lymphocytic leukemia, according to Rai and Binet classifications (based on [10–12])

Classification	Clinical period/risk group		Criteria
Rai	0	Low risk	Lymphocytosis*
	I	Intermediate risk	Lymphocytosis + lymphadenopathy
	II		Lymphocytosis* + splenomegaly and/or hepatomegaly (with or without lymphadenopathy)
	III	High risk	Lymphocytosis* + anemia (Hb <11.0 g/dL)
	IV		Lymphocytosis* + thrombocytopenia (PLT <100.0 g/dL)
Binet	A		Involvement of <3 node areas/organs**
	B		Involvement of ≥3 node areas/organs**
	C		Anemia and/or thrombocytopenia (Hb <10 g/dL, and/or PLT <100 G/L)

*Absolute peripheral blood lymphocyte count >5,000/μL; **enlarged head and neck lymph nodes and/or axillary nodes and/or inguinal nodes and/or spleen and/or liver (see text for details); Hb — hemoglobin; PLT — platelets

(iwCLL)], include the main cytogenetic and molecular risk parameters, i.e. *TP53* gene disorders (17p deletions including the *TP53* gene locus and *TP53* gene mutations) and IGHV mutation status [7, 8]. *TP53* gene disorders and the IGHV mutation status have both prognostic and predictive value. This is particularly important in relation to the advisability of using classical immunochemotherapy, and therefore currently plays an important role in the decision as to which treatment method to choose. The presence of del17p/*TP53* mutation is associated with the worst prognosis in patients treated with immunochemotherapy, resulting in overall survival (OS) of 2–5 years [15–17]. The treatment outcomes of these patients improved significantly due to the introduction of targeted therapies with BCR and BCL2 inhibitors [18–20]; however, the prognosis still remains poor compared to patients without these mutations. The frequency of del17p/*TP53* mutation is c.10% in patients with indications to start first-line therapy, and increases with subsequent relapses of CLL if classical chemotherapy is used in the treatment. Del17p is determined by fluorescence *in situ* hybridization (FISH) and *TP53* mutations are determined by Sanger sequencing or next generation sequencing (NGS). The negative prognostic value of del11q (detected using FISH) has been significantly reduced due to the addition of rituximab to fludarbine and cyclophosphamide (FCR), and especially by new targeted therapies [17, 18, 21]. The second most important negative prognostic factor is the so-called unmutated status of the immunoglobulin variable heavy chain (IGVH) genes. IGHV genes are defined as unmutated when their germline variation is less than 2%. The unmutated state occurs in c.60% of patients with CLL who have indications for therapy [22] and does not change in the further course of the disease. The absence of IGVH mutations is associated with a more

aggressive course of CLL, shorter survival [22], more frequent occurrence of del17p and del 11q, and a short-term response to FCR immunochemotherapy [23–26], as well as, to a much lesser extent, to venetoclax therapy [21]. However, many separate analyses in patients treated in clinical trials with various BTK inhibitors have shown their activity regardless of the IGHV mutation status [27–30]. The presence of a complex karyotype, most often defined as the presence of three or more independent cytogenetic aberrations, also has a very important prognostic significance. However, due to the complexity of karyotype assessment in CLL, this factor is currently very rarely determined in clinical practice.

There are also other molecular prognostic and predictive factors known, but they have not yet found an established place in clinical practice. These include mutations of other relatively frequently mutated genes in CLL, for example: *NOTCH1, SF3B1, BIRC3, RPS15*, as well as so-called subtypes of immunoglobulin gene rearrangements. The prognostic value of these parameters in various modern treatment methods requires further prospective validation. However, it is very likely that some of them will be important in the future due to the tendency to further individualize CLL therapy.

The clinical stage according to Rai or Binet classification is still an important prognostic factor in patients with CLL, although its importance is decreasing with the introduction of more, and more effective, therapies. The only recognized biochemical prognostic factor is β_2-microglobulin level. Immunophenotyping of CD38 and ZAP-70 expression is currently of no importance in clinical practice.

An important dynamic prognostic factor (available during or after therapy) that is gaining importance is the negativity of measurable residual disease (MRD), defined as the presence of less than one CLL cell per 10,000 leukocytes. MRD can be assessed at various stages of treatment in the blood and marrow using standardized methods, including multicolor flow cytometry and ASO-PCR, and NGS at a deeper level [31]. Undetectable MRD indicates a profound response, which translates into longer progression-free survival (PFS) and overall survival (OS), as demonstrated in the CLL8 study in patients treated with FC regimens (fludarabine, cyclophosphamide) and FCR immunochemotherapy [32]. The results of a retrospective single-center analysis of patients treated between 1997 and 2006 showed a significant impact of MRD eradication on 10-year survival, regardless of therapy type [33]. A correlation between achieving MRD eradication and longer PFS has also been demonstrated in studies with venetoclax in combination with rituximab, anti-CD20 monoclonal antibodies (MURANO study), and obinutuzumab (CLL14 study) [21, 34, 35]. In both cases, MRD eradication rates were significantly higher compared to immunochemotherapy, and achieving MRD eradication was associated with longer PFS, regardless of the treatment method. However, MRD has no prognostic value in relation to therapies with BTK inhibitors. Currently, MRD assessment is only recommended in clinical trials, but it is believed that, in the future, MRD assessment is likely to have an impact on therapeutic decisions e.g. duration of treatment.

Indications for treatment initiation

The aim of treatment is to extend and improve quality of life for the patient. Despite enormous progress in understanding the biology of leukemia, increasing the possibility of correctly predicting an unfavorable prognosis, the basic indication for treatment still remains the disease stage assessed according to the Rai or Binet scales. The predictive value of some new genetic and biological markers for OS is lower in people over 75 years of age, i.e. the great majority of patients, but del17p, *TP53* mutation and IGHV mutational status should be taken into account when choosing therapy also in this group of patients. The criteria for treatment initiation in clinical trials may differ from those adopted in daily clinical practice. Except for clinical trials, treatment should not be initiated in patients with newly diagnosed CLL in the early stages (i.e. Rai stage 0 or Binet A stage) without evidence of disease progression. These patients should be followed up, with disease status monitored every 3–12 months [7, 8]. Patients in the intermediate stage of disease, i.e. Rai stage I and II or Binet B stage, require close monitoring of certain leukemia parameters every 3–9 months, and in this group treatment should be initiated in the presence of signs of active disease or progression. Patients with advanced CLL (Rai stage III/IV or Binet C stage) require anti-leukemic treatment. If cytopenia is caused solely by autoantibodies, immunosuppressive therapy (glucocorticosteroids) is indicated, and antileukemic therapy is indicated if immunosuppressive therapy is ineffective. The criteria proposed by Hallek et al. [7] should be used to assess indications for therapy. Initiation of anti-leukemic therapy is indicated if the symptoms set out in Table II are observed.

Pre-treatment evaluation

In patients with CLL who are offered initiation of treatment, the following tests are recommended [7, 8]:

- history and physical examination with assessment of lymph nodes, including Waldeyer's ring, liver, and spleen;
- assessment of general condition and comorbidities;
- complete blood count with manual blood smear review;
- bone marrow examination (fine needle biopsy / trephine biopsy) is indicated in cases of cytopenia of unknown cause and in clinical trials. Bone marrow biopsy may

Table II. Indications (at least 1 must occur) for chronic lymphocytic leukemia (CLL) initiation according to International Workshop on Chronic Lymphocytic Leukemia (iwCLL) (source [7])

1. Progressive bone marrow involvement as manifested by anemia and/or thrombocytopenia [assumed hemoglobin (Hb) cut-off point <10 g/dL (<6.21 mmol/L) or platelet count <100 G/L]. However, these parameters should be reproducible and systematically decreasing, because often, especially in platelet count, parameter is only slightly reduced, up to <100 G/L, but stable for a long time, which should not be considered an indication for treatment. In sudden and extremely low cytopenia, differential diagnosis should include autoimmune diseases, and appropriate laboratory workup should be planned
2. Significant (≥6 cm below costal margin), progressive or symptomatic splenomegaly
3. Significant (≥10 cm in long axis), progressive or symptomatic lymphadenopathy
4. Rapid increase in lymphocyte count — increase of >50% in two months or doubling of lymphocytosis in less than six months (if baseline lymphocyte count is ≥30 G/L). Other possible causes of sudden increase in lymphocyte count or progression of lymphadenopathy (including SARS-CoV-2 infection) should be ruled out. An absolute number of lymphocytes, even a very high number, without other symptoms, is not a sufficient indication for treatment initiation. This definition indicates necessity of examining patient and assessing blood count at least every six months
5. Autoimmune anemia and/or immune thrombocytopenia refractory to corticosteroid therapy or other standard treatments
6. One or more systemic symptoms depending on underlying disease, defined as:
   - unintentional weight loss of ≥10% in the last six months
   - significant fatigue (ECOG PS ≥2; inability to work or perform normal activities)
   - fever >38.0°C for ≥2 weeks or more with no other indication of infection
   - night sweats for more than one month without any other evidence of infection. A common problem in CLL patients is increased susceptibility to infection. Unless other symptoms of active disease coexist, it is not an indication for anti-leukemic treatment
7. Symptomatic extra-nodal localization

ECOG PS — the Eastern Cooperative Oncology Group of performance status; Hb — hemoglobin; PLT — platelets; SARS-CoV-2 — severe acute respiratory syndrome-related coronavirus 2

also be used as a baseline parameter in assessing response to treatment;

- biochemical tests to assess organ function (evaluation of liver and kidney function) and possibly exclude causes of anemia other than CLL;
- immunoglobulin serum levels (IgA, IgG, and IgM);
- DAT, haptoglobin level;
- diagnostic imaging (outside clinical trials, if needed): chest X-ray, abdominal ultrasound, CT/MRI; (as part of clinical trials): chest, abdomen, and pelvis CT. Diagnostic imaging (CT, MRI) may be helpful in clinical practice in assessing tumor mass and risk of tumor lysis syndrome, especially before starting venetoclax treatment, as well as in assessing response to treatment. In older patients, abdominal ultrasound and chest X-ray should be considered instead of CT [8];
- virological tests [HBs antigen, anti-HBc total, anti-hepatitis C virus (HCV), anti-human immunodeficiency virus (HIV) antibodies].

It is also advisable to perform other tests useful for assessing the risk of an unfavorable course of disease, including:

- cytogenetics (FISH) for del17p and molecular tests for *TP53* mutation (in absence of del17p): at least exons 4–10, recommended 2–11; <6 months before starting each line of treatment [8];
- IGVH mutation status [7, 8] before initiation of first line of treatment;
- serological markers: β_2-microglobulin, lactate dehydrogenase (LDH).

Treatment

Antileukemic drugs used in CLL

Alkylating agents

Chlorambucil, the drug with the longest history in CLL, allows for the reduction or resolution of symptoms in 30–70% of patients, but complete remission (CR) is observed only rarely (2–10%). Chlorambucil is used in various schedules (Table III). In British studies, the highest response rate and the longest PFS were observed with the use of chlorambucil at 10 mg/m^2 from days 1–7 of a 28-day cycle (Table III) [36]. Currently, chlorambucil monotherapy is used rarely, and only in patients whose old age and/or comorbidities do not allow the use of immunochemotherapy.

Purine analogs

Purine analogs (fludarabine, cladribine, pentostatin) are a group of cytostatics with the most pronounced therapeutic activity in CLL. However, they induce numerous adverse effects, including hematological complications (neutropenia, thrombocytopenia, anemia), autoimmune hemolytic anemia, increased incidence of infections, including opportunistic [*Pneumocystis jiroveci,* cytomegalovirus (CMV), varicella zoster virus (VZV)] associated with myelosuppressive and immunosuppressive effects, and an increased risk of secondary tumors, including hematopoietic malignancies (mainly acute myeloid leukemia and myelodysplastic syndrome). The risk of serious adverse events is greater in the elderly due to slower renal excretion of the fludarabine metabolites. The incidence of autoimmune complications

Table III. Selected treatment protocols used in patients with chronic lymphocytic leukemia

Protocol/drug	Dose	Administration route	Days	Notes	References
Chlorambucil	0.1 mg/kg bw		Continuous infusion	28-day cycles	[36]
	0.4–0.8 mg/bw	Oral	1 and 15	28-day cycles	
	10 mg/m^2		1–7	28-day cycles	
	40 mg/m^2		1	28-day cycles	
FCR				28-day cycles	[17]
F	25 mg/m^2; 40 mg/m^2	i.v./oral	1–3		
CY	250 mg/m^2	i.v., oral	1–3		
R	375 mg/m^2 (cycle 1)	i.v.	1		
	500 mg/m^2 (cycles 2–6)		1		
BR				28-day cycles	[37, 38]
B	90 (70)* mg/m^2	i.v.	1–2		
R	375 mg/m^2 (cycle 1)		1		
	500 mg/m^2 (cycles 2–6)				
Chlorambucil + rituximab					[39]
Chlorambucil	0.5 mg/kg bw or 10 mg/m^2	Oral	1, 15	28-day, up to six cycles	
	375 mg/m^2 (cycle 1)	Oral	1		
Rituximab	500 mg/m^2 (cycles 2–6)	i.v.	1		
Chlorambucil + obinutuzumab					[21]
Chlorambucil	0.5 mg/kg bw	Oral	1, 15	28-day, up to six cycles	
Obinutuzumab	1,000 mg	i.v.	1, 8, 15 (cycle 1)	One infusion over two days	
			1 (cycles 2–6)		
Ibrutinib	420 mg/day	Oral	Continuous treatment	Until progression or unacceptable toxicity	[40]
Venetoclax	400 mg after a 5 week titration period 20–400 mg	Oral	Continuous treatment	Until progression or unacceptable toxicity	[41]
Venetoclax + rituximab					[34]
Venetoclax	400 mg after the titration period 20–400 mg	Oral	24 months		
Rituximab	375 mg/m^2 (D1, C1)	i.v.	6 cycles		
	500 mg/m^2 (D1, C2–C6) every four weeks after end of titration period				
Venetoclax + obinutuzumab					[21]
Venetoclax	400 mg after a 5 week titration period 20–400 mg	Oral	12 cycles (28 days each), starting from day 1 of day 1 of cycle 1 of administration of obinutuzumab		
Obinutuzumab	1,000 mg every four weekns after end of titration period	i.v.	1, 8, 15 (cycle 1)		
			1 (cycles 2–6)		
Acalabrutinib	100 mg twice/day	Oral	Continuous treatment	Until progression or unacceptable toxicity	[42]
Ibrutinib + venetoclax					[43]
Ibrutinib	420 mg	Oral	15 months (1–15)		
Venetoclax	400 mg after the titration period 20–400 mg	Oral	12 months. (4–15)		
Zanubrutinib	320 mg/day or 160 mg twice/day	Oral	Continuous treatment	Until progression or unacceptable toxicity	[44]

*Treatment of relapsed disease; bw — body weight; B — bendamustine; FCR — fludarabine, cyclophosphamide, rituximab; i.v. — intravenous; BR — bendamustine, rituximab

is significantly lower when purine analogs are used in combination with cyclophosphamide and rituximab compared to monotherapy [15, 35, 36]. Fludarabine should not be used in patients with creatinine clearance <30 mL/min, and a dose reduction of 50% is indicated when the clearance is <70 mL/min. Particular attention should be paid to recurrent infections due to the strong immunosuppressive effect of fludarabine and poor functioning of the immune system in the elderly.

Bendamustine

Bendamustine is a cytostatic drug combining the properties of alkylating compounds and purine analogs. It is now widely used in the treatment of lymphoproliferative neoplasms, usually in combination with rituximab. The most important side effects of bendamustine are myelosuppression, infections, nausea, vomiting, and skin lesions. The hematological toxicity of bendamustine is greater than that of chlorambucil, but less than that of purine analogs. Bendamustine, unlike fludarabine, can be used in full doses in patients with renal failure. Modification of bendamustine dose is recommended only in cases of severe kidney disease (creatinine clearance <10 mL/min).

Immunochemotherapy

FCR (fludarabine, cyclophosphamide, rituximab)

FCR immunochemotherapy helps achieve significantly higher response rates and prolongation of PFS and OS compared to FC chemotherapy in younger patients, in good general condition, without significant diseases [CLL8 clinical trial (Table IV)] [17]. However, the FCR regimen is associated with significant toxicity, in particular with regard to cytopenias and infections. In the light of the European Organization for Research and Treatment of Cancer (EORTC) recommendations of 2011, and the NCCN recommendations, FCR is one of the regimens in which the risk of febrile neutropenia is more than 20%, which is an indication for primary prevention with granulopoiesis-stimulating factors [52, 53].

Immunochemotherapy is ineffective in patients with del17p/*TP53* mutation [17]. The results of FCR immunochemotherapy treatment are significantly worse also in patients with unmutated IGHV gene mutation status: the PFS rate is 33.1% compared to 66.6% of patients with IGHV mutation, in whom the median OS remained unreached [26]. The results of the CLL13 study show that in the group of patients without comorbidities, treatment with venetoclax in combination with obinutuzumab ± ibrutinib is characterized by greater effectiveness and lower toxicity compared to FCR immunochemotherapy [47].

Bendamustine and rituximab

A combination of bendamustine and rituximab (BR) allows for high response rates in both relapsed/refractory CLL and first-line treatment [37, 54]. The German group CLL10 has shown that FCR is more effective in inducing complete remissions (CR), and results in longer PFS (Table IV) and eradication of MRD in the first-line treatment [38]. In patients >65 years, the efficacy of both regimens in terms of PFS was comparable. The FCR regimen was significantly more toxic, including hematological toxicity (90% vs. 67%), severe neutropenia (84% vs. 59%) and infections (39% vs. 25%), especially in elderly patients. In patients treated with the BR regimen, routine primary prophylaxis of febrile neutropenia is not recommended, although it should be considered, especially when using the BR regimen in patients with relapsed/refractory CLL.

Chlorambucil in combination with anti-CD20 monoclonal antibodies

The results of the CLL11 study demonstrated that chlorambucil in combination with obinutuzumab is more effective than chlorambucil and rituximab in terms of CR, PFS, OS and MRD eradication [39, 55]. This regimen is currently rarely used due to the significantly greater effectiveness of venetoclax in combination with obinutuzumab (study CLL14) [21].

B-cell receptor signaling inhibitors

Inhibitors of BCR signaling approved in the European Union (EU) for the treatment of CLL include the BTK inhibitors ibrutinib, acalabrutinib and zanubrutinib, and δ isoform of phosphatidylinositol-3 kinase (PI3Kδ) — idelalisib and umbralisib. The summary of product characteristics (SmPC) indications for BTK inhibitors includes both first line and refractory/relapsed CLL treatment. The efficacy of ibrutinib in patients with relapsed/refractory CLL was assessed in a phase Ib/II study (PCYC-1102) [40] and a randomized phase III study (RESONATE) in which ofatumumab was used in the control arm (Table IV) [48]. The response rate in the PCYC-1102 study was 88%, including 2% CR, 68% partial remission (PR), and 18% partial response with lymphocytosis (PR-L). The response rates were similar regardless of the presence or absence of del17p/*TP53* mutation [48]. The median PFS was 52 months, and the OS rate after 7 years of follow-up was 55% [56]. In the RESONATE study, patients treated with ibrutinib had a very significantly higher response rate (63% vs. 4%, p <0.001) and a significantly longer PFS (44.1 vs. 8.1 months, p <0.001) [48]. An update of the RESONATE study results shows that the benefits of ibrutinib are maintained, and the risk of progression is reduced by 89%, compared to ofatumumab treatment. Median progression-free survival was significantly longer in patients randomized to the ibrutinib arm compared to ofatumumab (44.1 vs. 8.1 months). The benefits of ibrutinib versus ofatumumab were maintained in the high-risk population with del17p, *TP53* mutation, del11q and/or unmutated *IGVH* genes. Overall survival, censored for crossover, was longer on ibrutinib

Table IV. Selected phase III clinical trials in treatment of chronic lymphocytic leukemia

Study	Protocol	Number of participants	Median age	ORR [%]	CR [%]	PFS (months)	OS (months)	Reference
CLL8	FC	409	61	80	22	33	86	[17, 26]
Hallek (2010)	FCR	408	61	90*	44*	52*	NA* (after 6 years)	[38]
CLL10	FCR	282	62	95	40	55.2	91%	[39]
Eichhorst (2016)	BR	279	61	96	31* No difference in patients aged >65 years	41.7* No difference in patients aged >65 years	92% (after 3 years)	
CLL11	Chl	118	72	31.4*	0*	11.1*	ND	[39]
Goede (2014)	Rituximab + Chl	233	73	65.7*	7.3*	16.3*	73.1%	
	Obinutuzumab + Chl	238	74	77.7*	22.3*	26.7*	NA*	
RESONATE-2	Chl	133	73	37	2	15*	68%	[27]
Burger (2015)	Ibrutinib	136	72	92*	30	NA*	83% (after 5 years)	
ECOG1219	FCR	175	56.7	81.1	30.3	72.9%	91.5%	[30]
	Ibrutinib + rituximab	354	56.7	95.8*	17.2*	89.4%* (after 3 years)	98.8% (after 3 years)	
ALLIANCE	BR	183	70	81	26	74%	95%	[28]
	Ibrutinib	182	70	93	7	87%	90%	
	Ibrutinib + rituximab	182	71	94	12	88% (after 2 years)	94% (after 2 years)	
ILLUMINATE	Chl + obinutuzumab	116	72	88	8	19	86%	[29]
	Ibrutinib + obinutuzumab	113	70	73	19*	NA*	85% (after 30 months)	
CLL14	Obinutuzumab + Chl	216	72	71.3	23.1	35.4%	83.1	[21]
	Venetoclax + obinutuzumab	216	72	84.7	49.5	74% (after 48 months)	85.3 (after 48 months)	
ELEVATE TN	Obinutuzumab + Chl	177	71	79	5	22.6	92	[45]
	Acalabrutinib	179	71	86	1	NA	95	
	Acalabrutinib + obinutuzumab	179	71	94	13	NA 93 vs. 87 vs. 47 (after 24 months)	95 (after 24 months)	

→

Table IV (cont.). Selected phase III clinical trials in treatment of chronic lymphocytic leukemia

Study	Protocol	Number of participants	Median age	ORR [%]	CR [%]	PFS (months)	OS (months)	Reference
GLOW	Obinutuzumab + Chl	105	71	84.8	11.4	21 months (44.1% afters 24 months)	ND	[46]
	Ibrutinib + venetoclax	106	71	86.8	38.7	NA (84.4% after 25 months)	ND	
CLL 13 (GAIA)	FCR/BR	229	61	80.8	31	75.5% (after 3 years)	87.4% (after 3 years)	[47]
	VenR	237	62	93.3	49.4	80.8%	93%	
	VenG	229	62	96.1	56.8	87.7%	92.4%	
	VenGI	231	60	94.4	61.9	90.5%	98.4%	
SEQUOIA	Zanubrutinib	241	70	94.6	7%	85.6% (after 24 months)	94.3% (after 24 months)	[44]
	BR	238	70	85.3	15%	69.5%	94.6%	
RESONATE	Ofatumumab	196	67	4	0	8.1	65.1	[48, 49]
	Ibrutynib	195	67	91	11	44.1*	67.7*	
MURANO	BR	195	65	72.3	3.6	17	62.2	[34, 35]
	VenR	194	65	92.3*	8.2*	53.6* 84.9 36.3 (after 24 months)	82.1 (after 5 years)	
ASCEND	Investigator's choice**	155	68	81	ND	88	91	[42]
	Acalabrutinib	155	67	75	ND	68 (after 12 months)	94	
ELEVATE RR	Ibrutinib	265	65	77	ND	38.4	After 40.9 months 62.5%	[50]
	Acalabrutinib	268	66	81	ND	38.4	66.5%	
ALPINE	Ibrutinib	325	68	75.7	ND	34.2	NA	[51]
	Zanubrutinib	327	67	86.2	ND	NA	NA	

*Statistically significant difference, **BR — 36 patients, idelalisib + rituximab — 119 patients; ORR — overall response rate; CR — complete remission; PFS — progression-free survival; OS — overall survival; FC — fludarabine, cyclophosphamide; FCR — fludarabine, cyclophosphamide, rituximab; NA — not achived; BR — bendamustine, rituximab; Chl — chlorambucil; ND — no data; R — rituximab; VenR — venetoclax, rituximab; VenG — venetoclax, obinutuzumab; VenGI — venetoclax, obinutuzumab, imatinib

than ofatumumab [49]. The efficacy of ibrutinib was analyzed in patients with relapsed/refractory CLL progressing on their last treatment with venetoclax. Median PFS and OS after initiation of BTK inhibitors treatment were 34 and 42 months, respectively. BTK inhibitors (ibrutinib, n = 21; zanubrutinib, n = 2) have brought lasting benefits in patients with the *Gly101Val* mutation associated with resistance to venetoclax [57].

The efficacy of ibrutinib in first-line treatment was assessed in RESONATE-2, a randomized, phase III trial

performed in a population of patients aged ≥65. Ibrutinib was shown to be significantly more effective in terms of response rates, PFS, and OS compared to chlorambucil, regardless of the presence of del17p/*TP53* mutation and IGVH mutation status (Table IV) [58]. Moreover, a significant improvement in hematological parameters (anemia, thrombocytopenia) was observed more frequently in patients treated with ibrutinib [58]. In subsequent phase III clinical trials, ibrutinib regimens were compared to first line immunochemotherapy regimens. In the iLLUMINATE study, patients aged 65 or younger with comorbidities were treated with ibrutinib and obinutuzumab versus chlorambucil and obinutuzumab. The response rates (ORR, CR, MRD negativity) were significantly higher (91%, 41%, and 35% vs. 81%, 16%, and 25%, respectively), and median PFS (with a median follow-up of 45 months) was significantly longer, in patients treated with ibrutinib (not achieved after 19 months) irrespective of risk factors (del17p/*TP53* mutation, IGVH mutation status). There was no difference in PFS between patients with and without del17p/*TP53* mutation (77% vs. 74%) after 48 months of follow-up. Treatment tolerance was good, with no new safety data in the final analysis [29, 59]. In the E1912 trial, patients up to the age of 70 received first-line treatment of ibrutinib and rituximab or FCR immunochemotherapy. Both PFS and 3-year OS were significantly longer in patients treated with ibrutinib (89.4% vs. 72.9%, p <0.001; 98.8% vs. 91.5%, p <0.001), but subgroup analysis showed that that the real benefit of ibrutinib treatment was achieved by patients with unmutated *IGVH*. 3-year PFS in the group with mutated *IGVH* treated with ibrutinib was 87.7% compared to 88% in FCR-treated patients. In patients with unmutated *IGVH*, 3-year PFS was 90.7% versus 62.5%, respectively [30]. Long-term follow-up of patients participating in the E1912 study (median 6 years after randomization) showed that patients with both unmutated and mutated IGHV gene status benefitted in terms of PFS, and 60% of patients continued ibrutinib treatment. Treatment tolerance was good, with an atrial fibrillation rate of 4.5% [30, 60]. In the third study conducted by the ALLIANCE group, patients aged 65 or older received ibrutinib monotherapy, or ibrutinib in combination with rituximab, or the BR regimen as first-line treatment. After 55 months of follow-up, median PFS was not achieved in the ibrutinib arms, and was 44 months in the BR arm [61]. The PFS rate after 48 months was significantly higher in patients treated with ibrutinib regimens (76%, 76% and 47%), and no PFS benefit was demonstrated by adding rituximab to ibrutinib. Patients with del17p particularly benefited from ibrutinib treatment [28].

Ibrutinib is well tolerated. Most of the adverse reactions in clinical trials have been described as grades 1–2. The most common adverse effects are diarrhea, fatigue, muscle and joint pain, infections, bleeding complications, hypertension, and atrial fibrillation. In January 2020, acalabrutinib, a selective irreversible BTK inhibitor, was registered by the European Medicines Agency (EMA) for both first-line treatment (in monotherapy or in combination with obinutuzumab) and in patients who had received at least one previous therapy (in monotherapy).

In the ASCEND study, the efficacy and safety of acalabrutinib in the treatment of patients with relapsed/refractory CLL who had not previously received BTK and BCR inhibitors was compared to an investigator's choice therapy (BR or idelalisib and rituximab). The median PFS was significantly longer with acalabrutinib monotherapy (not reached) compared to the investigator's choice therapy (16.5 months, p <0.0001). The estimated 12-month PFS rate was 88% for acalabrutinib and 68% for the investigator's choice therapy [42].

In the ELEVATE TN study, acalabrutinib, or acalabrutinib in combination with obinutuzumab, was used in the first line for CLL patients aged ≥65 with a creatinine clearance of between 30 and 69 mL/min or co-morbidities [younger with a ClCr between 30 and 69 mL/min or disease comorbidities (Cumulative Illness Rating Scale {CIRS}) score >6]. A control group received obinutuzumab and chlorambucil. Median PFS was significantly longer in patients treated with acalabrutinib-based regimens (not achieved vs. 22.6 months, p <0.001). The estimated 2-year PFS rate was 93%, 87%, and 43%, respectively [45]. After 6 years of follow-up, median PFS was significantly longer in patients treated with acalabrutinib (not achieved vs. 27.8 months) regardless of risk factors (del17p/*TP53* mutation, IGVH mutation status). The efficacy of the drug was similar in patients with mutated and non-mutated IGVH mutation status, del17p/*TP53* mutation [45, 62]. The treatment was well tolerated. Most adverse reactions observed in clinical trials were grades 1–2. The most common adverse effects of acalabrutinib are headache, diarrhea, fatigue, nausea, and bleeding complications. The most common grade 4 adverse reactions are neutropenia, anemia, pneumonia, and thrombocytopenia. In the ASCEND study, serious adverse events occurred in 29% of patients (44 of 154) treated with acalabrutinib monotherapy, 56% (66 of 118) in the IR group, and 26% (9 of 35) in the BR group [42]. A phase III randomized trial ELEVATE RR directly head-to-head comparing acalabrutinib with ibrutinib in previously treated CLL patients showed similar efficacy of both drugs. Acalabrutinib was, however, better tolerated [50]. The incidence of any grade atrial fibrillation/atrial flutter was significantly lower with acalabrutinib compared to ibrutinib (9.4% vs. 16.0%; p = 0.02); among other selected secondary endpoints, grade 3 or higher infections (30.8% vs. 30.0%) and Richter's transformations (RT) (3.8% vs. 4.9%) were comparable between groups. Treatment discontinuation due to adverse events occurred in 14.7% of acalabrutinib-treated patients and in 21.3% of ibrutinib-treated patients [50].

Another BTK inhibitor that has been approved by the EMA is zanubrutinib. In the phase III SEQUOIA clinical trial, zanubrutinib (arm A) or BR regimen (arm B) was used as first-line treatment in patients without del17p. Median PFS was significantly longer in patients treated with zanubrutinib (not achieved vs. 28 months). The most common grade 3 or higher adverse event with zanubrutinib was neutropenia (11%), while the incidence of atrial fibrillation was less than 5%. The drug's effectiveness was similar in patients with mutated and unmutated IGHV mutation status. In arm C of the study (patients with del17p), median PFS was not achieved after 30 months of follow-up, and the percentage of patients without progression was 88.9% after 24 months of follow-up [44].

In the phase III ALPINE trial, two BTK inhibitors, ibrutinib versus zanubrutinib, were head-to-head compared in the treatment of relapsed or refractory CLL. After a median follow-up of 29.6 months, zanubrutinib was found to be superior to ibrutinib in terms of PFS among 652 patients. At 24 months, PFS was 78.4% in the zanubrutinib group and 65.9% in the ibrutinib group. Interestingly, among patients with del17p and/or *TP53* mutation, zanubrutinib also showed greater efficacy than ibrutinib in relation to the PFS. The safety profile of zanubrutinib was better than that of ibrutinib, with fewer adverse events leading to treatment discontinuation and fewer cardiac events, including fewer cardiac events leading to treatment discontinuation or death [51].

New BTK inhibitors in advanced clinical trials include pirtobrutinib and nemtabrutinib, which bind to BTK in a reversible and non-covalent manner. In the phase II BRUIN clinical trial, 82% of patients who had previously received treatment with another BTK inhibitor responded. The treatment was effective in patients with the BTK C481 mutation (associated with ibrutinib resistance) and was well tolerated [63].

BCL2 antagonists

Venetoclax is an oral, selective inhibitor of BCL2, the only drug in this group approved for the treatment of CLL. The current indication, according to the EMA registration, is first-line treatment in combination with obinutuzumab and for the treatment of relapsed/refractory CLL either alone or in combination with rituximab. Venetoclax alone enables 79% response rates in relapsed CLL [41]. Complete remission was observed in 20% of patients, and in 5% very deep responses with negative MRD. Venetoclax in monotherapy is used continuously, while in combination with monoclonal antibodies and BTK inhibitors, the therapy is administered for a limited time only. A venetoclax and rituximab (VenR) regimen was approved based on the results of the MURANO phase III clinical trial, in which venetoclax was administered together with rituximab (six doses) for two years, and the efficacy was compared to bendamustine and rituximab. The reduction in the risk of progression was 81% and the risk of death was 60% in patients treated with VenR compared to BR [34]. The median time to progression and time to the next treatment were 53.6 and 57.8 months in patients receiving venetoclax plus rituximab, and 17 and 23.9 months in the BR arm, respectively (Table IV) [34]. Undetectable MRD was achieved in as many as 63.8% of patients treated with VenR. An update of the results of the MURANO study after five years of follow-up, presented at the American Society of Hematology (ASH) meeting in 2020, showed that the benefits were maintained for PFS (57.3% and 4.6%) and OS (85.3% vs. 66.8%), despite using new targeted therapies in patients treated according to the BR regimen in subsequent lines of treatment. Particularly long responses were observed in patients who achieved MRD negativity after completing a VenR regimen [35].

An earlier study had proven the efficacy of venetoclax monotherapy in CLL patients with del17p. For all patients, the objective response rate was 77% and the estimated progression-free survival after 24 months was 54%. For 16 patients who had previously received kinase inhibitors, the objective response rate was 63% (10/16 patients) and the estimated 24-month PFS was 50% [20].

The efficacy of venetoclax has been assessed in patients receiving ibrutinib in their previous therapy. In total, 59/91 (65%) patients responded to treatment with venetoclax [64].

In the CLL14 study, venetoclax in combination with obinutuzumab was used in the first-line treatment in patients with comorbidities. Obinutuzumab in combination with chlorambucil was administered in the control arm. Treatment duration for both regimens was 12 months. At 24 months after randomization, the PFS rate was significantly higher in patients treated with the venetoclax-containing regimen (88.2% vs. 64.1%) (Table IV). A benefit in terms of PFS was also observed in patients with del17p and unmutated IGVH [21, 65].

The CLL13 study evaluated new chemotherapy-free and time-limited combination treatment regimens with venetoclax in patients eligible for intensive therapy [66]. The efficacy and safety of three regimens: venetoclax + + rituximab, venetoclax + obinutuzumab, and venetoclax + + obinutuzumab + ibrutinib were compared to FCR/BR regimens. The results of this study showed a higher percentage of patients with undetectable MRD and longer PFS in patients treated with venetoclax + obinutuzumab and venetoclax + obinutuzumab + ibrutinib regimens compared to immunochemotherapy [66]. The toxicity of immunochemotherapy was higher in terms of infectious complications and secondary malignancies.

In two clinical trials, a combination of venetoclax and ibrutinib was used in the first-line treatment of CLL. In the phase II CAPTIVATE trial, in the group of CLL patients eligible for intensive treatment, patients were divided into two

Table V. Tumor lysis syndrome risk assessment and pre-treatment prophylaxis (source [46])

Tumor lysis syndrome risk assessment		
Low risk	**Medium risk**	**High risk***
Enlarged lymph nodes <5 cm and peripheral blood lymphocyte count <25 G/L	Lymph nodes ≥5 cm and <10 cm or peripheral blood lymphocyte count ≥25 G/L	Lymph nodes >10 cm (in imaging) or peripheral blood lymphocyte count ≥25 G/L and lymph nodes ≥5 cm
Prophylaxis of tumor lysis syndrome		
Allopurinol 300–600 mg orally from 72 h before starting treatment Hydration 1.5 L orally from 48 h prior to treatment	Allopurinol 300–600 mg orally from 72 h before starting treatment Hydration 2–3 L orally from 24 h before start of treatment and consider intravenously during hospitalization	Allopurinol 300–600 mg orally from 72 h before starting treatment Hydration 2–3 L orally from 24 h before start of treatment and intravenously during hospitalization Rasburicase 0.05–0.2 mg/kw bw (depending on local procedures, necessary in patients with uric acid level >8.0 mg/dL)

*An additional risk factor for tumor lysis syndrome is renal failure with creatinine clearance <80 mL/min

cohorts. In both cases, ibrutinib monotherapy was used for the first three months, followed by combined treatment with ibrutinib and venetoclax for 12 months. In the first cohort ('FD, fixed-duration, cohort'), treatment was completed after 15 months. In the second cohort, ('MRD cohort'), the further course of treatment depended on the MRD assessment after 15 months of treatment. Patients with undetectable MRD were randomized to one of two groups: ibrutinib or a placebo, and patients with current MRD were randomized to treatment with venetoclax and ibrutinib, or ibrutinib alone. In the FD cohort, the post-treatment CR rate was 56% and the post-treatment PFS and OS rates were 95% and 98%, respectively. The uMRD rates during 27.9 months of follow-up reached 77% in peripheral blood and 60% in bone marrow [67]. Fixed-term treatment allowed a deep and lasting response to be achieved even in patients with a high genetic risk [43].

The phase III GLOW clinical trial included patients over 65 or under 65 with a CIRS score greater than 6 and/or creatinine clearance of less than 70 mL/min. The treatment included ibrutinib + venetoclax (three cycles of ibrutinib, then 12 cycles of ibrutinib and venetoclax) or chlorambucil and obinutuzumab (six cycles). After a median follow-up of 27.7 months, PFS was significantly longer in patients treated with IbrVen. The proportion of patients with undetectable MRD 3–12 months after treatment completion was 84.5% versus 29.3%. The most common adverse event in both arms was neutropenia: 34.9% and 49.5% [68].

The most common side effects of venetoclax are neutropenia, diarrhea, nausea, anemia, upper respiratory tract infection, thrombocytopenia and fatigue. Serious complications can include pneumonia, febrile neutropenia, hemolytic anemia, and metabolic disorders associated with TLS.

Table VI. Biochemical markers of tumor lysis syndrome (to make a diagnosis, ≥2 criteria must be met)

Parameter	Value	Change after treatment
Uric acid	>8 mg/dL	>25%
Potassium	>6 mg/dL	>25%
Inorganic phosphates	>1.45 mmol/L	>25%
Calcium	<1.75 mmol/L	>25%

In all patients, the risk of tumor lysis should be assessed, and appropriate prophylaxis and treatment should be applied if laboratory or clinical symptoms of TLS appear (Tables V, VI) [46].

Regimens used to treat patients with CLL and the results of phase III clinical trials regarding currently used regimens are set out in Tables III and IV.

Cellular immunotherapy

Allogeneic hematopoietic stem cell transplantation

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is used much less often in the era of targeted therapies, but it remains the only method that can be used with intention to cure. However, because of the serious complications associated with this procedure, it is only recommended for high-risk patients. The introduction of new drugs has changed the site of allogeneic transplantation in the treatment of CLL. Currently, allo-HSCT is indicated in high-risk disease and after treatment failure with at least one BCR pathway inhibitor or a BCL2 antagonist [69, 70]. The decision should be made on an individual basis,

and patients with high-risk disease after novel BCR and BCL2 inhibitors failure should be carefully analyzed for alternative treatment options, risk of RT, complications, or transplant failure. A phase II study by a German group showed a 4-year survival rate of 65%, with no differences in the presence of negative cytogenetic prognosis or in patients refractory to previous treatment [71]. Similar results were obtained by other transplant groups, indicating a plateau of survival curves at a 40–50% level. Reduced-intensity conditioning protocols used by an American group resulted in 3-year survival in 59% of patients [72]. Long-term European Society for Blood and Marrow Transplantation (EBMT) analyses showed that 10-year event-free survival (EFS), OS, and non-relapse mortality (NRM) after allo-HSCT were 28%, 35%, and 40%, respectively [73].

New therapies in clinical and pre-clinical trials

The use of chimeric antigen receptor (CAR) T-cells is currently the most promising and dynamically developing cell therapy modality. Numerous CAR-T constructs are currently being evaluated in clinical trials that are at various stages of advancement, showing promising results in terms of therapeutic efficacy. In one long-term follow-up study, median PFS was 40.2 months in patients who achieved CR and did not reach median OS [74]. The addition of ibrutinib resulted in improved CAR-T efficacy in CLL patients. Novel BCL2 inhibitors (sonrotoclax, lisaftoclax), bispecific antibodies, BTK degraders, MDM2 antagonists (RG7112, RG7388), XPO1 inhibitors, and ATR inhibitors are being evaluated in clinical and preclinical studies.

First-line treatment

Currently there are three treatment strategies employed in first-line settings:

- continuous administration of targeted drugs: ibrutinib, acalabrutinib, zanubrutinib (reimbursement in Poland from January 2024);
- time-limited chemotherapy-free regimens: venetoclax + obinutuzumab, venetoclax + ibrutinib (not yet reimbursed in Poland; recommendations were being drawn up in December 2023);
- time-limited immunochemotherapy with anti-CD20 monoclonal antibodies.

Factors influencing choice of first-line treatment

The fundamental factors that should be taken into account when choosing the type of first-line treatment are genetic disorders with an unfavorable prognosis, del17p and/or *TP53* mutation, and the mutation status of the IGHV genes. Additionally, comorbidities, age, physical performance status [according to the Eastern Cooperative Oncology Group (ECOG), Karnofsky scales] and susceptibility to infections should be taken into account.

CIRS is the most widely used tool to assess comorbidities. It involves the evaluation of 14 organs/systems using a 5-point scale, where zero means disease-free/ /normal organ function and four points mean a life-threatening condition [75, 76]. However, the importance of this scale in the choice of targeted therapy is less than that of immunochemotherapy. When choosing a therapeutic option, the patient's preferences should also be considered, after a detailed presentation of the potential benefits and side effects, the route of administration, and the need for hospitalization related to the given treatment method.

The presence of del17p/*TP53* mutation, correlated with resistance to alkylating drugs and purine analogs, and the unmutated state of IGHV genes, is associated with a short duration of response to immunochemotherapy. Tests should be performed before starting first-line treatment towards del17p, *TP53* mutations and IGHV gene mutation status.

When choosing between a time-limited treatment (in Poland in December 2023, the reimbursed regimen is venetoclax + obinutuzumab) and the continuous administration of BTK inhibitors, the following factors should be considered: toxicity profile (renal function and risk of TLS vs. atrial fibrillation and risk of bleeding); the administration route [intravenously (i.v.) + oral (*p.o., per os*) vs. only oral]; the frequency of follow-up visits (5-week period of increasing the dose of venetoclax); and patient preference [8].

Patients without del17p/*TP53* mutation and with mutated IGVH

Patients in good general condition without significant comorbidities

Patients in good general condition, without significant comorbidities and with normal kidney function, are currently the only patients in whom FCR immunochemotherapy is still considered an effective treatment method (Figure 1) [8]. Due to the results of the CLL13 and CAPTIVATE studies, the NCCN, German and French guidelines no longer recommend immunotherapy as first-line therapy for this group of patients. Similarly, in accordance with the PALG-PTHiT guidelines, in the treatment of this group of patients, treatment without immunochemotherapy should be considered first, i.e. venetoclax with obinutuzumab (based on the CLL13 study), or venetoclax and ibrutinib (based on the results of the CAPTIVATE study). However, this study did not show any differences in the survival time of patients treated with venetoclax and obinutuzumab as opposed to venetoclax and rituximab. Alternatives may be ibrutinib, acalabrutinib (in Poland not reimbursed in the drug program in this group of patients), or the venetoclax and obinutuzumab regimens. FCR immunochemotherapy is also a treatment option.

Patients with comorbidities not qualified for intensive immunochemotherapy

In patients not eligible for intensive immunochemotherapy, the currently recommended treatment standards are venetoclax combined with obinutuzumab, or BTK inhibitors: ibrutinib, acalabrutinib, zanubrutinib [8, 77]. Currently, in Poland, only the regimens of venetoclax and obinutuzumab, and of obinutuzumab and chlorambucil are reimbursed under the drug program. The latter regimen is currently rarely used due to the much greater efficacy of venetoclax in combination with obinutuzumab. From January 2024, zanubrutinib will be reimbursed for patients in this group.

In patients of very advanced age, in poor general condition, when the use of i.v. drugs is impossible, monotherapy with chlorambucil or cyclophosphamide may be used.

Patients without 17p deletion/*TP53* mutation with unmutated IGHV gene status

Patients in good general condition with no significant comorbidities

The recommended therapy for this group of patients is BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib) or venetoclax in combination with obinutuzumab or ibrutinib. Chemoimmunotherapy is not recommended due to poor survival rates. In Poland, treatment with BTK inhibitors as monotherapy: ibrutinib, acalabrutinib, zanubrutinib (this drug from January 2024 acc. to the rules indicated in the drug program) is reimbursed for this group of patients. A regimen of venetoclax and obinutuzumab will also be reimbursed from January 2024.

Patients in worse general condition with comorbidities

The recommended treatment regimen for this group of patients is venetoclax with obinutuzumab, ibrutinib, acalabrutinib, and zanubrutinib.

Currently, in Poland, the following are reimbursed for this group of patients: venetoclax and obinutuzumab, ibrutinib and acalabrutinib (under the B.79 drug program). From January 2024, zanubrutinib will also be reimbursed for patients in this group.

Patients with 17p deletion/*TP53* mutation

Patients with del17p/*TP53* mutation should not be treated with immunochemotherapy [8, 77]. BCR and BCL2 inhibitors are currently considered the most effective conventional regimens in patients with del17p/*TP53* mutation. The recommended first-line treatment regimens are BTK inhibitors. Venetoclax in combination with obinutuzumab, or venetoclax in monotherapy, could be alternatives. Idelalisib, according to the ESMO recommendation, can be used in the first line of CLL treatment in patients with del17p/*TP53* mutation who are ineligible for alternative treatments, and it is necessary to adhere to the recommendations to reduce the risk of infectious complications [8]. BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib — this drug from January 2024 acc. to the rules indicated in the drug program) are reimbursed in Poland. The current recommendations for selecting the first-line therapy are set out in Figure 2.

It should be underscored that when choosing first-line treatment (excluding patients with a del17p/mutation in the *TP53* gene), the type of therapy sometimes depends on the patient's preference and should be discussed with the patient, particularly when there is a high likelihood of non-adherence to therapy during long-term treatment with BTK inhibitors.

According to the current guidelines of international societies (NCCN, German guidelines, French guidelines), in all patients with CLL, regardless of genetic prognostic factors, the first-line therapy of choice is treatment without chemotherapy [77–79]. Currently, in Poland, targeted therapies registered in EU countries are not reimbursed to such a wide extent. In our recommendations for Polish hematologists, we take into account the availability of individual drugs in Poland, but we also present EMA registration indications.

Treatment of relapsed/refractory CLL

Indications for second and subsequent lines of treatment are the same as indications for first-line treatment. As in the case of the decision to start first-line treatment, also in patients with relapse, unfavorable prognostic biological features (LDH, β_2-microglobulins, chromosomal aberrations, unmutated IGHV gene status, *TP53* mutation) are not an indication to start treatment if the patient does not meet the above criteria demonstrating the progression of CLL. In the event of termination of treatment with a BTK inhibitor (e.g. due to side effects), it is not necessary to start another treatment immediately, especially if the leukemia is in remission. On the other hand, in a case of rapid progression during targeted therapies, an immediate change to another type of treatment is recommended.

Currently, in second- and subsequent-line treatment, the therapeutic decision depends to a greater or lesser extent on the duration of remission, the type of previous treatment, the presence of del17p/*TP53* mutations, the patient's general condition, any comorbidities, the patient's preference, and the availability of drugs.

According to the recommendations of international scientific societies, the optimal methods of treating patients with relapsed/refractory CLL are novel targeted therapies i.e. BCR and BCL2 inhibitors [8, 77].

One of two treatment options should be used:

1) venetoclax + rituximab (for 24 months); or
2) BTK inhibitors (as continuous treatment).

In a case of a relapse requiring therapy after first-line treatment according to the venetoclax + obinutuzumab

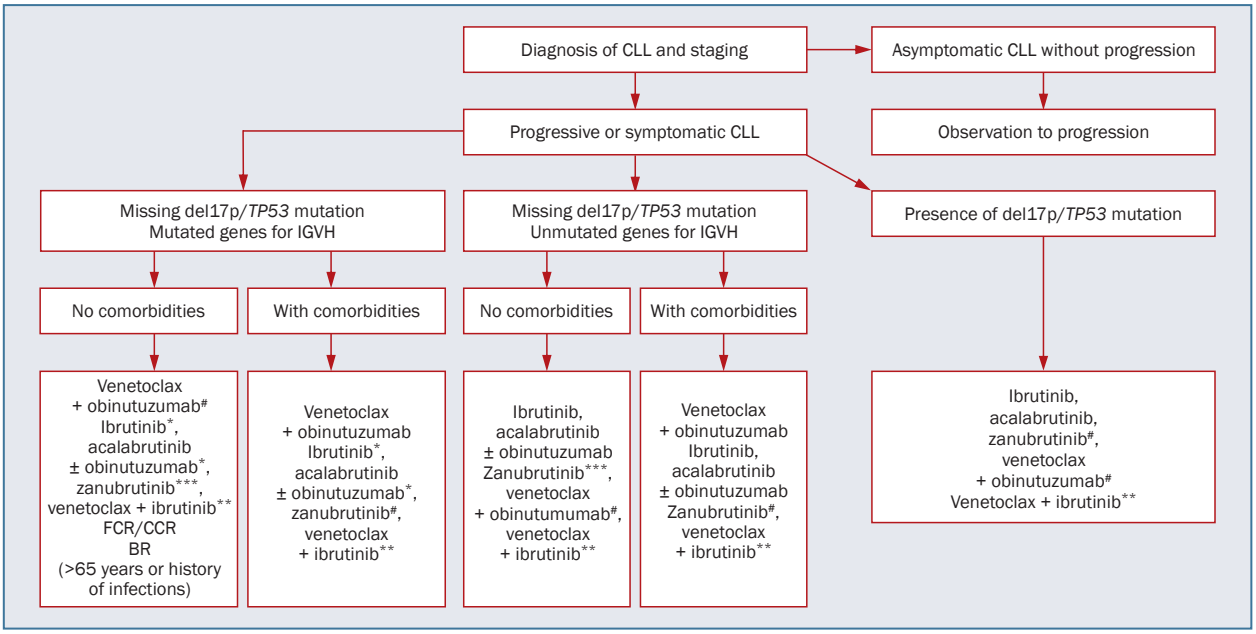

Figure 2. Recommendations for first-line treatment of patients with chronic lymphocytic leukemia (CLL) with indications to start therapy; #refund from January 2024; *not reimbursed in Poland for this indication; **not reimbursed in Poland; ***refund from January 2024, provided that: age ≥65 years or age 18–65 years and occurrence of in the last 2 years ≥1 severe infection (requiring hospitalisation or parenteral antibiotic therapy) or ≥3 infections (requiring oral antibiotic therapy) confirmed by the patient's medical records in the patient's medical records; order of Bruton tyrosine kinase (BTK) inhibitors by date of European Medicines Agency (EMA) registration. Note: Acalabrutinib is reimbursed in Poland only in monotherapy; BR — bendamustine, rituximab; CCR — cladribine, cyclophosphamide, rituximab; FCR — rituximab, fludarabine, cyclophosphamide; IGVH — immunoglobulin variable heavy chain

regimen, re-treatment with venetoclax + rituximab may be considered in cases of remission lasting 3+ years, or changing the therapy to a BTK inhibitor. If the time to symptomatic recurrence was shorter, and there are no contraindications to BTK therapy, the preferred choice will be a BTK inhibitor. When choosing another therapy after a BTK inhibitor, changing to another BTK inhibitor can be considered, especially in cases of intolerance, bearing in mind that data on the use of another BTK inhibitor after the previous one in the case of resistance indicates lower effectiveness than in the population of previously untreated patients. Another option will be therapy according to the venetoclax + rituximab regimen. However, there are no head-to-head comparisons indicating the choice of optimal therapy in the case of BTK inhibitor resistance i.e. switching to the venetoclax + rituximab regimen versus switching to another BTK inhibitor. Currently, studies are being conducted with new BTK inhibitors in this patient population.

A much less frequently used alternative is idelalisib in combination with rituximab (continuous treatment) or re-treatment with immunochemotherapy in patients with lack of del17p/*TP53* mutations and mutated IGHV gene status and if no other treatment options are available.

New targeted therapies should be used in patients with del17p or *TP53* mutation, regardless of the duration of response to first-line treatment:

- BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib);
- venetoclax in combination with rituximab or as monotherapy;
- idelalisib with rituximab.

In Poland, new targeted therapies are available under the B.79 drug program.

Ibrutinib, zanubrutinib (from January 2024) and venetoclax with rituximab are reimbursed in patients after one line of previous therapy, regardless of del17p/*TP53* mutation status.

Acalabrutinib may be used as part of the drug program in patients with resistant/relapsed CLL with del17p/*/TP53* mutation, and in patients with resistant/relapsed CLL who meet at least one of the following criteria:

- disease recurrence/progression after, or lack of response to, treatment with a regimen containing venetoclax in combination with an anti-CD20 antibody;
- medical contraindications to the use of a regimen containing venetoclax in combination with an anti-CD20 antibody (i.e. failure to meet the appropriate qualification criteria for therapy with venetoclax with an anti-CD20 antibody);
- toxicity not allowing continuation of treatment with venetoclax and anti-CD20 antibody.

The introduction of BCR inhibitors and BCL2 antagonists has significantly improved the treatment options for patients with refractory/relapsed CLL, and has changed the

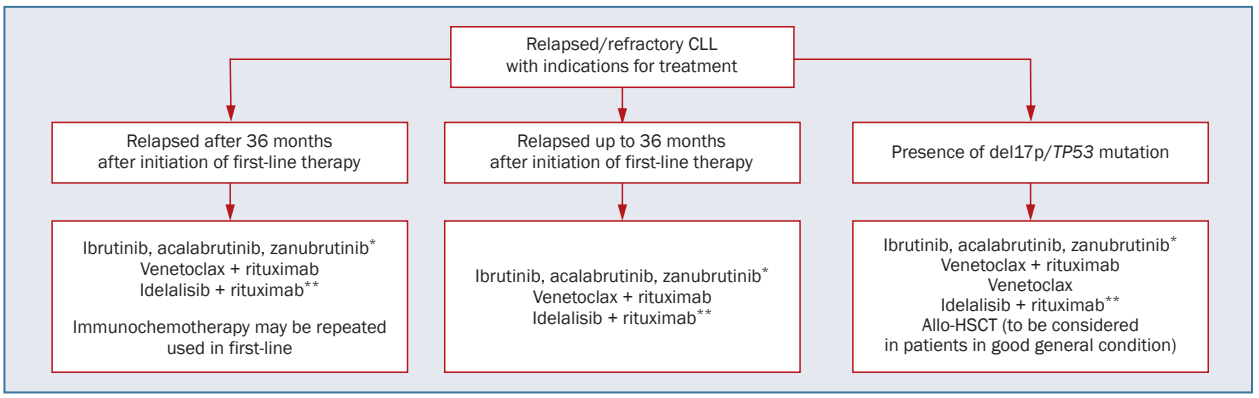

Figure 3. Recommendations for the treatment of patients with refractory or relapsed chronic lymphocytic leukemia (CLL); *refunded from January 2024; **not reimbursed in Poland; order of Bruton tyrosine kinase (BTK) inhibitors according to the date of registration with the European Medicines Agency (EMA); allo-HSCT — allogeneic hematopoietic stem cell transplantation

indications for allo-HSCT, which is currently recommended in these two clinical situations:

- resistance to new targeted therapies;
- RT clonally related to CLL after achieving remission after pharmacological treatment [8].

To summarize the available therapeutic options, the use of BCR and BCL2 inhibitors (in combination with rituximab or as monotherapy) should be considered in subsequent treatment lines).

In selected patients, especially those with a poor prognosis who are resistant to targeted therapies, allogeneic hematopoietic cell transplantation should be considered. Current recommendations regarding the selection of therapy in patients with refractory or relapsed CLL are set out in Figure 3.

Richter's transformation

RT is one of the most serious complications of CLL. RT is defined as the occurrence of secondary aggressive B-cell lymphoma in a patient diagnosed with CLL [80]. The most common histological subtype, accounting for 80–95% of all cases, is diffuse large B-cell lymphoma (DLBCL) [81]. The second and much less common form is transformation to classical Hodgkin's lymphoma (HL), often called the Hodgkin's lymphoma variant of Richter's transformation (HLvRT) [82]. This variant affects 5–15% of all cases of RT.

Despite the widespread belief, RT is neither a very rare nor a late complication. Based on many observational studies, RT occurs in up to 5–15% of patients with CLL. The median time from the diagnosis of CLL to the onset of RT is 2–4 years, and in rare cases both tumors are diagnosed simultaneously [81]. It should be emphasized that the percentage of patients with RT in a given center depends significantly on the frequency of surgical biopsies of lymph nodes in the event of rapid progression of CLL [83]. A more intensive biopsy strategy should be considered, especially in patients with risk factors for RT (Table VII).

Table VII. Risk factors associated with Richter's syndrome in course of chronic lymphocytic leukemia

Patient dependent factors
CD38 gene polymorphism
LPR-4 gene polymorphism
BCL2 gene polymorphism
Age (controversial)
Environmental factors
EBV reactivation (controversial)
Treatment with purine analogs (controversial)
Factors associated with leukemia biology
Karyotype (lack of del13q14)
Lack of IGHV mutation
Stereotyped BCR
Short telomeres
High expression of CD38
Clinical factors
Lymphadenopathy >3 cm
Stage of advancement according to Rai III/IV

BCR — B-cell receptor; EBV — Epstein-Bárr virus; IGVH — immunoglobulin variable heavy chain

The pathomechanism of RT has not been definitively elucidated, but the molecular basis has been quite well characterized [84–86]. Molecular analyses of a series of patients with RT revealed, among other things, a high frequency of defects in genes directly or indirectly regulating the course of the cell cycle, including *TP53*, NOTCH1 and CDKN2A/B [87]. Two types of transformation have been distinguished, and they are characterized by different clinical courses. In the first, RT occurs as a result of clonal evolution of CLL (this is known as RT 'clonally related to CLL'), while in the remaining patients the aggressive lymphoma comes from another lymphocytic clone (RT 'clonally unrelated to CLL').

RT clonally related to CLL is much more frequent (80–90%) and has a very unfavorable prognosis [84]. RT clonally unrelated to CLL occurs less frequently, but its prognosis is similar to DLBCL and *de novo* HL. In one analysis, the median survival of patients with RT clonally related to CLL was only 14 months, compared to 62 months in a group of patients with clonally unrelated RT [87].

Clinically, RT is usually characterized by a deterioration in the general condition, often with the appearance of systemic symptoms such as weight loss, fever, and night sweats, plus rapidly progressive local or generalized lymph node enlargement or, less frequently, extranodal lesions [81]. To diagnose RT, histopathological evaluation of a surgical specimen of the lymph node or the involved extranodal organ is required. Histopathological diagnosis is crucial in order to differentiate RT from similar clinical conditions such as progression of CLL and prolymphocytic transformation. It is recommended to take the node with the largest diameter or the one that is growing the fastest. PET/CT imaging may be of significant assistance, and the most metabolically active node should be sampled [88]. Exceptionally, if surgical biopsy of the node is impossible, the diagnosis can also be made by an experienced diagnostician based on cytological examination with cytometric immunophenotyping. After the diagnosis of RT, standard tests should be performed to assess its severity, similarly to primary DLBCL and HL. However, staging is difficult due to the impossibility of distinguishing nodal from organ lesions resulting from RT and CLL in imaging studies.

RT is most often characterized by an aggressive course, resistance to treatment, and short survival [81]. In the first line of treatment in patients with RT of the DLBCL type, the R-CHOP regimen is most often used, although the effectiveness of such treatment is not satisfactory [87]. Another option is the DA-EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab) regimen, but there is no direct evidence that it is more effective. The use of stronger chemotherapy regimens has been shown to allow for an increase in the rate and depth of response, but it was associated with significantly greater toxicity, and did not generally lead to an improvement in prognosis. In phase II studies, intensive OFAR-1, OFAR-2, R-hyper-CVAD regimens (rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone) allowed CR to be achieved in 39–51% of patients, but median survival was only 6–10 months [89, 90]. New targeted therapies, which have resulted in a dramatic improvement in the prognosis of refractory/relapsed CLL, have not yet demonstrated a satisfactory rate of durable responses in patients with RT. However, clinical trials are still being conducted on the optimal use of monotherapy or combination therapy with drugs such as BTK inhibitors, PI3K inhibitors, BCL2 inhibitors (venetoclax) and programmed death receptor 1/programmed death-ligand 1 (PD-1/PD-L1) checkpoint inhibitors [91–93]. In a phase II clinical trial, Davis et al. used venetoclax in combination with DA-EPOCH-R, achieving CR in 50% of patients with a median PFS and OS of 10.1 and 19.6 months, respectively [94].

Initial trials of using CAR-T immunotherapy are also underway [95].

Due to the low incidence of RT, which makes it impossible to conduct randomized trials, no standard treatment has yet been developed. Moreover, due to the often advanced age and poor performance status of patients, it is often necessary to reduce the intensity of chemotherapy in clinical practice. Currently, in each patient with a new diagnosis of RT, it is first recommended to establish a clonal relationship with CLL by comparing immunoglobulin gene rearrangements of CLL cells and aggressive lymphoma infiltration. In patients with RT clonally unrelated to CLL (c.20% of patients), treatment should be conducted in accordance with the standard of therapy for *de novo* DLBCL. In RT clonally related to CLL or when it is impossible to ascertain a clonal relationship, there is no effective treatment method and participation in a clinical trial should be the first choice. If this is impossible, immunochemotherapy with an anti-CD20 antibody should be used, but the R-CHOP regimen still seems to be a rational choice. Given the expected short response time, the next step in all patients who achieve at least a partial response to chemotherapy and are in good clinical condition and age should be consolidation of the response using high-dose chemotherapy with hematopoietic stem cell transplantation (HSCT) [96]. The preferred method of consolidation, especially in younger patients, is allo-HSCT, but autologous hematopoietic stem cell transplantation (auto-HSCT) may also improve the prognosis in some patients [97]. It should be emphasized that due to the clinical context, allo-HSCT can only be performed in 10–15% of patients diagnosed with RT [97].

Patients with HLvRT are usually given chemotherapy according to the ABVD regimen (adriamycin, bleomycin, vinblastine, dacarbazine). The results obtained are better than in the clonally dependent form of ZR-DLBCL, but worse than in *de novo* HL [81, 82]. Therefore, if the patient cannot be qualified for a clinical trial, the recommended therapy is the ABVD regimen. The importance of consolidation with HSCT in this type of transformation is not yet established.

The treatment of resistant and relapsed forms is not standardized and is mainly based on combination chemotherapy used in aggressive lymphomas. The results of treatment are usually unfavorable. Therefore, the preferred option should always be for the patient to participate in a clinical trial. The prognosis for patients with RT is unfavorable. In most published reports, median survival of patients with RT of the DLBCL type ranges from six to 18 months after transformation [85, 97]. Patients who developed TR due to untreated CLL have a longer expected

Table VIII. Richter syndrome risk score (adapted from [97])

Parameters with independent negative predictive value for survival	
ECOG performance status >1	
LDH >1.5 upper limit of normal	
PLT <100 G/L	
Largest node or non-nodal lesion >5 cm	
Number of previous lines of therapy >1	
Prognostic index	
Score	**Estimated survival time**
0–1	13 months
2	11 months
3	4 months
4–5	1 month

ECOG — Eastern Cooperative Oncology Group; LDH — lactate dehydrogenase; PLT — platelets

survival than patients previously treated with chemotherapy for CLL [98]. Most reports indicate that the prognosis in HLvRT is better than in patients with classic transformation to DLBCL, although the available data on this subject is inconclusive [81, 82]. For a more detailed assessment of the prognosis of RT, a simple prognostic system has been developed based on basic clinical and laboratory parameters (Table VIII) [97].

Diagnosis and treatment of autoimmune complications

Autoimmune complications in patients with CLL are the result of disorders in the immune system that lead to the production of antibodies directed against self-antigens, usually located on blood cells or their precursors. These disorders lead to autoimmune cytopenias, primarily autoimmune hemolytic anemia (AIHA) and immunological thrombocytopenia (IT). The coexistence of AIHA and IT is called Evans syndrome, which has an estimated prevalence of 5–10%. It is caused by warm class IgG autoantibodies detected by a DAT or, less commonly, by cold class IgG autoantibodies.

Autoimmune hemolytic anemia is the most common autoimmune cytopenia reported in patients with CLL. Its incidence is estimated at 5–10%. It is caused by warm-type IgG autoantibodies detected in the DAT or, less commonly, by cold-type IgG autoantibodies [99, 100]. A positive DAT result is also the most important risk factor for the development of AIHA, although it does not guarantee its occurrence. Similarly, a negative DAT result does not exclude the occurrence of AIHA in the future (positive predictive value c. 30%, negative predictive value c.90%) [101].

Autoimmune cytopenias can also occur during cytoreductive treatment [102]. In particular, it has been observed that treatment with purine analogs as monotherapy can increase the risk of AIHA [103–105]. The incidence of autoimmune cytopenias during treatment with ibrutinib or venetoclax as monotherapy and in combination with rituximab is small, and in most studies does not exceed 5% [34, 106–109].

The basis for the diagnosis of AIHA is the detection of laboratory signs of hemolysis (increased free bilirubin concentration, increased LDH activity, decreased haptoglobin concentration, and an increased number of reticulocytes). However, it should be remembered that each of these indicators has significant limitations in sensitivity and specificity. An increase in the number of reticulocytes may not occur when the red blood cell system in the marrow is suppressed. Elevated LDH activity is a very non-specific laboratory symptom and can also result from progression of the underlying disease, while indirect hyperbilirubinemia requires differentiation from Gilbert's syndrome — testing for *UGT1A1* gene mutations is helpful here. An important diagnostic element is a positive DAT result detecting IgG immunoglobulins and/or complement component C3, which is observed in more than 90% of patients [101].

The mainstay of treatment for AIHA is glucocorticosteroids, usually prednisone or prednisolone as monotherapy or in combination with rituximab, at a dose of 1 mg/kg body weight (bw), increased to 1.5 mg/kg bw if there is no response. Prednisone treatment remains effective in most patients, and it is recommended to maintain the therapeutic dose of corticosteroid for 2–6 weeks and then gradually discontinue the drug over three months. To obtain a faster response to treatment, methylprednisolone can be used in a single dose of 1.0 g or immunoglobulin i.v. at a dose of 0.4 g/kg bw/day for 4–5 days. There is no generally accepted standard of second-line treatment in patients who do not respond to prednisone treatment or whose hemolysis recurs after attempting to discontinue it. In such cases, four weekly administrations of rituximab at a dose of 375 mg/m^2 (if it was not administered in the first-line of treatment) and cyclosporine at a dose of 5–8 mg/kg bw/day are recommended to achieve a serum drug concentration of 100–150 ng/mL, or mycophenolate mofetil, cyclophosphamide or azathioprine can also be used orally [110–112]. The ineffectiveness of drug therapy is an indication for splenectomy. Dearden [110] proposed an algorithm for the management of patients who do not respond to corticosteroid therapy or with recurrence of hemolysis when trying to reduce the dose. In a case of ineffectiveness of two-week administration of prednisone at a dose of 1.5 mg/kg bw, rituximab at a dose of 375 mg/m^2 should be used, and after obtaining a response, supportive treatment with cyclosporine or mycophenolate mofetil should be used. However, the ineffectiveness of rituximab justifies recommending splenectomy. Recurrence of hemolysis when reducing the dose of prednisone can be controlled by

adding cyclosporine at a dose of 5–8 mg/kg bw/day. A response is expected within six weeks. Once such a response has been achieved, then maintenance treatment with cyclosporine or mycophenolate mofetil or rituximab should be considered, followed by splenectomy. Maintenance treatment with cyclosporine or mycophenolate mofetil is also recommended after splenectomy [110]. To maintain the response, the dose of cyclosporine can be reduced to 3 mg/kg bw/day — so that its serum concentration does not exceed 100 µg/L. Both cyclosporine and mycophenolate mofetil can be administered chronically. However, patients should be monitored for adverse effects when using cyclosporine, especially for nephrotoxicity and hypertension.

Due to the risk of alloimmunization, red cell concentrate transfusions should only be used in cases of profound [hemoglobin (Hb) concentration <6 g/dL] and/or symptomatic anemia. In situations of the rapid development of life-threatening hemolysis, methylprednisolone in an intravenous bolus is used, and immunoglobulins may also be given at a dose of 0.4 g/kg bw for five days or 1 g/kg bw for two days.

Autoimmune hemolytic syndrome unresponsive to or poorly controlled by immunosuppressive treatment is an indication for cytoreductive treatment. Regimens with increased immunosuppressive potential, developed for other lymphoproliferative diseases, are preferred. RCD is most often used (rituximab 375 mg/m^2 i.v. on day 1, cyclophosphamide 750 mg/m^2 on day 2, dexamethasone 12 mg i.v. on days 1 and 2, then *p.o.* on days 3–7, cycles repeated every 3–4 weeks) or R-COP (cyclophosphamide 750 mg/m^2, vincristine 1.4 mg/m^2, maximum 2 mg, rituximab 375 mg/m^2 on day 1, prednisone 40 mg/m^2 on days 1–5 every 21 days) [113, 114]. Treatment with purine analogs as monotherapy can increase the risk of AIHA, especially if they are used as monotherapy [38]. However, cases of hemolysis and/or DAT negativity restoration have been observed during treatment with regimens containing purine analogs [115]. The combination of bendamustine with rituximab is also highly effective [116]. Treatment with ibrutinib or idelalisib may have a beneficial effect on the course of autoimmune cytopenia [107, 108, 117]. Individual reports also suggest that venetoclax may have a similar effect [118, 119], although cases of AIHA induction in CLL patients treated with venetoclax have also been described [120, 121].

Immunothrombocytopenia is observed less frequently than AIHA, with an incidence of 1–5% [122–125]. It should be taken into account in every case of a sudden decrease in the number of platelets not explained by other reasons, especially disease progression or treatment. The diagnosis of immunothrombocytopenia is indicated by a rapid (< 2 weeks) and significant (< 100 G/L and or by at least half of the initial value) reduction in the number of platelets, normal or increased megakaryopoiesis in the bone marrow, the absence of splenomegaly, and not having received cytostatic treatment in the previous month [123]. Due to the lack of sufficiently sensitive tests detecting antiplatelet antibodies in clinical practice, the diagnosis of IT is most often a diagnosis by exclusion.

The goal of immunothrombocytopenia treatment is to maintain the platelet count above the hemostatic safety threshold, i.e. above 20–30 G/L. The principles of management are similar to those in AIHA and essential immunothrombocytopenia. The basis of first-line treatment remains corticosteroid therapy, including prednisone at a dose of 1 mg/kg bw, dexamethasone at a dose of 40 mg/day for 4 days every 2–3 weeks, or a single dose of methylprednisolone at a dose of 1 g. There is no clear data regarding the preferability of one of these steroid therapy methods over the others.

In a case of resistance or relapse, when trying to reduce the dose of corticosteroids, cyclosporine with prednisone, vincristine at a dose of 1 mg weekly for 4–6 weeks, rituximab monotherapy or RCD are suggested [110, 126–128]. Another option is the use of thrombopoietin receptor agonists, eltrombopag or romiplostim [129–131]. Failure of conservative treatment is a justification for splenectomy.

Pure red cell aplasia (PRCA) and autoimmune neutropenia are the rarest autoimmune complications in CLL, occurring in less than 1% of patients. In clinical practice, their diagnosis is most often a diagnosis of exclusion. This requires a bone marrow trephine biopsy, which in the case of PRCA shows atrophy of the red blood cell system with preserved granulopoiesis and thrombopoiesis, while in autoimmune neutropenia no precursors of granulopoiesis are detected. PRCA shows an Hb concentration not exceeding 11 g/dL in the absence of hemolysis, absolute reticulocytopenia, and a normal number of granulocytes and platelets. A viral background to aplasia should also be ruled out. The diagnosis of autoimmune granulocytopenia should be considered in the case of prolonged neutropenia below 0.5 G/L in a patient who has not received cytostatic treatment in the preceding eight weeks. As yet, there are no generally accepted rules for the management of these cytopenias. In the treatment of PRCA, in addition to transfusions of red blood cell concentrates, prednisone, cyclosporine, rituximab monotherapy or RCD are suggested [114, 125–128, 132, 133]. The basis of treatment in immunological neutropenia is prevention and combating infection.

It should be emphasized that the occurrence of isolated autoimmune cytopenia is not an indication for cytostatic treatment. Such an indication is AIHA or immunothrombocytopenia that is resistant to treatment or accompanied by the progression of the underlying disease.

In the course of CLL, autoimmune phenomena affecting other organs may occur, which can be manifested by the presence of autoantibodies, such as antinuclear antibodies

or rheumatoid factor, as well as the coexistence of autoimmune diseases [99]. Non-hematological autoimmune complications of CLL include paraneoplastic pemphigus, glomerulonephritis, and acquired angioedema. Due to its rarity, there are no established standards of care.

Prevention and treatment of infections

Chronic lymphocytic leukemia is a disease classified as a secondary immunodeficiency. The clinical picture in 50% of patients (regardless of the stage of CLL) is dominated by recurrent infections, often severe, and more than one in three deaths is infection-related [134–137]. Infections in patients with CLL result not only from immune disorders related to the leukemia itself, but also from the advanced age of the patients, the presence of comorbidities (e.g. diabetes, circulatory failure) and — in people undergoing therapy — from immunosuppression caused by anticancer treatment. The pathogenic factors responsible for the development of infections in CLL patients are dominated by bacteria (67%), to a lesser extent viruses (25%), and, rarely, fungi (7%) [138–140]. Immune disorders in the course of CLL in some patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) lead to impaired elimination of the virus from the body. Positive PCR and antigen tests lasting even more than 8–12 weeks, or recurrence of infection shortly after obtaining negative test results for SARS-CoV-2 infection, have been observed in many CLL patients [141, 142, our own observations].

Prevention of infection

Prevention of infections and related complications is an important element of the treatment of patients with CLL. Prophylaxis of *Pneumocystis jirovecii* pneumonia is recommended in patients receiving treatment regimens containing fludarabine, cladribine, bendamustine or idelalisib. Cotrimoxazole is most often administered at a dose of 960 mg every other day during treatment with the above-mentioned drugs, and then for a minimum 3–6 months after completion of treatment. Prophylaxis against *Pneumocystis jirovecii* infection is not required when using BTK inhibitors and venetoclax. Prevention of *Herpes simplex* and *Herpes zoster* viral infections is recommended in patients treated with fludarabine, bendamustine, and anti-CD20 antibodies, especially in patients with a history of recurrent infections with these viruses and with a low percentage/number (<0.2 G/L) of lymphocytes CD4+ T [136]. Prophylactic use of antiviral drugs, such as acyclovir or valacyclovir, should continue for 2–6 months after the end of chemotherapy or until the CD4+ T-cell count is greater than 0.2 G/L, if it is possible to measure it. In patients treated with anti-CD20 monoclonal antibodies who have anti-HBc antibodies and/or a positive HBs antigen in their blood serum, a PCR test for the presence of hepatitis B virus (HBV) DNA should be performed. HBsAg-positive patients with or without detectable HBV DNA, and HBsAg-negative/anti-HBc-positive patients, should also start HBV reactivation prophylaxis with entecavir or tenofovir [142]. Screening and prevention of reactivation of HBV infection are also recommended in patients treated with ibrutinib [143, 144].

Antifungal prophylaxis in the form of fluconazole, and in the case of suspected *Aspergillus* infection — itraconazole, voriconazole, posaconazole or caspofungin — is recommended in patients at high risk of infection, with a low number of CD4+ T lymphocytes, receiving purine analogs or alemtuzumab. Ibrutinib increases the risk of developing invasive mycosis (especially aspergillosis) and pneumocystis (*Pneumocystis jiroveci*) in the first months of use (median three) [145, 146]. Yet despite this, prophylactic use of antifungal drugs is not recommended, and concomitant use of ibrutinib with corticosteroids or other immunosuppressive therapy should be avoided.

Prophylactic and therapeutic use of immunoglobulins

Prophylactic use of immunoglobulins in patients with CLL can reduce the frequency of bacterial infections, but does not affect the frequency of viral and fungal infections, or prolong survival [147, 148]. Recurrent or severe infections, especially with encapsulated bacteria, despite prophylactic antibiotic therapy *p.o.* in patients with a serum IgG concentration below 5 g/L, is an indication for immunoglobulin substitution [a procedure reimbursed by the National Health Fund [NHF]) i.v. or subcutaneously (s.c.)]. Human immunoglobulin preparations can be administered i.v. every 3–4 weeks, at an initial dose of 0.4 g/kg bw or every two weeks in an s.c. infusion [136]. Preparations for s.c. infusions are better tolerated and very rarely cause the side effects such as fever, chills, and symptoms of anaphylaxis that occur when using i.v. preparations. Ultimately, such treatment should lead to IgG concentrations exceeding 6–8 g/L after four months of treatment [149]. The dose of immunoglobulin should be adjusted according to the clinical response and the achieved antibody titer. Maintaining higher trough concentrations may be beneficial in patients with coexisting chronic bronchial and pulmonary diseases [150, 151]. If a decision is made to discontinue human immunoglobulin replacement therapy, this should occur during the summer months and IgG levels should be checked before the onset of winter. Treatment should be discontinued if no reduction in the frequency or severity of bacterial infections is observed after 12 months [152]. Hypogammaglobulinemia does not significantly affect the clinical course of coronavirus disease 2019 (COVID-19) [153], although CLL patients with low IgG concentration in blood serum may be more likely to develop secondary bacterial infections, which can cause sepsis and death [154, 155].

Protective vaccinations

It has been shown that one of the important factors influencing the frequency and severity of infections in some patients with CLL, apart from the reduced IgG concentration, is the simultaneous low titer of specific antibodies against polysaccharides contained in the pneumococcal capsule [154]. This indicates the possibility of a beneficial effect of vaccinations against *Streptococcus pneumoniae* in this group of patients. An assessment of the post-vaccination response in CLL patients found that they show a weaker response to immunization against pneumococci and influenza virus than healthy people [156–159]. Numerous studies have shown that protective vaccinations in patients with CLL are safe and some of them respond properly, especially to conjugate vaccines against *Streptococcus pneumoniae* and *Haemophilus influenzae* type B, administered immediately after the diagnosis of the disease, at least two weeks before the start of treatment [160]. Seasonal influenza vaccination in patients who have not responded to the first immunization should be administered in a two-dose program, with a minimum interval of one month between vaccinations [161].

The vaccination schedule should be adapted to the planned treatment, with particular emphasis on anti-CD20 antibody therapy, which leads to the depletion of B lymphocytes and may cause hypogammaglobulinemia. It has been shown that CLL patients do not achieve protective antibody titers after influenza vaccination when vaccination was performed more than two weeks before, or during, or up to six months after, rituximab treatment [162]. If the patient received an unconjugated pneumococcal vaccine many years ago and if the titers of specific antibodies against *Streptococcus pneumoniae* remain low, re-vaccination is recommended, preferably before the initiation of substitution therapy with human immunoglobulin.

According to CDC guidelines, the recombinant shingles vaccine, available in Poland, is recommended for people with immune disorders [163].

Recommendations regarding vaccinations

Vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* type B is recommended immediately after diagnosis and before treatment. Patients who, despite an initial response to vaccination, demonstrate a decrease in the specific antibody titer that leads to the development of infection, should be re-vaccinated. It is recommended to vaccinate against seasonal influenza annually (September/October) with vaccines containing the current strains of this virus in that particular season. In patients with CLL, vaccinations with live vaccines against tuberculosis (BCG) and measles, rubella, mumps, chickenpox/*Herpes zoster*, polio myelitis (Sabin and Koprowski vaccine), and yellow fever should be avoided. Vaccinations should not be administered less than two weeks before the start of chemoimmunotherapy, or during its duration, or up to six months after the end of treatment. Protective vaccinations are also not used during serious infections or acute diseases with fever. Mild infections (colds) should not be a reason to postpone vaccinations. Table IX sets out the recommended vaccinations for patients with CLL and the methods of their administration.

Recommendations regarding vaccination against SARS-CoV-2 in patients with CLL

Many questions regarding vaccination against SARS-CoV-2 in patients with CLL remain unanswered because cancer patients were not included in clinical trials. Currently, the only absolute contraindication to administering vaccines is hypersensitivity to the active substance or to any of the excipients in the vaccine preparation. In people with a history of severe allergic reactions, vaccination decisions should be made individually. Taking into account the risk of severe complications in the course of COVID-19 in cancer patients, and the good safety profile of vaccines, then according to the opinion of experts from international scientific societies [European Hematology Associacion (EHA), ASH, NCCN, ESMO], vaccination against SARS-CoV-2 is recommended in cancer patients, including CLL. Anticancer treatment is not a contraindication to vaccination. The challenge is to obtain an effective protective response to vaccination in patients with CLL, especially in patients undergoing immunochemotherapy with anti-CD20 antibodies, treatment with BTK inhibitors or high-dose glucocorticosteroids. The protective effect of the vaccine will depend on the degree of immunosuppression associated with the disease and/or treatment of cancer. Patients with CLL should be vaccinated as soon as possible due to the fact that they are more vulnerable than the general population to hospitalization or death due to severe COVID-19. This also applies to patients several years after completing oncological treatment [164]. On 31 August, 2023, a new monovalent vaccine targeting the XBB.1.5 variant was approved in the EU, used as a single dose regardless of previous vaccination history. Further doses of the vaccine may be administered to immunosuppressed patients depending on national recommendations [165].

Treatment of infections

Treatment of infections in patients with CLL depends not only on the type of etiopathogenetic factor, but also on the patient's general condition and risk factors for the development of life-threatening infectious complications, such as hypogammaglobulinemia (including IgG subclass deficiency) and neutropenia [139]. In many countries, antibiotic prophylaxis is used in patients with CLL, despite a lack of evidence as to the effectiveness of such treatment. Especially in patients with bronchiectasis, prophylactic

Table IX. Vaccinations recommended in patients with chronic lymphocytic leukemia (CLL)

Type of vaccine	Method of administration
13-valent conjugate vaccine against *Streptococcus pneumoniae* (PCV13): (Prevenar 13®) 20-valent conjugate vaccine against *Streptococcus pneumoniae* (PCV20): (Apexxnar®)	Vaccination should be performed as soon as diagnosis of CLL is made. PCV13 and PCV20 are administered in a single dose, intramuscularly (i.m.) into deltoid muscle. Currently, there is no data on need to repeat vaccination
Polysaccharide vaccine against *Streptococcus pneumoniae* (PPSV23): only Pneumovax 23® is available in Poland	Not earlier than two months after PCV13; PPSV23 should be administered i.m. or subcutaneously (s.c.) into deltoid muscle or s.c. Booster dose should be administered after 3–5 years, earlier administration may be considered depending on response to vaccine (it is not in line with SmPC); monitoring of antibody levels is advisable. PPSV23 vaccination is not used in patients previously vaccinated with PCV20
Vaccine against *Hemophilus influenzae* type B (HiB)	Vaccine against HiB is administered in a single dose, i.m. into deltoid muscle or s.c. There is currently no data on need for repeated vaccination
Flu vaccine Multivalent inactivated vaccines against strains recommended each year by WHO for vaccine production. These products are available in Poland: • Influvac® — inactivated sub-unit vaccine containing influenza virus surface antigens • Vaxigrip® — inactivated split vaccine with split influenza virion as an antigen • IDflu® — inactivated split vaccine with split influenza virion as an antigen	Intramuscularly into deltoid muscle or s.c. vaccination should be repeated annually before flu season (preferably in September) in patients with secondary immunodeficiency (especially severe hypogammaglobulinemia <5 g/L) and poor response to vaccination (if a titer of specific antibodies against influenza antigens is not doubled, revaccination after one month may be considered
Vaccine against HBV	Primary vaccination according to this schedule: 0; 1; 6 months in previously unvaccinated patients, preferably straight after diagnosis In patients undergoing immunosuppressive therapy, it is recommended to maintain antibody levels >100 IU/L. Antibody control is performed every six months; when concentration drops below <100 IU/L, a double dose of vaccine should be administered. In patients with profound immunodeficiency (hypogammaglobulinemia IgG requiring IVIG/SCIG supplementation), when concentration of HBs antibodies is <10 IU/L after primary immunization, it is recommended to administer another 1–3 doses of vaccine. If antibody concentration is still <10 IU/L, no further vaccinations are performed
SARS-CoV-2 vaccine	It is recommended to administer one or two doses of vaccine, depending on preparation and manufacturer's recommendations

*According to authors, in patients with blood diseases, it is better to use sub-unit vaccines containing surface subunits (hemagglutinin and influenza virus neuraminidase). In our practice, after administration of split vaccines containing split virion in patients with secondary immunodeficiency, more side effects were observed; SmPC — summary of product characteristics; WHO — World Health Organization; HBV — hepatitis B virus; IVIG/SCIG — intravenous immunoglobulin/subcutaneous immunoglobulin; SARS-CoV-2 — severe acute respiratory syndrome-related coronavirus 2

administration of azithromycin at a dose of 250 mg three times a week should be considered [137]. Patients who are not at risk of sepsis and with an absolute neutrophil count above 0.5 G/L may be treated with antibiotics with a narrower range of action directed against the most likely pathogen previously detected in cultures from biological material [140].

Suspicion of the development of sepsis and/or an absolute neutrophil count of below 0.5 G/L should be treated as a life-threatening condition, and treatment with i.v. antibiotics should be initiated as soon as possible until the results of bacteriological tests with a broad spectrum of action are received [140]. *Herpes simplex* and *Herpes zoster* infections often occur in patients with advanced CLL, and complicate the use of anti-leukemic therapy. The course of the infection is usually mild, and oral antiviral drugs are sufficient. If DNA CMV is detected, antiviral treatment with gancyclovir at a dose of 5 mg/kg bw should be initiated i.v. twice daily for at least two weeks or valgancyclovir at a dose of 900 mg twice daily. In patients refractory to this treatment, foscarnet or cidofovir are recommended. If CMV DNA is detected, antiviral treatment should be initiated with gancyclovir 5 mg/kg bw i.v. twice daily for at least two weeks or valgancyclovir at a dose of 900 mg twice daily. In patients resistant to this treatment, foscarnet or cidofovir are indicated.

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Lek XOSPATA

Wskazany w monoterapii nawrotowej lub opornej na leczenie ostrej białaczki szpikowej z mutacją FLT3 u dorosłych pacjentów i stosowany doustnie, pozwala uzyskać trwałą supresję mutacji FLT3, jednocześnie oferując wygodę leczenia w warunkach domowych[1]

Rozpoznanie

Nawrotowa AML
z obecnością mutacji FLT3-TKD

Lucyna, 57 lat

XOSPATA | Nawrót | Dobry stan ogólny

dla dorosłych pacjentów w dobrym stanie ogólnym z R/R FLT3m+ AML, takich jak Lucyna[1]

Rozpoznanie

Oporna na leczenie AML
z obecnością mutacji FLT3-ITD

Józef, 67 lat

XOSPATA | Odporność | Dobry stan ogólny

dla dorosłych pacjentów w dobrym stanie ogólnym z R/R FLT3m+ AML, takich jak Józef[1]

Rozpoznanie

Nawrotowa AML z mutacjami
FLT3-ITD i IDH2 oraz
zidentyfikowanie odpowiedniego
dawcy do HSCT

Paweł, 43 lata

XOSPATA | Nawrót | Dobry stan ogólny

dla dorosłych pacjentów w dobrym stanie ogólnym z R/R FLT3m+ AML, takich jak Paweł[1]

Rozpoznanie

Nawrotowa AML
z mutacjami
FLT3-ITD, NPM1 i IDH1

Joanna, 77 lat

XOSPATA | Nawrót | Gorszy stan ogólny

dla dorosłych pacjentów w gorszym stanie ogólnym z R/R FLT3m+ AML, takich jak Joanna[1]

XOSPATA może pomóc pacjentom w dobrym i gorszym stanie ogólnym, takim jak Lucyna, Józef, Paweł i Joanna, w osiągnięciu dłuższego czasu przeżycia[1]

Lucyna, Józef, Paweł i Joanna nie są prawdziwymi pacjentami.

1. Charakterystyka Produktu Leczniczego XOSPATA.

Numery pozwoleń na dopuszczenie do obrotu: EU/1/19/1399/001 – wydane przez Komisję Europejską. Kategoria dostępności: Produkt leczniczy wydawany na receptę do zastrzeżonego stosowania – Rpz. Charakterystyka Produktu Leczniczego dostępna u przedstawiciela Astellas Pharma Sp. z o.o.

astellas

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XOSPATA™
gilterytynib 40 mg tabletki

Informacja o leku

▼ Niniejszy produkt leczniczy będzie dodatkowo monitorowany. Umożliwi to szybkie zidentyfikowanie nowych informacji o bezpieczeństwie. Osoby należące do fachowego personelu medycznego powinny zgłaszać wszelkie podejrzewane działania niepożądane. Aby dowiedzieć się, jak zgłaszać działania niepożądane – patrz punkt 4.8 ChPL.

Nazwa produktu leczniczego: Xospata 40 mg, tabletki powlekane. **Skład jakościowy i ilościowy:** Każda tabletka powlekana zawiera 40 mg gilterytynibu (w postaci fumaranu). Pełny wykaz substancji pomocniczych, patrz punkt 6.1 Charakterystyki Produktu Leczniczego (ChPL). **Postać farmaceutyczna:** Tabletka powlekana (tabletka). **Wskazania do stosowania:** Produkt Xospata jest wskazany w monoterapii nawrotowej lub opornej na leczenie ostrej białaczki szpikowej (ang. *acute myeloid leukaemia*, AML) z mutacją *FLT3* u dorosłych pacjentów (patrz punkty 4.2 i 5.1 ChPL). **Dawkowanie i sposób podawania:** Leczenie produktem Xospata powinien rozpocząć i nadzorować lekarz mający doświadczenie w stosowaniu terapii przeciwnowotworowych. Przed przyjęciem gilterytynibu u pacjentów z nawrotową lub oporną na leczenie AML należy potwierdzić mutację FMS-podobnej kinazy tyrozynowej 3 (ang. *FMS-like tyrosine kinase 3*, FLT3) [wewnątrztandemową duplikację genu (ang. *internal tandem duplication*, ITD) lub mutację w obrębie domeny kinazy tyrozynowej (ang. *tyrosine kinase domain*, TKD)] przy użyciu zwalidowanego testu. Podawanie produktu Xospata można wznowić u pacjentów po przeszczepieniu krwiotwórczych komórek macierzystych (ang. *haematopoietic stem cell transplantation*, HSCT). Dawkowanie: Zalecana dawka początkowa to 120 mg gilterytynibu (trzy tabletki po 40 mg) raz na dobę. Przed rozpoczęciem leczenia, w 15. dniu, a następnie co miesiąc przez cały czas trwania leczenia należy ocenić badania biochemiczne krwi, w tym aktywność fosfokinazy kreatynowej. Przed rozpoczęciem leczenia gilterytynibem, w 8. i 15. dniu pierwszego cyklu oraz przed rozpoczęciem każdego kolejnego miesiąca leczenia przez następne trzy miesiące należy wykonać badanie elektrokardiograficzne (EKG) (patrz punkty 4.4 i 4.8 ChPL). Leczenie należy kontynuować do czasu, kiedy pacjent nie będzie już odnosić korzyści klinicznych z leczenia produktem Xospata lub do momentu wystąpienia niedopuszczalnej toksyczności. Odpowiedź na leczenie może być opóźniona, dlatego należy rozważyć kontynuowanie stosowania zaleconej dawki do 6 miesięcy, aby zapewnić czas na odpowiedź kliniczną. W przypadku braku odpowiedzi [pacjent nie osiągnął złożonej całkowitej remisji (CRc)] po 4 tygodniach leczenia można zwiększyć dawkę do 200 mg (pięć tabletek po 40 mg) raz na dobę, jeżeli leczenie jest tolerowane lub uzasadnione klinicznie. Modyfikacje dawki: Zalecenia dotyczące przerwy w podawaniu, zmniejszenia dawki i zaprzestania podawania produktu Xospata u pacjentów z nawrotową lub oporną na leczenie AML: *Zespół różnicowania:* W przypadku podejrzenia zespołu różnicowania podać kortykosteroidy i rozpocząć monitorowanie hemodynamiczne (patrz punkt 4.4 ChPL). Przerwać stosowanie gilterytynibu, jeśli ciężkie objawy przedmiotowe i/lub podmiotowe utrzymują się przez ponad 48 godzin po rozpoczęciu stosowania kortykosteroidów. Wznowić leczenie gilterytynibem, podając taką samą dawkę, gdy nasilenie objawów przedmiotowych i podmiotowych zmniejszy się do stopnia 2[a] lub niższego. *Zespół odwracalnej tylnej encefalopatii:* Zaprzestać stosowania gilterytynibu. *Odstęp QTcF > 500 ms:* Przerwać stosowanie gilterytynibu. Wznowić leczenie gilterytynibem, podając zmniejszoną dawkę (80 mg lub 120 mg[b]), gdy odstęp QTcF powróci do wartości w zakresie 30 ms wartości początkowej lub ≤ 480 ms. *Zwiększenie odstępu QTcF o więcej niż 30 ms w badaniu EKG w 8. dniu pierwszego cyklu:* Potwierdzić w badaniu EKG w 9. dniu. W przypadku potwierdzenia należy rozważyć zmniejszenie dawki do 80 mg. *Zapalenie trzustki:* Przerwać podawanie gilterytynibu aż do ustąpienia zapalenia trzustki. Wznowić leczenie gilterytynibem, podając zmniejszoną dawkę (80 mg lub 120 mg[b]). *Inna toksyczność stopnia 3[a] lub wyższego uznawana za związaną z leczeniem:* Przerwać stosowanie gilterytynibu aż do ustąpienia toksyczności lub zmniejszenia jej nasilenia do stopnia 1[a]. Wznowić leczenie gilterytynibem, podając zmniejszoną dawkę (80 mg lub 120 mg[b]). *Planowane HSCT:* Przerwać stosowanie gilterytynibu na jeden tydzień przed zastosowaniem leczenia kondycjonującego w HSCT. Leczenie można wznowić 30 dni po HSCT, jeśli nastąpiło wszczepienie, u pacjenta nie wystąpiła ostra postać choroby przeszczep przeciw gospodarzowi (stopień ≥ 2.) i znajdował się on w złożonej całkowitej remisji (CRc)[c]. *a. Stopień 1.* oznacza nasilenie „łagodne", stopień 2. oznacza nasilenie „umiarkowane", stopień 3. oznacza nasilenie „ciężkie", stopień 4. oznacza nasilenie „zagrażające życiu". *b. Dawka dobowa może być zmniejszona ze 120 mg do 80 mg lub z 200 mg do 120 mg. c. CRc jest definiowana jako współczynnik remisji wszystkich całkowitych remisji (definicja całkowitej remisji, patrz punkt 5.1 ChPL), CRp [całkowita remisja z niepełną regeneracją płytek krwi (< 100 x 10^9/l)] i CRi (spełnione kryteria całkowitej remisji z wyjątkiem pełnej regeneracji hematologicznej, z utrzymującą się neutropenią < 1 x 10^9/l i całkowitą regeneracją płytek krwi lub bez niej).* Produkt Xospata należy podawać mniej więcej o tej samej porze każdego dnia. Jeśli dawka zostanie pominięta lub nie zostanie przyjęta o zwykłej porze, należy podać dawkę jak najszybciej tego samego dnia, a pacjent powinien powrócić do zwykłego schematu dawkowania następnego dnia. Jeśli po podaniu dawki wystąpią wymioty, pacjenci nie powinni przyjmować kolejnej dawki, tylko powinni powrócić do zwykłego schematu dawkowania następnego dnia. Osoby w podeszłym wieku: Nie jest wymagane dostosowanie dawki u pacjentów w wieku ≥ 65 lat (patrz punkt 5.2 ChPL). Zaburzenia czynności wątroby: Nie ma konieczności dostosowania dawki u pacjentów z łagodnymi (klasa A wg skali Child-Pugh) lub umiarkowanymi (klasa B wg skali Child-Pugh) zaburzeniami czynności wątroby. Produktu Xospata nie zaleca się do stosowania u pacjentów z ciężkimi zaburzeniami czynności wątroby (klasa C wg skali ChildPugh), ponieważ w tej populacji nie oceniano bezpieczeństwa stosowania i skuteczności (patrz punkt 5.2 ChPL). Zaburzenia czynności nerek: Nie ma konieczności dostosowania dawki u pacjentów z zaburzeniami czynności nerek o nasileniu łagodnym, umiarkowanym lub ciężkim (patrz punkty 4.4 i 5.2 ChPL). Dzieci i młodzież: Nie określono dotychczas bezpieczeństwa stosowania ani skuteczności produktu leczniczego Xospata u dzieci w wieku poniżej 18 lat. Dane nie są dostępne. Ze względu na wiązanie się z receptorem $5HT_{2B}$ w warunkach *in vitro* (patrz punkt 4.5 ChPL) u pacjentów w wieku mniej niż 6 miesięcy istnieje możliwość oddziaływania na rozwój serca. Sposób podawania: Produkt Xospata jest przeznaczony do podania doustnego. Tabletki można przyjmować z posiłkiem lub bez. Należy je połykać w całości, popijając wodą i nie należy ich przełamywać ani rozkruszać. **Przeciwwskazania:** Nadwrażliwość na substancję czynną lub na którąkolwiek substancję pomocniczą wymienioną w punkcie 6.1 ChPL. **Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania:** Zespół różnicowania: Stosowanie gilterytynibu wiązało się z występowaniem zespołu różnicowania (patrz punkt 4.8 ChPL). Zespół różnicowania polega na szybkiej proliferacji i różnicowaniu komórek mieloidalnych. Nieleczony może zagrażać życiu lub prowadzić do zgonu. Objawy podmiotowe i stan kliniczny w zespole różnicowania obejmują gorączkę, duszność, wysięk opłucnowy, wysięk osierdziowy, obrzęk płuc, niedociśnienie tętnicze, szybki przyrost masy ciała, obrzęk obwodowy, wysypkę i zaburzenia czynności nerek. W przypadku podejrzewania zespołu różnicowania należy rozpocząć leczenie kortykosteroidami wraz z monitorowaniem hemodynamicznym aż do ustąpienia objawów podmiotowych. Jeśli ciężkie objawy przedmiotowe i/lub podmiotowe utrzymują się przez ponad 48 godzin po rozpoczęciu stosowania kortykosteroidów, należy przerwać stosowanie produktu Xospata do czasu ustąpienia ciężkiego nasilenia objawów przedmiotowych i podmiotowych (patrz punkty 4.2 i 4.8 ChPL). Dawkę kortykosteroidów można zmniejszyć po ustąpieniu objawów podmiotowych i podawać je przez minimum 3 dni. Przedwczesne zakończenie leczenia kortykosteroidami może spowodować nawrót podmiotowych objawów zespołu różnicowania; Zespół odwracalnej tylnej encefalopatii: Zgłaszano występowanie zespołu odwracalnej tylnej encefalopatii (ang. *posterior reversible encephalopathy syndrome*, PRES) u pacjentów otrzymujących produkt leczniczy Xospata (patrz punkt 4.8 ChPL). PRES to rzadkie, odwracalne zaburzenie neurologiczne, które może manifestować się szybko rozwijającymi się objawami podmiotowymi obejmującymi drgawki, ból głowy, stan splątania, zaburzenia widzenia i zaburzenia neurologiczne z towarzyszącym nadciśnieniem tętniczym i zaburzeniami stanu psychicznego lub bez nich. W przypadku podejrzewania PRES należy to potwierdzić radiologicznym badaniem obrazowym mózgu, najlepiej metodą rezonansu magnetycznego (ang. *magnetic resonance imaging*, MRI). Zaleca się zaprzestanie leczenia produktem Xospata u pacjentów, u których wystąpił PRES (patrz punkty 4.2 i 4.8 ChPL). Wydłużony odstęp QT: Stosowanie gilterytynibu wiązało się z wydłużeniem czasu repolaryzacji komór serca (odstęp QT) (patrz punkty 4.8 i 5.1 ChPL). Wydłużenie odstępu QT można zaobserwować w pierwszych trzech miesiącach leczenia gilterytynibem. Dlatego też przed rozpoczęciem leczenia, w 8. i 15. dniu pierwszego cyklu i przed rozpoczęciem każdego kolejnego miesiąca leczenia, przez następne trzy miesiące należy wykonać badanie elektrokardiograficzne (EKG). Należy zachować ostrożność u pacjentów z istotnym wywiadem kardiologicznym. Hipokaliemia lub hipomagnezemia mogą zwiększać ryzyko wydłużenia odstępu QT. Dlatego też przed rozpoczęciem leczenia produktem Xospata i w jego trakcie należy wyrównać hipokaliemię lub hipomagnezemię. Należy przerwać stosowanie produktu Xospata u pacjentów, u których odstęp QTcF > 500 ms (patrz punkt 4.2 ChPL). Decyzję o wznowieniu leczenia gilterytynibem po wystąpieniu wydłużenia odstępu QT należy podjąć po dokładnej ocenie korzyści i ryzyka. Jeżeli stosowanie produktu Xospata wznawia się w zmniejszonej dawce, po 15 dniach dawkowania i przed rozpoczęciem każdego kolejnego miesiąca leczenia, przez następne trzy miesiące należy wykonać badanie EKG. W badaniach klinicznych 12 pacjentów miało odstęp QTcF > 500 ms. Trzech pacjentów przerwało i ponownie rozpoczęło leczenie bez nawrotu wydłużenia odstępu QT. Zapalenie trzustki: Zgłaszano przypadki zapalenia trzustki. Należy badać i monitorować pacjentów, u których wystąpią objawy przedmiotowe i podmiotowe sugerujące zapalenie trzustki. Należy przerwać stosowanie produktu Xospata, ale można je wznowić, podając zmniejszoną dawkę, gdy ustąpią objawy przedmiotowe i podmiotowe zapalenia trzustki (patrz punkt 4.2 ChPL). Ciężka niewydolność nerek: Narażenie na gilterytynib może być zwiększone u pacjentów z ciężkimi zaburzeniami czynności nerek lub schyłkową niewydolnością nerek. Podczas stosowania produktu leczniczego Xospata należy ściśle monitorować pacjenta pod kątem toksyczności (patrz punkt 5.2 ChPL). Interakcje: Jednoczesne podawanie leków indukujących CYP3A/P-gp może prowadzić do zmniejszonej ekspozycji na gilterytynib i, w konsekwencji, ryzyka braku skuteczności. Dlatego należy unikać jednoczesnego stosowania gilterytynibu z silnymi induktorami CYP3A4/P-gp (patrz punkt 4.5 ChPL). Należy zachować ostrożność w przypadku jednoczesnego przepisywana gilterytynibu z produktami leczniczymi, które są silnymi inhibitorami CYP3A, P-gp i/lub białka oporności raka piersi (ang. *breast cancer resistant protein*, BCRP) (takimi jak między innymi: worykonazol, itrakonazol, pozakonazol i klarytromycyna), ponieważ mogą one zwiększać ekspozycję na gilterytynib. Należy rozważyć zastosowanie alternatywnych produktów leczniczych, które nie hamują silnie aktywności CYP3A, P-gp i/lub BCRP. W sytuacjach, gdy nie istnieją zadowalające alternatywy terapeutyczne, pacjentów należy ściśle monitorować pod kątem wystąpienia toksyczności w trakcie podawania gilterytynibu (patrz punkt 4.5 ChPL). Gilterytynib może zmniejszyć działanie produktów leczniczych, dla których receptorem docelowym jest receptor $5HT_{2B}$ lub nieswoiste receptory sigma. Dlatego też należy unikać równoczesnego stosowania gilterytynibu z tymi produktami, chyba że jego stosowanie uznaje się za niezbędne dla pacjenta (patrz punkt 4.5 ChPL). Działanie toksyczne na zarodek lub płód i antykoncepcja: Należy poinformować kobiety w ciąży o potencjalnym ryzyku dla płodu (patrz punkty 4.6 i 5.3 ChPL). Kobietom w wieku rozrodczym należy doradzić wykonanie testu ciążowego w ciągu siedmiu dni przed rozpoczęciem leczenia produktem Xospata i stosowanie skutecznej metody antykoncepcji w trakcie leczenia produktem Xospata i przez co najmniej 6 miesięcy od zakończenia leczenia. Kobiety stosujące antykoncepcję hormonalną powinny dodatkowo stosować antykoncepcję barierową. Mężczyznom, których partnerki są w wieku rozrodczym, należy doradzić stosowanie skutecznej metody antykoncepcji w trakcie leczenia i przez co najmniej 4 miesiące od przyjęcia ostatniej dawki produktu Xospata. **Działania niepożądane:** Podsumowanie profilu bezpieczeństwa: Bezpieczeństwo produktu Xospata oceniono u 319 pacjentów z nawrotową lub oporną na leczenie AML, którzy otrzymali co najmniej jedną dawkę 120 mg gilterytynibu. Najczęstszymi działaniami niepożądanymi gilterytynibu były zwiększenie aktywności aminotransferazy alaninowej (ang. *alanine aminotransferase*, ALT) (82,1%), zwiększenie aktywności aminotransferazy asparaginianowej (ang. *aspartate aminotransferase*, AST) (80,6%), zwiększenie aktywności fosfatazy alkalicznej we krwi (68,7%), zwiększenie aktywności kinazy kreatynowej we krwi (53,9%), biegunka (35,1%), zmęczenie (30,4%), nudności (29,8%), zaparcia (28,2%), kaszel (28,2%), obrzęki obwodowe (24,1%), duszność (24,1%), zawroty głowy (20,4%), niedociśnienie tętnicze (17,2%), ból kończyny (14,7%), astenia (13,8%), ból stawów (12,5%) i ból mięśni (12,5%). Najczęstszymi ciężkimi działaniami niepożądanymi były ostre uszkodzenie nerek (6,6%), biegunka (4,7%), zwiększenie aktywności AIAT (4,1%), duszność (3,4%), zwiększenie aktywności AspAT (3,1%) i niedociśnienie tętnicze (2,8%). Inne, kliniczne istotne, ciężkie działania niepożądane obejmowały zespół różnicowania (2,2%), wydłużenie odstępu QT na elektrokardiogramie (0,9%) i zespół odwracalnej tylnej encefalopatii (0,6%). Działania niepożądane zaobserwowane w trakcie badań klinicznych wymieniono poniżej według kategorii częstości. Kategorie częstości są zdefiniowane następująco: bardzo często (≥ 1/10), często (≥ 1/100 do < 1/10), niezbyt często (≥ 1/1000 do < 1/100), rzadko (≥ 1/10 000 do < 1/1000), bardzo rzadko (< 1/10 000) i częstość nieznana (nie może być określona na podstawie dostępnych danych). W obrębie każdej grupy częstości występowania działań niepożądanych przedstawiono według zmniejszającej się ciężkości. Zaburzenia układu immunologicznego: Często: reakcja anafilaktyczna (1,3**; 1,3***). Zaburzenia układu nerwowego: Bardzo często: zawroty głowy (20,4**; 0,3***). Niezbyt często: zespół odwracalnej tylnej encefalopatii (0,6**; 0,6***). Zaburzenia serca: Często: wydłużenie odstępu QT w elektrokardiogramie (8,8**; 2,5***), wysięk osierdziowy (4,1**; 0,9***), zapalenie osierdzia (1,6**; 0***), niewydolność serca (1,3**; 1,3***). Zaburzenia naczyniowe: Bardzo często: niedociśnienie tętnicze (17,2**; 7,2***). Zaburzenia układu oddechowego, klatki piersiowej i śródpiersia: Bardzo często: kaszel (28,2**; 0,3***), duszność (24,1**; 4,4***). Często: zespół różnicowania (3,4**; 2,2***). Zaburzenia żołądka i jelit: Bardzo często: biegunka (35,1**; 4,4***), nudności (29,8**; 1,9***), zaparcia (28,2**; 0,6***). Zaburzenia wątroby i dróg żółciowych: Bardzo często: zwiększenie aktywności aminotransferazy alaninowej* (82,1**; 12,9***), zwiększenie aktywności aminotransferazy asparaginianowej* (80,6**; 10,3***). Zaburzenia mięśniowo-szkieletowe i tkanki łącznej: Bardzo często: zwiększenie aktywności fosfokinazy kreatynowej we krwi* (53,9**; 6,3***), zwiększenie aktywności fosfatazy alkalicznej we krwi* (68,7**; 1,6***), ból kończyny (14,7**; 0,6***), ból stawów (12,5**; 1,3***), ból mięśni (12,5**; 0,3***). Często: ból mięśniowo-szkieletowy (4,1**; 0,3***). Zaburzenia nerek i dróg moczowych: Często: ostre uszkodzenie nerek (6,6**; 2,2***). Zaburzenia ogólne i stany w miejscu podania: Bardzo często: zmęczenie (30,4**; 3,1***), obrzęki obwodowe (24,1**; 0,3***), astenia (13,8**; 2,5***). Często: złe samopoczucie (4,4**; 0***). ** Częstość opiera się na wartościach laboratorium centralnego. ** Wszystkie stopnie ciężkości (%). *** Stopnie ciężkości ≥ 3. (%).* Opis wybranych działań niepożądanych: *Zespół różnicowania:* W badaniach klinicznych z udziałem 319 pacjentów leczonych produktem Xospata u 11 (3%) wystąpił zespół różnicowania. Zespół różnicowania polega na szybkiej proliferacji i różnicowaniu komórek szpiku i nieleczony może zagrażać życiu lub prowadzić do zgonu. Objawy podmiotowe i stan kliniczny w zespole różnicowania u pacjentów leczonych produktem Xospata obejmowały gorączkę, duszność, wysięk opłucnowy, wysięk osierdziowy, obrzęk płuc, niedociśnienie tętnicze, szybki przyrost masy ciała, obrzęk obwodowy, wysypkę i zaburzenie czynności nerek. W niektórych przypadkach jednocześnie wystąpiła ostra gorączkowa dermatoza neutrofilowa. Zespół różnicowania wystąpił od jednego dnia (najwcześniej) do 82 dni od rozpoczęcia leczenia produktem Xospata i przebiegał ze współistniejącą leukocytozą lub bez niej. Z 11 pacjentów, u których wystąpił zespół różnicowania, 9 (82%) powróciło do zdrowia po okresie leczenia lub po przerwie w dawkowaniu produktu Xospata. Zalecenia w przypadku podejrzewanego zespołu różnicowania podano w punktach 4.2 i 4.4 ChPL. *PRES:* W badaniach klinicznych z udziałem 319 pacjentów leczonych produktem Xospata u 0,6% wystąpił zespół odwracalnej tylnej encefalopatii (PRES). PRES to rzadkie, przemijające zaburzenie neurologiczne, które może objawiać się szybko rozwijającymi się objawami podmiotowymi obejmującymi drgawki, ból głowy, stan splątania, zaburzenia widzenia i zaburzenia neurologiczne z towarzyszącym nadciśnieniem tętniczym lub bez niego. Objawy podmiotowe ustąpiły po zaprzestaniu leczenia (patrz punkty 4.2 i 4.4 ChPL). *Wydłużenie odstępu QT:* Spośród 317 pacjentów leczonych gilterytynibem w dawce 120 mg w badaniach klinicznych, którym zmierzono QTc po rozpoczęciu badania (ang. *post-baseline*), u 4 pacjentów (1%) stwierdzono odstęp QTcF > 500 ms. Ponadto, w zakresie wszystkich dawek, u 12 pacjentów (2,3%) z nawrotową lub oporną na leczenie AML maksymalna wartość odstępu QTcF po rozpoczęciu badania (ang. *post-baseline*) wynosiła > 500 ms (patrz punkty 4.2, 4.4 i 5.1 ChPL). Zgłaszanie podejrzewanych działań niepożądanych: Po dopuszczeniu produktu leczniczego do obrotu istotne jest zgłaszanie podejrzewanych działań niepożądanych. Umożliwia to nieprzerwane monitorowanie stosunku korzyści do ryzyka stosowania produktu leczniczego. Osoby należące do fachowego personelu medycznego powinny zgłaszać wszelkie podejrzewane działania niepożądane za pośrednictwem Departamentu Monitorowania Niepożądanych Działań Produktów Leczniczych Urzędu Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych, Al. 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REVIEW ARTICLE

VIA MEDICA

Emergencies in patients undergoing hematopoietic stem cell transplantation

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Abstract

Despite its high effectiveness, hematopoietic stem cell transplantation (HSCT) can sometimes be associated with multiple peri-transplant complications requiring urgent intervention. Life-threatening complications in the transplantation unit affect non-relapse mortality. This article sets out a practical approach to the essential peri-transplant clinical conditions, divided into infectious complications and complications related to immune response and endothelial damage. An early diagnosis of life-threatening conditions, and prompt implementation of the best therapy, can save patients' lives. This is especially the case regarding infectious complications in neutropenic patients and in the advanced stages of immunological complications such as graft-versus-host disease, veno-occlusive disease, graft failure, diffuse alveolar hemorrhage, and thrombotic microangiopathy associated with HSCT. These emergencies are discussed below, along with their risk factors and a summary of the management of patients in the early post-transplant period.

Key words: hematopoietic stem cell transplantation, HSCT, infectious complications after HSCT, immunological complications after HSCT

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Introduction

Hematopoietic stem cell transplantation (HSCT), both autologous (auto-HSCT) and allogeneic (allo-HSCT), is a complex medical procedure that is used to treat various malignant and non-malignant hematological disorders [1].

Despite advances in HSCT techniques, patients undergoing this procedure are at risk for varying complications, including emergencies that require prompt medical attention. The transplant committee qualifying a patient for treatment must consider indications for HSCT and risk factors of complications. During the qualification, various scales determining the stage of the disease and the general condition of the patient are helpful, including the Eastern Cooperative Oncology Group (ECOG) performance scale, and the Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI), enabling the determination of the risk of HSCT procedure [2] and indications for HSCT [3].

A life-threatening condition is a sudden, or predictable in the short term, severe clinical deterioration following serious damage to the body's functions requiring immediate treatment [4]. Emergencies occurring in the early post-transplant period, such as infections and complications related to the immune response, affect non-relapse mortality (NRM), estimated at 30% in allo-HSCT recipients and 13% after autologous transplant [5]. An early diagnosis of a life-threatening condition in patients undergoing HSCT, and the prompt implementation of the most effective therapy, can save the patient's life.

This article discusses the practical approach to emergencies in patients undergoing HSCT, along with their risk factors (Tables I, II) and management. This approach is divided into infectious complications and complications

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Table I. Common risk factors for emergencies in hematopoietic stem cell transplantation (HSCT) recipients

Patient-related risk factors	Transplant-related factors
Advanced recipient age	Unrelated donor
General condition of patient: according to Karnofsky index <90 or ECOG >1	Major HLA disparity
Relapse/refractory disease	Myeloablative conditioning
Medical history of organ failure, comorbidities*	High doses of busulfan
Medical history of infections and co-existing infections in post-transplant period	Use of fludarabine in reduced-intensity conditioning
Previous alloimmunization (including pregnancy, multiple transfusions)	Total body irradiation (high-dose)
Iron overload	*Ex vivo* T-cell depletion
Previous therapy toxicity	Second HSCT

*According to the Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI); ECOG — Eastern Cooperative Oncology Group performance scale; HLA — human leukocyte antigen

Table II. Risk factors and estimated incidence of selected complications in hematopoietic stem cell transplantation (HSCT) recipients

Complication	Estimated incidence	Risk factors
Graft-versus-host disease	~40%	Recipient seropositivity for cytomegalovirus
		Use of peripheral blood as opposed to bone marrow
		Use of female donor for male patient
Sinusoidal obstruction syndrome/veno-occlusive disease	10–15%	Prior liver radiation/hepatotoxic treatment
		Medical history of liver cirrhosis/fibrosis/thalassemia
		Prior treatment with gemtuzumab or inotuzumab ozagamicin
		Genetic factors (GSTM1-null genotype, MTHFR 677C/1298CC haplotype)
		Concomitant therapy with progestogens, azoles
		Increased aspartate transferase, bilirubin levels before HSCT
Diffuse alveolar hemorrhage	2–14%	Late granulopoiesis and platelet reconstitution
		Use of umbilical cord blood
Graft failure	<3–5%	Non-malignant underlying disease as indication for HSCT
	10%*	Extensive marrow fibrosis, extensive prior treatment
		Low count of CD34+ cell
		Cryopreservation
Thrombotic microangiopathy associated with HSCT	0.5–76%	Use of calcineurin inhibitors in immunosuppressive prophylaxis
		Administration of granulocyte-colony stimulating factor
		Genetic polymorphism
		Pre-transplant kidney dysfunction

*Cord blood and haploidentical HSCT

related to the immune response and endothelial damage. Moreover, we have devised figures that summarize practical algorithms for each complication (Figures 1–6).

Infectious complications

Infections during neutropenia are life-threatening and remain among the leading early complications after HSCT [6, 7]. According to data from the Center for International Blood and Marrow Transplant Research (CIBMTR), within 100 days post-transplant, infectious complications account for significant percentages of the cause of death, estimated at 21% of patients undergoing auto-HSCT and 16–28% of allo-HSCT recipients, depending on the donor source [8]. It is essential to identify the population at high risk for infections and introduce effective standard prophylaxis [9]. The risk of infection results from the interaction of many factors related to the patient, the type of transplant, and the exposure to microorganisms. In the course of transplantation, the use of central venous catheters and

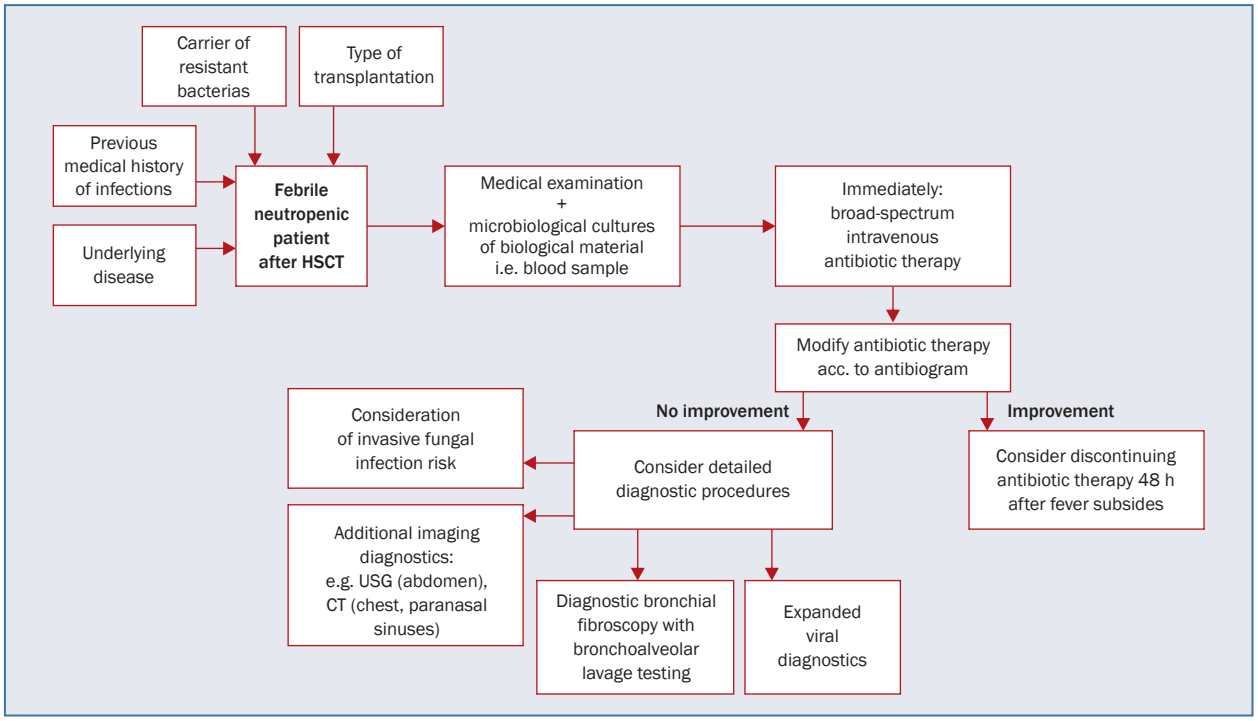

Figure 1. Practical algorithm of febrile neutropenic patient after hematopoietic stem cell transplantation (HSCT); USG — ultrasonography; CT — computed tomography

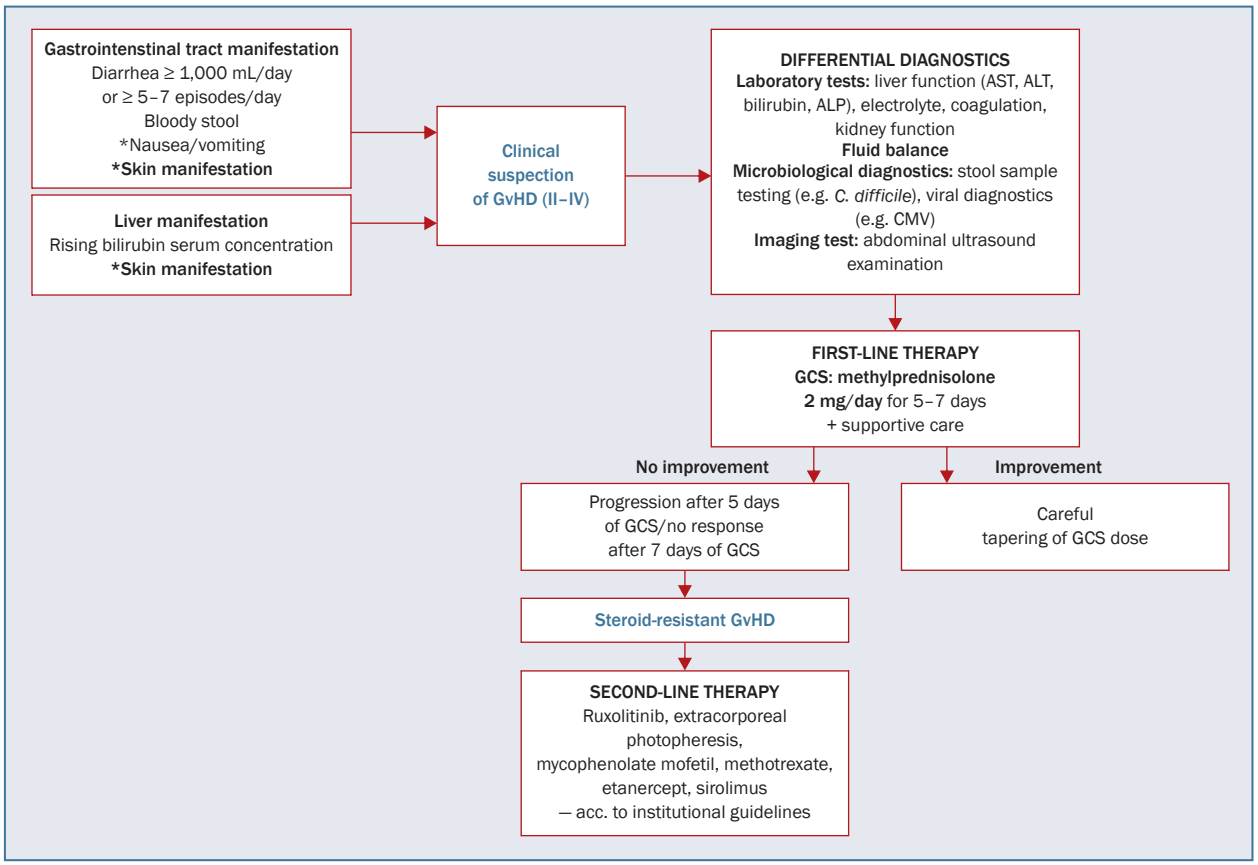

Figure 2. Practical algorithm of severe graft-versus-host disease (GvHD); AST — aspartate aminotransferase; ALT — alanine aminotransferase; ALP — alkaline phosphatase; CMV — cytomegalovirus; GSC —— glucocorticosteroids

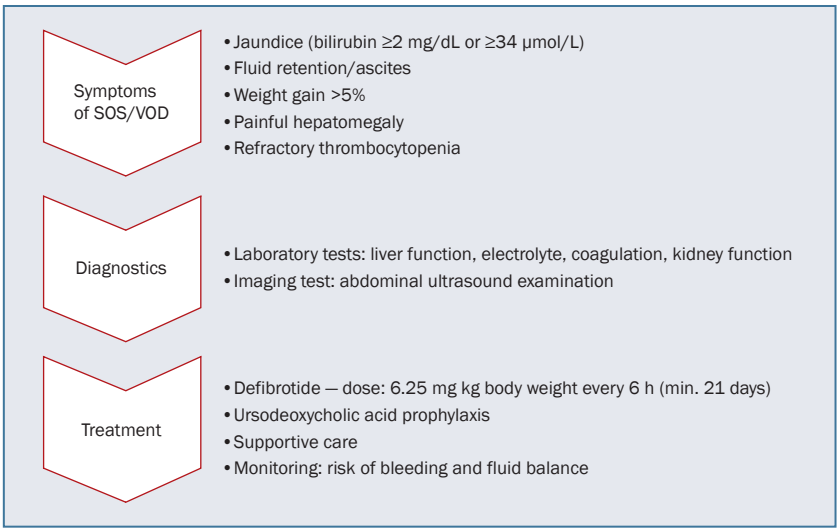

Figure 3. Practical algorithm of severe hepatic sinusoidal obstruction syndrome /veno-occlusive disease (SOS/VOD)

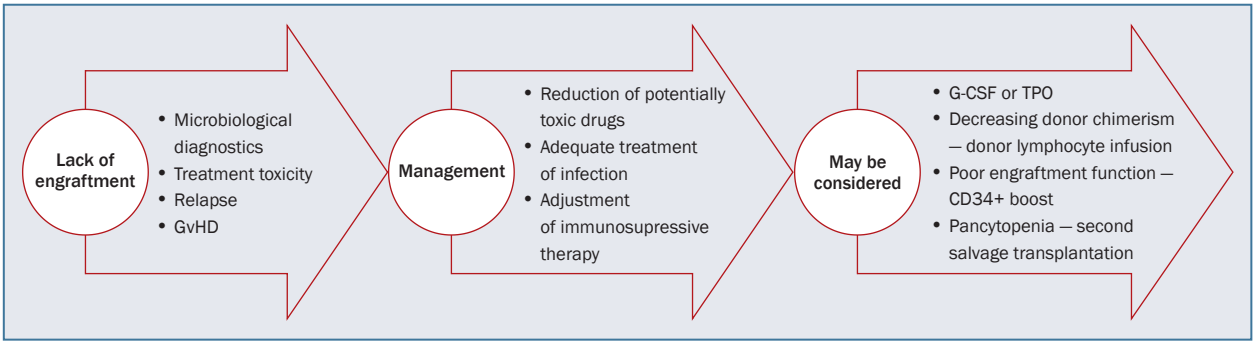

Figure 4. Practical algorithm of graft failure; GvHD — graft-versus-host disease; G-CSF — granulocyte-colony stimulating factor; TPO — thrombopoietin

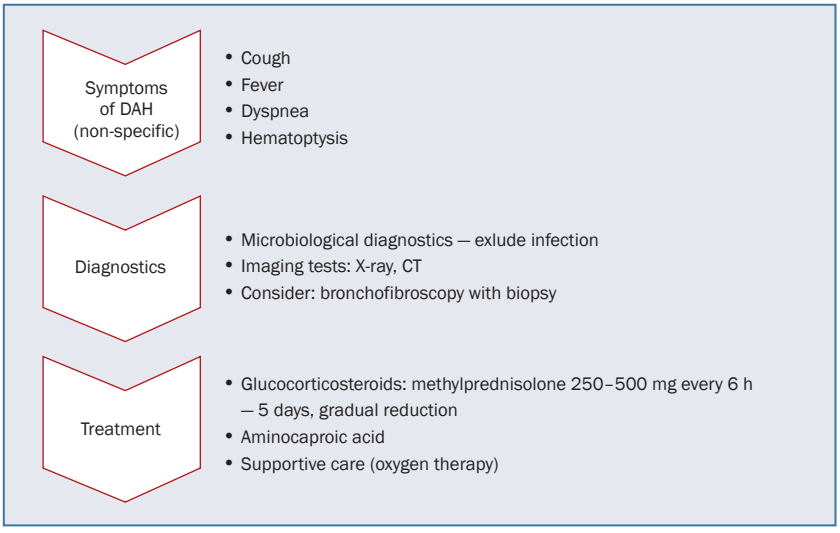

Figure 5. Practical algorithm of diffuse alveolar hemorrhage (DAH); CT — computed tomography

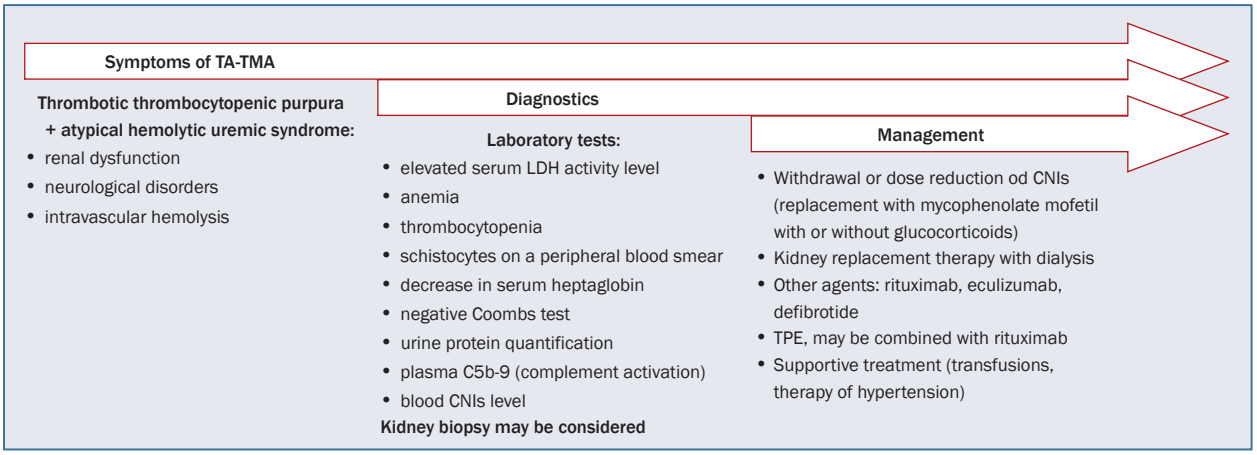

Figure 6. Practical algorithm of thrombotic microangiopathy associated with HSCT (TA-TMA); LDH — lactate dehydrogenase; CNIs — calcineurin inhibitors; TPE — therapeutic plasma exchange

mucocutaneous damage which might occur disrupt the natural barriers of the skin and mucous membranes, and may be a potential trigger point of infection. The previous microbiological history of the patient [i.e. a medical history of fungal infection, presence of pretransplant-specific immunity to cytomegalovirus (CMV), herpes simplex virus (HSV), varicella-zoster virus (VZV), and Epstein-Barr virus (EBV)], as well as the viral status of the donor, should be taken into account. Moreover, the underlying disease in the setting of prior therapy and the type of HSCT (donor, source, conditioning, and immunosuppressive regimens) determine the risk of infection. Any other complication related to prolonged neutropenia, such as graft-versus-host disease and graft failure, increases the incidence of the infectious complication [10].

Bacterial infections are relatively common during neutropenia in both allo-HSCT recipients and patients undergoing auto-HSCT, while fungal and viral infections occur less frequently. For a proper diagnosis of patients with neutropenic fever (FN), detailed diagnostics are recommended, including microbiological cultures of biological material, i.e. venous blood, blood collected through a vascular catheter, urine, stool, and/or cerebrospinal fluid, depending on the accompanying symptoms [7, 10, 11].

Bacteremia is documented in 13–60% of patients with neutropenic fever, with a mortality rate reaching 12–42% [7, 11]. About half of the bacterial infections are caused by Gram-positive bacteria, particularly methicillin-resistant coagulase-negative *Staphylococci* and *Streptococcus spp.*, with a favorable prognosis. Recent years have seen a challenging increase in infections caused by resistant pathogens i.e. vancomycin-resistant *Enterococci* (VRE) and *Staphylococci* (vancomycin-intermediate *Staphylococcus aureus* (VISA), and hetero-resistant *Staphylococcus aureus* [hVISA]).

However, infections with resistant Gram-negative bacteria (MDR, multi-drug resistant), such as *Escherichia coli, Klebsiella sp., Pseudomonas aeruginosa*, and *Acinetobacter sp.*, are actually the most dangerous complications, as these are accompanied by a high mortality rate of c.50% [7, 12, 13].

In patients with FN, broad-spectrum intravenous antibiotic therapy should be implemented immediately even without identifying the pathogen and its susceptibility determination. The infection can spread quickly, causing a direct threat to life. The antibiotic therapy should cover the spectrum of Gram-positive and Gram-negative bacteria and then be modified depending on the patient's clinical condition, response to treatment, and potential microbiological identification. The choice of empirical therapy relies on the sensitivity of pathogens in the transplant center and the experience of the center's clinicians. Due to the potential toxicity and the development of bacterial resistance, there is a clear need to use narrowly-targeted therapy consistent with the antibiogram, and to consider discontinuing antibiotic therapy 48 h after the fever subsides, depending on the patient's general condition. In addition, if no clinical improvement is observed despite broad-spectrum empirical antibiotic therapy and the lack of microbiological identification, the imaging and microbiological diagnostics should be extended by the use of imaging diagnostics (ultrasonography of the abdominal cavity, computed tomography: high-resolution chest, paranasal sinuses) as well as invasive procedures, e.g. diagnostic bronchial fibroscopy with bronchoalveolar lavage testing [7, 10–14].

Recurrent or persistent FN, despite antibiotic therapy administration, might suggest invasive fungal infection (IFI), diagnosed mainly in allo-HSCT recipients with a high mortality rate. The incidence of IFI depends on the donor source and is estimated at 6–17%. The pathogens responsible for neutropenic infections are *Aspergillus sp., Mucorales*, and *Candida sp.* A medical history of IFI in transplant patients should always be considered. IFI is a significant clinical

problem, primarily in patients with graft-versus-host disease (GvHD) in the later post-transplant period. A strategy of antifungal therapy and prophylaxis during neutropenia has been described by the European Conference on Infections in Leukemia (ECIL) [7, 10, 15].

Among the viral infections in patients after allo-HSCT, the most important clinical problem is CMV reactivation [10, 16]. Both CMV viremia and CMV disease are associated with higher mortality. Historically, CMV reactivation occurred in 20–30% of HSCT recipients without adequate treatment, with a mortality rate exceeding 70%, as the first cause of treatment-related mortality (TRM). Pneumonia and enteritis are the most significant clinical manifestations associated with CMV disease, which can be fatal. The major risk factors for CMV reactivation and disease are GvHD, high-dose glucocorticoids (GCS), and prior CMV viremia. Nowadays, in the era of primary prophylaxis with letermovir, the occurrence of CMV disease has decreased to c.5%, as has the rate of deaths related to CMV disease, which is 2–3%.

However, CMV reactivation is related to an increased incidence of cytopenia and other infectious complications, and worsens survival rates of seropositive allo-HSCT recipients. Therefore, monitoring for CMV viremia to detect early CMV reactivation and, when it occurs, promptly implementing the use of pre-emptive therapy with anti-viral agents such as gancyclovir, valgancyclovir, foscarnet, cidofovir, and maribavir is essential [10, 16, 17].

Another potentially life-threatening complication is post-transplant lymphoproliferative disorder (PTLD), occurring in allo-HSCT recipients, in which B cells transformed by EBV proliferate uncontrollably. EBV infection occurs in 30% of HSCT recipients, and the incidence of PTLD is estimated at 1.1–1.7%, with a mortality rate exceeding 80% before the introduction of today's treatment methods. The development of EBV-PTLD is closely related to the use of anti-thymocyte globulin (ATG) and the type of transplant. Immediate therapy of established EBV-PTLD, due to the risk of the rapid growth of high-grade lymphoid tumors and its life-threatening consequences, should be introduced. This includes using rituximab (RTX) and the reduction of immunosuppression for first-line therapy, with an efficacy of over 80%. In the case of RTX failure, chemotherapy or the use of cellular therapy with cytotoxic T lymphocytes (EBV-CTL), well-tolerated and effective, is indicated [10, 18–20].

Complications related to immune response and endothelial damage after HSCT

Acute graft-versus-host disease

Acute GvHD (aGvHD) is a common complication of allo-HSCT, which occurs when immune cells from the graft recognize the host as foreign, thereby initiating a complex immune reaction that causes disease in c.40% of allo-HSCT recipients in the early post-transplantation period — around the white blood cell reconstitution, classically before day +100. Clinical manifestations of severe or life-threatening aGvHD include grade II or higher. Regarding the gastrointestinal tract and liver, the patient may present symptoms such as persistent nausea, vomiting, abdominal cramps with or without ileus, and, most importantly, diarrhea with a volume >1,000 mL/day or >5–7 episodes/day or bloody stool (regardless of stool volume) and liver dysfunction — with rising bilirubin serum concentration (>3.1 mg/dL). Skin-limited manifestation is a mild condition, but when a rash coexists with other forms of aGvHD and includes >50% of the body surface area, it affects the severity of the disease. The gastrointestinal form of aGvHD (GI-aGvhD) occurs in varying degrees in about half of patients with aGvHD. The watery mucous diarrhea in stages III/IV of GI-GvHD leads to water, electrolyte, and functional disorders that can lead to paralytic obstruction of the gastrointestinal tract and rapid decompensation of the patient. Abnormal liver function tests, most commonly bilirubin and alkaline phosphatase, reflect the pathology associated with hepatic GvHD: damage to the bile canaliculi, leading to cholestasis. Coagulopathy and hyperammonemia occur rarely, and mostly in severe cases. Patients may present painful hepatomegaly, dark urine, pale stool, fluid retention, and pruritus. The advanced stages of liver and GI-aGvhD can be fatal and require urgent intervention [10, 21].

The first-line therapy of grades II–IV aGvHD includes using systemic GCS in high doses — methylprednisolone at an initial dose of 2 mg/kg/day for 7–14 days (or equivalent). In cases of upper GI involvement, non-absorbable oral steroids are given, along with systemic GCS, e.g. budesonide (9 mg/day). During the treatment, individualized symptomatic and supportive therapy should be used to maintain vigilance in every single case of severe aGvHD. Long-term use of high doses of corticosteroids increases the risk of infection, including CMV reactivation, which is clinically significant in transplant recipients, as well as electrolyte disturbances and therapy-induced diabetes [21, 22].

Steroid-resistant aGvHD (SR-aGvHD) occurs in about half of the patients and is associated with mortality rates of up to 90%. When there is clear progression after five days of GCS, or when there is no response after seven days of GCS, it is recommended to introduce second-line therapy. Until now, there has been no standard second-line treatment for acute GvHD, and prospective clinical trials are still being conducted to examine the effectiveness of components. Ruxolitinib was approved by the US Food and Drug Administration and the European Medicines Agency for SR-aGVHD treatment in patients ≥12 years, with efficacy exceeding 70% and a favorable toxicity profile [23]. Moreover, in SR-aGvHD patients, depending on the institutional guidelines of transplant centers, the following agents may be used: extracorporeal photopheresis, mycophenolate

mofetil, methotrexate, etanercept, sirolimus, anti-thymocyte globulin, alemtuzumab, and vedolizumab; efficacies are 40-70%. There has been research into using fecal microbiota transplantation in second-line therapy, but this is yet to be approved [22, 24, 25].

Hepatic sinusoidal obstruction syndrome; veno-occlusive disease

Sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) is a life-threatening systemic complication of HSCT caused by injury to sinusoidal endothelial, hepatic cells that usually appears in the first 35–40 days after HSCT. The syndrome is characterized by hepatomegaly, fluid retention, jaundice, and refractory thrombocytopenia, and it can rapidly progress to multiorgan dysfunction and death. The incidence is estimated at 10–15% after myeloablative conditioning, while in the case of reduced intensity conditioning (RIC), it is c.5%. Before the patient's conditioning, the risk of SOS/VOD should be determined each time, as reducing the modifiable risk factors plays an important role in preventing this complication. The mild stage of SOS symptoms is self-limiting; however, the subsequent stages, especially taking into account the criteria of weight gain (>5%, <10%) and developing multiple organ failure, should be considered as a severe life-threatening condition. The mortality rate with severe hepatic SOS/VOD without adequate treatment exceeds 80% [10, 26].

The diagnosis of SOS/VOD should be made using the European Society for Blood and Marrow Transplantation (EBMT) revised diagnostic criteria for adults or alternative models (e.g. Seattle, Baltimore) which include: serum bilirubin (≥2 mg/dL; ≥34 μmol/L) plus two of the following three: painful hepatomegaly, weight gain >5%, and ascites. Abdominal ultrasound examination and laboratory findings defining liver and kidney functions help determine the severity of SOS/VOD [10, 26].

Defibrotide is indicated for managing severe SOS/VOD in HSCT recipients at a dose of 6.25 mg/kg every six hours, administered for a minimum of 21 days depending on the response [6, 26]. In patients who have developed severe SOS/VOD while receiving ursodeoxycholic acid (UDCA) prophylaxis, UDCA can be continued while they are treated with defibrotide [28]. Moreover, during the treatment, we should implement supportive care, and oversee vital signs, organ function parameters, fluid balance, and bleeding risk, because hemorrhage and hypersensitivity can be rare but life-threatening adverse effects. Early diagnosis of SOS/VOD and the introduction of defibrotide therapy significantly improve survival, as the percentage of complete remissions goes up to 50% [29–30].

Graft failure

Graft failure (GF) is a severe complication of allo-HSCT, characterized by the failure of donor hematopoietic cell reconstitution (at +28 days in bone marrow (BM) or peripheral blood (PB) and +42 days in umbilical cord blood (UCB). Primary GF is defined as a lack of initial donor engraftment; in contrast, secondary GF is characterized by losing donor cells after initial hematological recovery. In differential diagnosis, infectious causes (especially CMV reactivation and HHV-6 infection), treatment toxicity, relapse of the underlying disease, and GvHD should all be considered. The incidence of GF is estimated at 3–5% in allo-HSCT from a matched donor. This reaches up to 10% when using an alternative donor, i.e. a haploidentical donor (haplo-HSCT) or UCB. The mortality rate of GF is high due to the implications of cytopenia, such as severe infections and hemorrhagic complications [10, 31–33].

The critical aspects in managing GF are taking preventive measures and the early identification and withdrawal of potential causes if they might be reverted, i.e. reduction of drug toxicity, adequate infectious treatment, and adjustment of immunosuppressive therapy. Moreover, a trial of using granulocyte-colony stimulating factor (G-CSF) or thrombopoietin analogs (TPO) may be justified. In patients with an observed decrease in donor chimerism, the use of donor lymphocyte infusion (DLI) should be considered, although a high risk of aGvHD development is to be expected. The infusion of a CD34+ boost of the donor can be taken into account in patients with poor engraftment function. A second salvage transplantation from the same donor or an alternative donor remains the treatment of choice, promising for selected patients with primary GF or acute graft rejection related to trilinear cytopenia. New therapeutic and preventive approaches, such as mammalian target of rapamycin inhibitors, mesenchymal stromal cells, Tregs, or statins, could be an option for GF in the future [10, 31–34].

Diffuse alveolar hemorrhage

Diffuse alveolar hemorrhage (DAH) is associated with blood leakage from the pulmonary capillaries into the alveoli, diagnosed in 2–14% of patients, most often in the first month after HSCT (median +23 days). The onset of DAH is usually abrupt. Symptoms are non-specific, including cough, fever, dyspnea, and hemoptysis (occurring in one in three patients). DAH can have both an infectious and a non-infectious etiology, and microbiological and imaging diagnostics may be insufficient to make a proper differential diagnosis. In selected clinical situations, bronchial fibroscopy should be considered, where blood is usually visualized in the orifices of segmental bronchi and bronchoalveolar. The diagnosis is confirmed by the presence of >20% of macrophages loaded with hemosiderin (though note that the absence of macrophages does not exclude the diagnosis of DAH, and their presence may occur after 72 h). The prognosis in DAH is very unfavorable, and mortality reaches 70–100% [10, 35–39].

The management of DAH without infectious evidence includes the prompt use of high doses of GCs — methylprednisolone at a dose of 250–500 mg every six hours for five days, followed by a gradual reduction of dose for 2–4 weeks and aminocaproic acid [10, 36]. A study has shown the validity of using GCs in lower doses (methylprednisolone <250 mg/d); however, further randomized prospective studies are indicated [37]. The addition of VIIa factor does not seem to improve the course of DAH. For patients with infection-associated DAH, treatment of the infection is crucial. Supportive care, including platelet transfusions and oxygen therapy, should be given. It is recommended to avoid mechanical ventilation, if possible. Patients with DAH may require intensification of therapy in the ICU due to its dynamic clinical course and frequently coexisting multi-organ failure [36–39].

Thrombotic microangiopathy associated with HSCT

Thrombotic microangiopathy associated with HSCT (TA-TMA) is a potentially life-threatening complication of HSCT caused by endothelial injury. The clinical manifestation of TA-TMA includes renal dysfunction and/or unexplained neurological dysfunction co-existing with evidence of intravascular hemolysis. The symptoms are associated with thrombotic thrombocytopenic purpura (TTP) and atypical hemolytic uremic syndrome (aHUS), which typically occur up to 100 days after transplantation (median time +32 to +40 days). TA-TMA incidence differs widely due to various diagnostic criteria — 0.5–76%, according to a multicenter study — 3% [7, 40]. TA-TMA frequently has a poor prognosis with a mortality rate of up to 60%, mainly when the patient develops multiple organ failure. TA-TMA is not associated with calcineurin inhibitors (CNIs) [40, 41].

Most definitions of TA-TMA include a combination of characteristic clinical symptoms and the following laboratory findings: elevated serum lactate dehydrogenase (LDH) activity level, anemia, thrombocytopenia, presence of schistocytes on a peripheral blood smear, decrease in serum haptoglobin, negative Coombs test, urine protein quantification, and plasma C5b-9 (a product of complement activation). Moreover, in cases where the diagnosis is uncertain based on clinical findings, a kidney biopsy may be helpful to establish the diagnosis of TA-TMA.

The treatment of TA-TMA withdrawal or dose reduction of CNIs should be considered, especially when the blood CNI level is higher than expected. Replacement with mycophenolate mofetil, with or without GCS, may be reasonable. In patients with severe TA-TMA that progresses despite supportive measures, kidney replacement therapy with dialysis and additional treatments such as rituximab, eculizumab, and defibrotide may be needed. The efficiency of therapeutic plasma exchange (TPE), which can be combined with rituximab, reaches 60% CR, whereas the effectiveness of therapy with defibrotide or eculizumab is up to 70%. Moreover, supportive treatment with transfusions, and the appropriate management of hypertension, are indicated [10, 40–43].

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Author contributions

JK — concept, manuscript writing. MM — data check, critical revision. LG — idea for manuscript, critical revision. All authors — final approval of manuscript.

Conflict of interests

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Supplementary material

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REVIEW ARTICLE

VIA MEDICA

Identifying frailty in older people living with diffuse large B-cell lymphoma: a systematic review

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Abstract

Introduction: Diffuse large B-cell lymphoma (DLBCL) is a common neoplasm in older people; in this group, personalized therapies are important because while some patients are frailer, others are fitter. However, knowledge is lacking as to which frailty identification tools are most commonly used in older patients living with DLBCL. The aim of this systematic review was to address this knowledge gap.

Material and methods: We searched the PubMed, EMBASE, and Cochrane databases and Google Scholar for studies published before December 2022. We included studies conducted with DLBCL patients aged 60 years or older, where a frailty classification (i.e. fit, unfit, or frail) had been reported in the context of prognostication and/or personalization of treatment.

Results: Sixteen studies were included in our review, with a total of 8,705 DLBCL patients (mean age 76 years, 54% men). Overall, 42% were classified as 'frail', and 40% as 'fit'. The most frequent frailty identification method was the Comprehensive Geriatric Assessment (CGA) (simplified: 75%, full: 13%), followed by the physical phenotype (6%) and the cumulative deficits index (6%) tools. The most common CGA domains utilized in the classification of frailty were the evaluation of basic activities of daily living (86%), instrumental activities of daily living (63%), comorbidities (81%), and geriatric syndromes (19%).

Conclusion: Two in five DLBCL patients aged 60 years or older were classified as frail, and an almost equal proportion as fit, most commonly post-application of simplified CGA. More studies are required to validate specific frailty identification instruments in this population.

Key words: frailty, geriatric oncology, comprehensive geriatric assessment, diffuse large B-cell lymphoma

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Introduction

The geriatric evaluation of older cancer patients is very important in order to guide oncological treatment decisions and provide opportunities for non-oncological management [1]. A systematic study that included hematological malignancies found that after a geriatric assessment, the oncological treatment plan was altered in a median 31% of patients [2].

The gold standard geriatric assessment is the Comprehensive Geriatric Assessment (CGA), which is

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a multi-dimensional diagnostic process focused on determining an older person's medical, functional and psychosocial capabilities in order to develop a coordinated and integrated plan for treatment and follow-up [3]. While the identification of frailty is an indication for CGA, CGA can also help in placing patients along the fitness-frailty continuum [4], informing patient optimization strategies, helping to personalize treatments, and improving prognostication in older oncological patients [5–8].

Although CGA offers a more complete perspective of an older patient [9], over the past two decades multiple frailty identification tools have emerged in clinical practice and research [10], the most commonly used being the phenotype and the cumulative deficits (frailty index) models. The phenotype identifies physical frailty when three or more of the following are present: exhaustion, shrinkage (unintentional weight loss), weakness (low handgrip strength), slowness (low gait speed), and low physical activity [11, 12]. The cumulative deficits model measures the proportion of health deficits present in an older individual from a list of 30–70 possible deficits, wherein a higher proportion indicates greater frailty [13, 14].

Diffuse large B-cell lymphoma (DLBCL) accounts for more than 30% of non-Hodgkin lymphomas (NHL), and its frequency is higher in those over 60 years of age [15]. Importantly, even in older people, it is a potentially curable disease if chemotherapy is administered at the appropriate doses and if the adverse reactions to treatment are minimized [16]. The efficacy and safety of DLBCL treatment is difficult to predict in older people for various reasons, including changes in the pharmacokinetics and pharmacodynamics of drugs associated with the aging process, the presence of comorbidities, polypharmacy, and social factors. The International Society of Geriatric Oncology (SIOG) recommends CGA with the aim of detecting previously unidentified impairments, predicting adverse reactions related to chemotherapy and overall mortality, and improving cancer treatment selection [17]. The SIOG in an expert opinion considered CGA as an important instrument in evaluating older/frail patients and choosing appropriate therapies in patients with DLBCL [18].

In 2019, the SIOG recommended that CGA be used in patients with prostate cancer, with the aim of being classified into three groups: 'healthy' or 'fit' patients, who should have the same treatment options as younger patients; 'vulnerable' patients who are candidates for geriatric optimization interventions, which if successful could receive standard treatment; and 'frail' patients with major impairments who should receive adapted or palliative treatment [19]. Currently, knowledge is lacking as to which frailty identification/classification tools are most commonly used in older patients living with DLBCL [20]. The objective of this systematic review was to address this knowledge gap.

Material and methods

We searched PubMed, Google Scholar and the Cochrane Database of Systematic Reviews for studies related to patients aged 60 or more years living with DLBCL, published before December 2022. Case reports, editorials, comments, and reviews were excluded. Our study followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [21] (Supplementary Table 1: *see* this article on the journal's website).

Search strategy

The search terms were "Comprehensive geriatric assessment", "elderly", "diffuse large B-cell lymphoma", and "frailty".

Inclusion criteria

We included studies conducted with DLBCL patients aged 60 years or older, where a frailty classification (fit, unfit/vulnerable, frail) had been reported using CGA or any frailty identification tool in the context of prognostication and/or personalization of treatment.

Quality assessment

The quality of observational studies and randomized controlled trials was appraised with STROBE [22] and the Consolidated Standards of Reporting Trials (CONSORT) [23], respectively. Two investigators independently evaluated the quality of the studies.

Data extraction

By using a common data extraction template, all relevant information was independently abstracted from the selected studies by both reviewers. Information was collated on study characteristics including authors' names, country, year of publication, design, sample size, and the frailty identification method used.

Statistical analysis

For each study, the proportions of frail/vulnerable/fit patients were ascertained and averaged across studies.

Results

Sixteen studies were included, with a total of 8,705 DLBCL patients (mean age 75.9 years, 53.8% men). Figure 1 shows a flowchart of these studies. Nine studies were observational (cohort) and the other seven were non-randomized clinical trials (*see* Table I). The 16 studies were conducted in Italy [24–31], China [32–34], Australia [35], Taiwan [36], Norway [37], Mexico [38], and Canada [39].

In 11 studies, patients were classified into three categories (fit, unfit, or frail), while in the other five studies, they were classified into two groups (fit or frail). One study

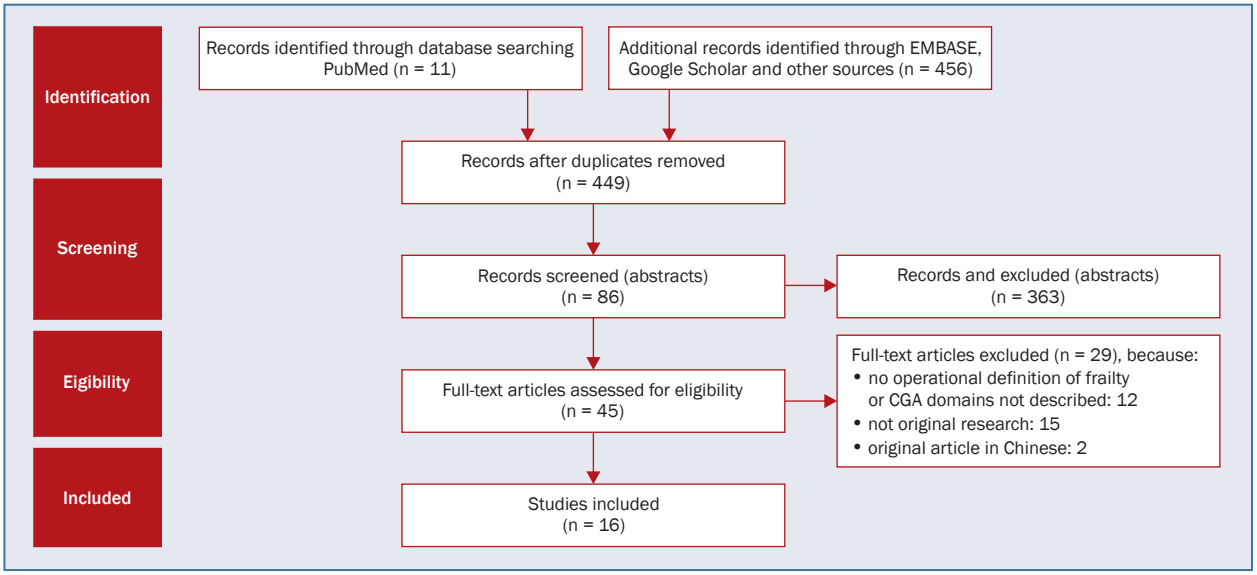

Figure 1. Study screening flowchart; CGA — Comprehensive Geriatric Assessment

Table I. Characteristics of included studies

Study	Country	Type of study	Age (mean)	Sex (male %)	Number of patients	Frailty classification			Quality assessment: STROBE [%]
						Frail [%]	Unfit	Fit [%]	
Zhang et al. (2022)	China	Non-randomized clinical trial	73	52	31	4 (12.9)	10	17 (54.8)	83.3
Vijenthira et al. (2022)	Canada	Cohort	75	57.1	5,527	2,699 (48.8)		2,828 (51.2)	93.3
Xu et al. (2022)	China	Non-randomized clinical trial	80	77	30	24 (80.0)	6	(0)	96.7
Bocci et al. (2022)	Italy	Non-randomized clinical trial	84	64	22	22 (100.0)		(0)	93.3
Merli et al. (2021)	Italy	Cohort	76	50	1,207	221 (18.3)	334	652 (54.0)	90
Isaksen et al. (2021)	Norway	Cohort	79	52	747	228 (30.5)	265	254 (34.0)	90
Bai et al. (2020)	China	Non-randomized clinical trial	69	57.7	78	28 (35.9)	5	45 (57.7)	76.6
Chou et al. (2020)	Taiwan	Cohort	73	57.9	76	27 (35.5)		49 (64.5)	80
Ong et al. (2019)	Australia	Cohort	73	55.8	138	52 (37.7)	29	57 (41.3)	96.7
Storti et al. (2018)	Italy	Non-randomized clinical trial	81	58	45	45 (100.0)		(0)	90
Lastra-German et al. (2018)	Mexico	Cohort	70	42.9	49	20 (40.8)	23	6 (12.2)	83.3
Tucci et al. (2015)	Italy	Cohort	77	52.6	173	66 (38.2)	28	79 (45.7)	90
Merli et al. (2013)	Italy	Non-randomized clinical trial	78	43	318	94 (29.6)		224 (70.4)	90

→

Table I (cont.). Characteristics of included studies

Study	Country	Type of study	Age (mean)	Sex (male %)	Number of patients	Frailty classification			Quality assessment: STROBE [%]
						Frail [%]	Unfit	Fit [%]	
Marchesi et al. (2013)	Italy	Cohort	78	49.32	73	21 (28.8)	28	24 (32.9)	90
Spina et al. (2012)	Italy	Non-randomized clinical trial	75	41	100	13 (13.0)	32	55 (55.0)	90
Olivieri et al. (2012)	Italy	Cohort	74	50.5	91	15 (16.5)	22	54 (59.3)	83.3

STROBE — Strengthening the Reporting of Observational studies in Epidemiology

used the term "superfrail" referring to patients with ADL ≤4; IADL ≤5; age ≥80 years; 1 CIRS grade 3 or >8 CIRS grade 2 [28]. Overall, 41.7% were classified as 'frail', and 39.6% as 'fit', with significant variability across studies (Table I).

The most frequent frailty identification method used was the CGA (simplified: 75%, full: 13%), followed by the physical phenotype (6%) and the cumulative deficits (6%) models. The most common CGA domains used in the classification of frailty were the evaluation of basic activities of daily living (BADLs) (86%), instrumental activities of daily living (IADLs) (63%), comorbidities (81%), and geriatric syndromes (19%). The most commonly used disability tools were the Katz Activities of Daily Living scale (ADL) (81%) [40], and the Lawton Instrumental Activities of Daily Living scale (IADL) (63%) [41]. The most common comorbidity scale was the Cumulative Illness Rating Scale-Geriatric (CIRS-G) (69%) [42] (Supplementary Table 2: *see* this article on the journal's website).

In three studies, the aim was to validate the use of a simplified CGA (sCGA) at diagnosis and to integrate it into a prognostic score for older patients with DLBCL [25, 29, 37]. The study by Merli et al. [25] validated an sCGA model that identified those who were frail, and found that poor results were achieved in this group only if they were treated with rituximab-containing combination chemotherapy. Isaksen et al. [37] validated an sCGA model that managed to identify frail patients, who, when treated with R-CHOP, achieved better survival, without a significant increase in treatment-related mortality. Although full-dose R-CHOP was associated with superior survival in fit patients, it was not better than R-miniCHOP in the unfit and the frail [37]. Tucci et al. validated a CGA model that was able to identify older DLBCL non-fit patients in whom curative treatment was not better than palliation [29]. Lastra-German et al. [38] used modified frailty phenotype criteria, and Vijenthira et al. [39] used a frailty index [43].

Discussion

Our systematic review found that two in five DLBCL patients aged 60 years or older were classified as frail, and an almost equal proportion were classified as fit, most commonly post-application of simplified CGA, which in turn most frequently consisted of disability and multimorbidity scales (ADL, IADL and CIRS-G). The data suggests that the population of older people living with DLBCL has remarkable biological heterogeneity, and that when it comes to treatment, one size most certainly does not fit all.

This means that a geriatric assessment is highly likely to add value in terms of patient optimization, treatment personalization, and prognostication.

Currently, five CGA-based frailty classification schemes have been described in older cancer patients. Three of them classify patients into fit, vulnerable, or frail [5, 44–46]. The Lymphoma Italian Foundation (FIL) has also proposed an sGCA that has three categories (fit, unfit and frail) [47]. This has been used in patients with lymphoma, takes less than 10 minutes to perform, and has been used in the context of treatment options and outcomes in patients with DLBCL [24, 25]. It therefore seems the most optimal method of geriatric assessment devised so far. Ferrat et al. [48] have described a classification system which they call 'latent class typology', which classifies patients into four groups (relatively healthy or 'LC1', malnourished or 'LC2', cognitively and/or mood impaired or 'LC3', and globally impaired or 'LC4'). The performance of four frailty classifications has recently been compared, and the authors concluded that all had good prognostic performance in both older inpatients and older outpatients living with various cancers [5].

Our study found that most studies used sCGA to categorize frailty in older people living with DLBCL, which mostly uses ADL, IADL and CIRS-G; this mirrors the FIL model [25, 29, 49, 50], which consists of evaluating ADL, IADL, chronological age (>80 years vs <80 years), and comorbidities assessed by CIRS-G (adjusted for hematological comorbidities).

The operational criteria for classifying patients as frail are those aged ≥80 years with dependence in multiple ADL (score <6), IADL (score <8), and/or with significant comorbidities (≥1 comorbidity with a score of 3–4, ≥5 comorbidities with a score of 2 [47]. The sCGA FIL model adds the IPI (International Prognostic Index), the Elderly Prognostic

Index (EPI), and hemoglobin levels [47]. Currently, other instruments are validated for use in non-Hodgkin lymphoma patients, among which are the ACA index and IADL--ACA [age, albumin <3.7 g/dL, Charlson Comorbidity Index (CCI), IADL], Geriatric-8 (G8), fTRST (Flemish version of the triage-screening tool), Vulnerable Elders Survey (VES-13), CRASH (Chemotherapy Risk Assessment Scale for High--Age Patients), and CARG-TT (Cancer Aging and Research Group toxicity tool) [47].

In 2021, Tavares et al. [51] published a systematic review on treatment of very elderly (>80 years) patients with DLBCL. They found that of 38 studies (13 retrospective and 25 phase II/III clinical trials), only 16% used CGA as an inclusion criterion or as a guide to therapeutic regimen choice [51].

Our study found that the average prevalence of frailty in older patients living with DLBCL was 42%. Handforth et al. published in 2015 a systematic study of a total of 20 studies evaluating 2,916 older patients with cancer, also finding a prevalence of frailty of 42%. Another finding was that 80% of the studies used CGA as the reference standard for frailty identification, 16% used the phenotype model, and 4% used both CGA and the phenotype model. It should be noted that in Handforth et al.'s study [52], only 10% of patients were living with lymphoma.

Our study has some limitations. The included studies did not elaborate on important aspects of the implementation of CGA, such as the average time required for the evaluation nor which health professionals performed it. Since most of the studies we included implemented sCGA as opposed to full CGA, the time required may be an important practical consideration. Furthermore, our study could not compare different versions of sCGA in their ability to predict clinical outcomes (e.g. adverse events, overall survival, progression-free survival, and adverse drug reactions), and there is scope for future studies to help validate, homogenize and standardize frailty stratification models in geriatric oncology, in such a way that the categorization of patients would be accurate and of high patient and professional value.

In the meantime, the identification of frailty in older DLBCL patients by means of CGA is an opportunity for patient optimization and treatment personalization. More studies are required to validate specific frailty identification instruments in this population.

Article information and declarations

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Conflict of interests
The authors declare no conflict of interest.

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Ethic statement
The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

Supplementary material
Supplementary Tables 1 and 2.

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Pathogenesis of hematological parameters in hypertension

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Abstract

Hypertension is a significant risk factor for cardiovascular disease and is often assessed in clinical settings using reference ranges for various hematological and immunological parameters. This review article specifically focuses on red blood cells, hematocrit, platelet count, white blood cells, lymphocytes, neutrophils, monocytes, neutrophil-to--lymphocyte ratio, monocyte-to-lymphocyte ratio, and platelet-to-lymphocyte ratio in hypertension. It also highlights the pathophysiological aspects of hematological parameters in the pathogenesis of hypertension.

Key words: hematological parameters, hypertension, pathogenesis, red blood cells, white blood cells, platelets

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Introduction

Hypertension poses a significant danger for cardiovascular disorders. If left untreated, it can lead to severe consequences such as sudden cardiac death, atherosclerosis, heart failure, brain hemorrhagic stroke, and renal failure. The occurrence of hypertension is on the increase in both developed and developing countries. The implementation of new guidelines is expected to result in a substantial increase in the number of individuals with hypertension [1]. In clinical settings, reference ranges are commonly employed to assess the state of health and disease by analysing hematological and immunological parameters. These reference ranges can also serve as vital indicators for monitoring the progression of a disease or the effectiveness of treatment. It should be noted that these criteria can vary based on factors such as age, gender, race, environment, and genetic background [2, 3].

The study conducted by Göbel et al. [4] revealed statistically significant associations between mean arterial blood pressure and various measurements such as hemoglobin concentration, hematocrit, and red blood cell count. It has been suggested that whole blood viscosity may act as a mediator in the connection between blood pressure and red cell measurements [5]. Also, Emamian et al. [6] reported that the hematological parameters in individuals with hypertension were higher compared to a control group. This review article specifically only focuses on red blood cells (RBC), hematocrit (Hct), platelet count, white blood cells (WBC), lymphocytes, neutrophils, monocytes, neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) in hypertension. These parameters and their involvement in hypertension are elaborated in Figure 1. Additionally, Figure 2 illustrates the pathophysiological aspects of hematological parameters in hypertension.

To conduct this literature review, multiple databases such as Google Scholar, PubMed, and Science Direct were searched. The search process was concluded on 10 March, 2023. Various key words, including 'hematological parameters', 'hypertension', 'pathogenesis', 'red blood cells', 'white blood cells', and 'platelets' were employed. It should be

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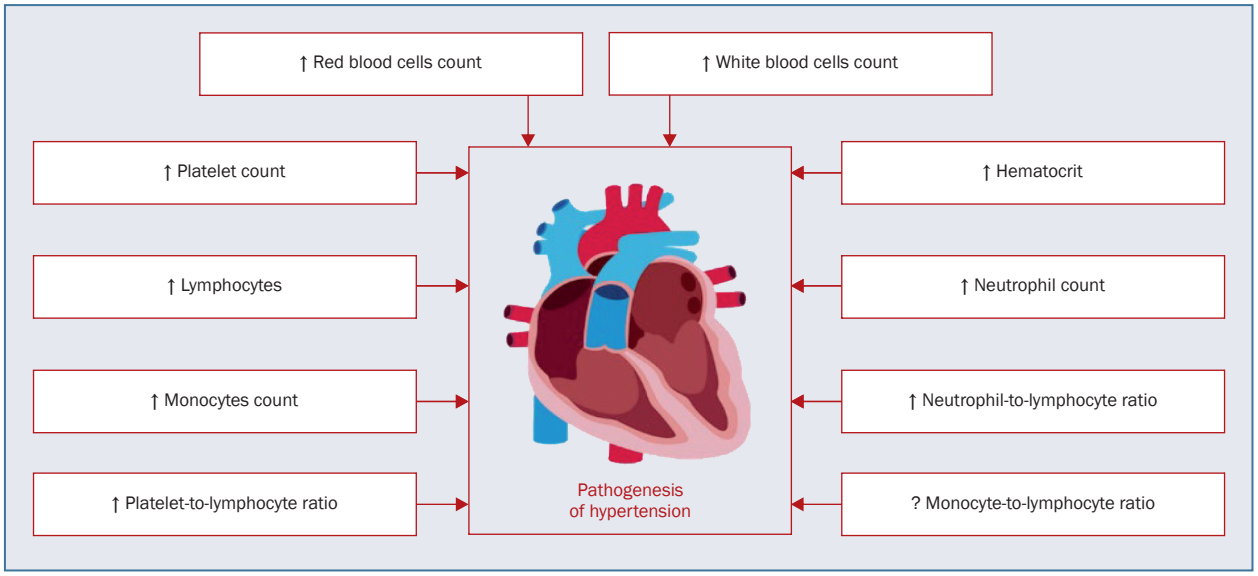

Figure 1. Circulating levels of hematological parameters in hypertensive patients (designed by authors with help of articles); ↑ — increased levels; ? — no study is reported yet on hypertension

noted that the clinical investigations were limited to articles published in English. While the focus was on more recent studies, no specific time limit was set. Furthermore, the reference lists of relevant articles were examined, leading to the discovery of additional related articles for comparison.

Role of major hematological parameters in pathogenesis of hypertension

Red blood cells

Hypertensive men have been shown to exhibit elevated plasma levels of the amino acid asymmetric dimethylarginine (ADMA), which is associated with a reduction in the flexibility of red blood cell membranes [7]. Hypertensive individuals experienced impaired deformability of red blood cells, and this impairment was dependent on their current blood pressure control rather than damage to target organs [8].

The findings from an electron paramagnetic resonance (EPR) study indicated a potentially strong correlation between abnormalities in RBC membranes in hypertension and two factors: hyperresistinemia and heightened oxidative stress. It was observed that reduced fluidity of RBC membranes was associated with elevated levels of plasma resistin and 8-iso-prostaglandin F2, indicating the presence of oxidative stress. Hyperresistinemia was found to be closely linked to abnormal rheological behavior and microcirculation of RBCs, and it appears to contribute to circulatory disorders in hypertensive men, partly through a mechanism dependent on oxidative stress [9].

Hypertension is associated with significant changes in the rheological, mechanical, and biochemical properties of erythrocytes, as well as alterations in blood flow. Several important factors have been observed, including the formation of RBC 'rouleaux' and RBC aggregates, increased blood viscosity, and changes in red blood cell deformability. These hemorheological factors can contribute to the elevation of peripheral resistance and arterial blood pressure, potentially causing or worsening hypertension. Moreover, they might lead to reduced oxygen delivery to tissues, impaired peripheral perfusion, and a decrease in the active exchange surface area in the microvasculature, particularly in complicated cases of hypertension. Studies have shown various abnormalities in hypertensive individuals, such as decreased erythrocyte deformability (measured by Elongation Index), elevated fibrinogen levels, an increased shear rate required to disaggregate erythrocytes, reduced cellular oxygen supply, compromised tissue oxygenation, and impaired microcirculation. These changes could play a role in the pathophysiology and development of arterial hypertension (AH) [10].

When compared to their effects on the aortas of normotensive Wistar-Kyoto (WKY) rats, red blood cells were found to increase tension in isolated aortas of spontaneously hypertensive (SHR) rats during the pre-hypertensive stage. This ability of red blood cells to elevate blood pressure was observed in both WKY and SHR rats at 16 weeks of age. Furthermore, the contraction caused by red blood cells was augmented by removing the endothelium, particularly in SHR rats compared to WKY rats [11].

Hematocrit

To determine hematocrit (HCT), the length of the packed layer of RBCs is divided by the total length of both the cells and plasma. HCT is expressed as a ratio and does not have

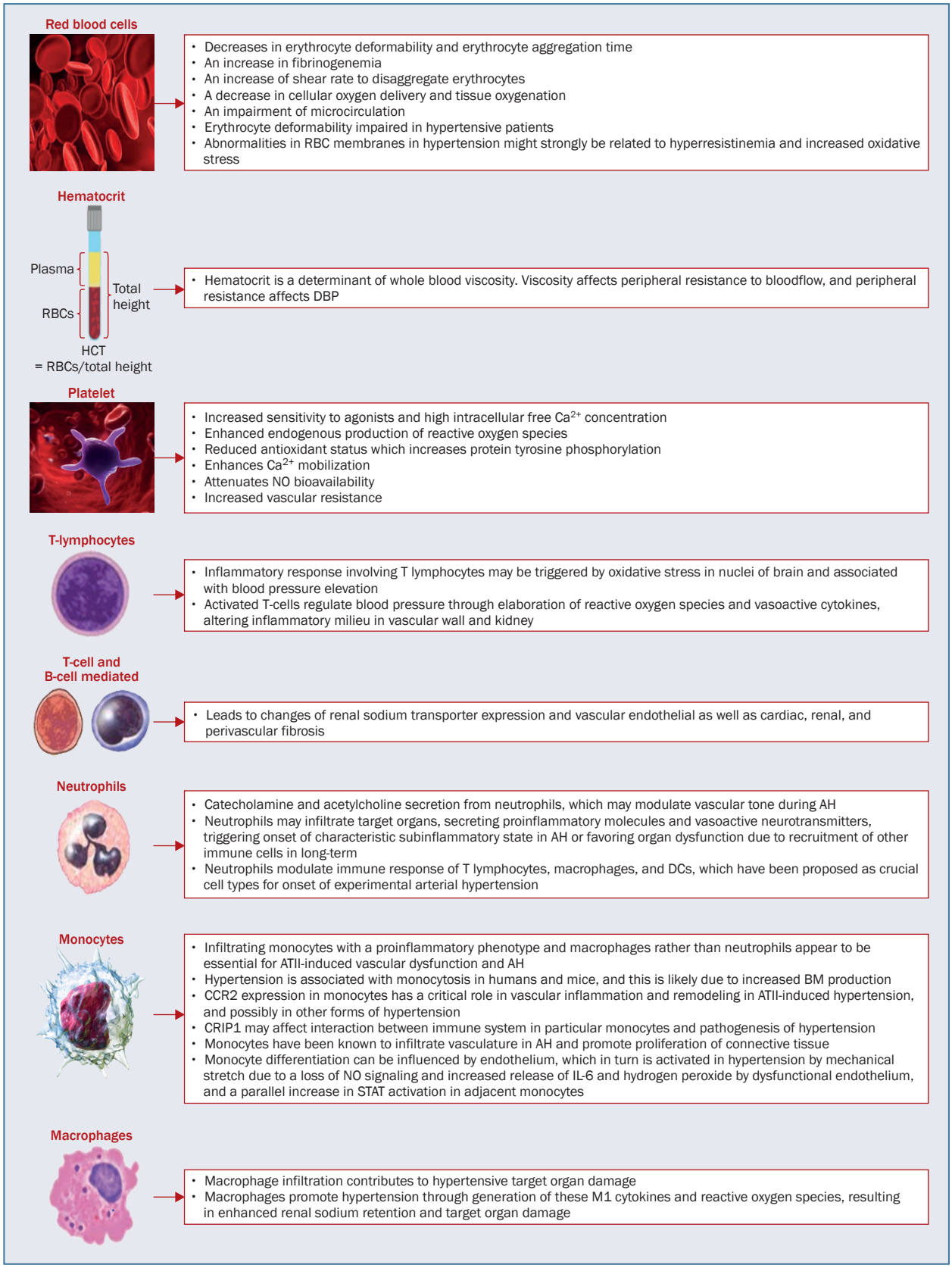

Figure 2. Pathophysiological aspects of hematological parameters in hypertension (designed by authors with help of articles); RBC — red blood cell; HCT — hematocrit; DBP — diastolic blood pressure; Ca — calcium; NO — nitric oxide; AH — arterial hypertension; DCs — dendritic cells; ATII — angiotensin II; CRIP1 — cysteine-rich protein 1; BM — bone marrow; IL-6 — interleukin-6; STAT — signal transducers and activators of transcription

a unit [12]. The significant correlation between blood pressure and hematocrit, a major determinant of blood viscosity, suggests that considerations related to bloodflow characteristics play a role in the long-term regulation of blood pressure [10]. Another study strongly indicated that among these markers, hematocrit independently contributed to the risk of hypertension [6]. Additionally, the exponentiation of multiple logistic coefficients revealed that individuals with hematocrit levels higher by 10 units had a prevalence of hypertension at least twice as high as those with lower levels [13]. Similarly, hemoglobin (Hb) count and HCT were positively correlated with systolic and diastolic blood pressure. In children and adolescents between the ages of 10 and 18, Hb count and HCT showed a positive correlation with both systolic and diastolic blood pressure [14].

Furthermore, Vázquez et al. [15] concluded that acute anemic conditions, although limited, lead to an increase in mean arterial blood pressure during the initial two-hour period. Interestingly, this effect was quantitatively similar to, but opposite to, the acute increase in hematocrit during the same period. In addition, it was discovered that individuals with hypertension who had unilateral renal atrophy due to ischemia were more likely to have a higher hematocrit level compared to those with parenchymal disease caused by pyelonephritis [16].

Platelet count

Platelet activity can play a role in the development of hypertension, as an elevated mean platelet volume (MPV) has been associated with an increased incidence of hypertension, independent of other risk factors [17]. The relationship between homocysteine and blood pressure was found to be stronger in individuals with low platelet counts compared to those with high platelet counts, with platelet counts partially attenuating this relationship [18].

Platelets in individuals with hypertension demonstrate elevated intracellular free calcium (Ca^{2+}) levels and heightened sensitivity to agonists. Furthermore, these platelets show the increased generation of endogenous reactive oxygen species (ROS) and decreased antioxidant capacity, which collectively contribute to enhanced protein tyrosine phosphorylation, augmented mobilization of Ca^{2+}, and reduced availability of nitric oxide (NO). Anomalies in platelet function observed in hypertensive individuals have the potential to guide the development of novel pharmacological strategies for preventing and treating hypertension-related complications associated with platelet hyperactivity [19]. According to Mehta et al., there appears to be a correlation between higher vascular resistance and increased platelet activation in primary hypertension [20].

In cases of prolonged hypertension, there has been shown to be no correlation between MPV levels, the non-dipping pattern of blood pressure (lack of night-time blood pressure decline), and the left ventricular mass index (LVMI) [21]. Compared to the normotensive group, the hypertensive group in a study exhibited a significant increase in both platelet volume and count. Notably, hypertensive individuals who were smokers showed an even greater platelet count compared to non-smokers with normal blood pressure, despite low doses of nicotine not inducing platelet release reaction. This suggests that smoking might contribute to higher platelet counts in hypertensive males [22].

Notably, increased morning blood pressure surge (MBPS) and higher MPV levels have been associated with atherothrombotic cardiovascular events [23]. Similarly, a study conducted by Zhao et al. [24] suggested that certain platelet indices might be utilized for early detection of high blood pressure in adults who have been exposed to prolonged severe platelet index values.

Furthermore, elevated MPV and C-reactive protein (CRP) levels have been implicated as potential reasons for the increased cardiovascular risk observed in individuals with masked hypertension [25]. In a study conducted by Surgit et al. [26], it was observed that patients with resistant hypertension (RHTN) had significantly higher MPV levels compared to controlled hypertensive individuals and normotensive participants. A higher platelet count was causally associated with an increased risk of hypertension. However, further investigations are required to elucidate the underlying biological pathways and pathogenic processes involved [27].

Essential hypertension has been associated with an increased risk of arterial thrombosis. The use of antiplatelet medication has been shown to improve prognosis in hypertensive patients with high cardiovascular risk or established atherosclerotic disease, as platelet activation plays a significant role in the development of thrombotic events. However, the use of antiplatelet therapy in hypertensive patients with modest cardiovascular risk is less certain [28]. Similarly, alpha-blocker or angiotensin-converting enzyme inhibitor (ACEI) monotherapy has been shown to reverse platelet activation observed in patients with essential hypertension. These medications have the potential to prevent platelet activation in individuals with essential hypertension, thereby reducing the occurrence of hypertensive vascular complications [29].

White blood cells

Even after accounting for average 24-hour blood pressure, established risk factors, and target organ damage, a high WBC count remains an independent predictor of cardiovascular morbidity in hypertensive patients [30]. Observational and genetic analysis has revealed a consistent and positive association between lymphocyte count and both systolic and diastolic blood pressure, indicating a potential causal link [31].

In a Japanese population, there was shown a general association between WBC count and the development of

hypertension. Utilizing a high-risk approach based on WBC count may provide enhanced prevention strategies for hypertension in the future [32]. In a predominantly white population, elevated WBC count was found to be associated with the incidence of hypertension in both men and women, regardless of smoking and most traditional cardiovascular risk factors [33]. Correlations between WBC count, neutrophils, and blood pressure readings were only observed in the later stages of hypertension.

Another study was unable to differentiate between individuals with optimal blood pressure (OBP) and high normal blood pressure (HNBP) based on WBC count, suggesting that inflammation may not be a factor in prehypertension. It is also possible that WBC count is not a sufficiently sensitive biomarker [34]. However, the NHANES I Epidemiological Follow-up Study (NHEFS) reported an association between higher WBC count and increased incidence of hypertension in white men, and possibly in older white and black women [35]. In a study conducted by Shi et al. [36], it was found that certain types of circulating leukocytes in hypertensive patients using antihypertensive medications might be linked to left ventricular hypertrophy (LVH).

Lymphocytes

In hypertension, T lymphocytes infiltrate various organs involved in cardiovascular control, including the kidneys and vasculature. Notably, T cell accumulation occurs in the adventitia of the aorta during hypertension. This infiltration of T lymphocytes has been associated with increased collagen deposition, exacerbated stiffness of the aorta, and dysfunction of the endothelium [37]. The contribution of T lymphocytes to hypertension is influenced by their level of activation. Activated T cells produce reactive oxygen species and vasoactive cytokines, which regulate blood pressure by modulating the inflammatory environment in the kidneys and vascular walls. Recent genome-wide association studies (GWAS) have also provided evidence suggesting the involvement of T cells in human hypertension [38].

Additionally, Schiffrin et al. [39] have proposed that oxidative stress in brain nuclei could trigger an inflammatory response involving T cells, ultimately leading to an increase in blood pressure. The initiation of hypertension and the development of target organ damage are both influenced by adaptive immune responses, specifically T-cell and B-cell mediated responses. In the early stages of the disease, activation of adaptive immunity triggers the involvement of both T cells and B cells, leading to the release of pro-inflammatory cytokines and antibodies. These immune-mediated processes contribute significantly to pathological changes. These alterations include modifications in the expression of renal sodium transporters and vascular endothelial cells, as well as the development of cardiac, renal, and perivascular fibrosis. While these pathways have been well studied in animal models, there is still limited information available for humans. Nevertheless, the evidence strongly supports the development of innovative anti-hypertensive strategies that target the processes of adaptive immunity in hypertension [40].

Neutrophils

The current understanding suggests that the involvement of neutrophils in AH is most likely related to vascular injury caused by reactive oxygen species (ROS). However, it is important to consider not only the production of catecholamine and acetylcholine by neutrophils, which can affect vascular tone during AH, but also the adrenergic control of neutrophils. In AH, the presence of neutrophils infiltrating target organs and releasing proinflammatory substances and vasoactive neurotransmitters might contribute to the development of a sub-inflammatory state. This infiltration can lead to prolonged organ dysfunction or the recruitment of other immune cells. Neutrophils can modulate the immune response, affecting T lymphocytes, macrophages, and dendritic cells, which are crucial for the development of experimental AH. However, it is important to note that the exact causal role of neutrophils in AH has not been definitively established. Further research is needed to validate this hypothesis and explore the potential mechanisms underlying the interaction between neutrophils and AH [41]. Also, Krishnan et al.'s study [42] showed that isoLGs (isolevuglandins) play a crucial role in neutrophil migration and NET formation (NETosis) in hypertension, and offer a potential treatment for disorders linked to neutrophil extracellular traps (NET) such as hypertension and its accompanying end-organ damage.

Monocytes

Monocytes play a critical role in the development of hypertension, and there are different types of circulating monocytes in humans, namely classical, intermediate, and non-classical monocytes. The endothelium, which is subjected to mechanical stretch in hypertension, can influence the differentiation of monocytes. This activation is probably influenced by various factors, including the increased release of interleukin-6 (IL-6) and hydrogen peroxide from the dysfunctional endothelium, impaired NO signaling, and signal transducers and activators of transcription (STAT) activation in the nearby monocytes. Interventions aimed at increasing bioavailable NO, reducing IL-6 or hydrogen peroxide production, or inhibiting STAT3 might have anti-inflammatory effects in hypertension and related diseases [43].

Monocytes play a significant role in the immunological activation associated with the development of hypertension. Deletion of monocytes has been shown to prevent experimental hypertension, while macrophages and dendritic cells derived from monocytes promote T cell activation and tissue damage. Carmo et al. [44] revealed that hypertension in both humans and mice is associated with

an increase in monocytosis, possibly due to enhanced production in the bone marrow. This elevation in monocyte levels could lead to immune system activation and increased tissue inflammation. The number of circulating monocytes may serve as a valuable biomarker for inflammation in hypertension [44].

Both animal models and humans with hypertension exhibit activated monocytes within the walls of their arteries. The presence of monocyte chemoattractant protein-1 (MCP-1) regulates monocyte activity through the CCR2 receptor, and has been associated with inflammatory changes in the arterial wall during hypertension. However, the impact of monocyte CCR2 expression on vascular remodeling in hypertension has not been extensively studied. In a study conducted by Ishibashi et al. [45], the role of CCR2 expression in monocytes was investigated in vascular remodeling and inflammation in angiotensin II-induced hypertension, as well as in other types of hypertension. Their findings indicated that CCR2 expression in monocytes significantly influenced vascular remodeling and inflammation in hypertension [45].

The contribution of underlying immune system dysregulation to the development of hypertension is not yet fully understood. However, emerging evidence suggests that macrophage infiltration plays a role in hypertensive target organ damage. The release of chemokines and adhesion molecules by the vascular wall due to vasoactive hormones and high blood pressure promotes the infiltration of macrophages. Furthermore, these factors might directly activate macrophages [46].

The involvement of tissue macrophages and circulating monocytes in the development of hypertension is also not fully understood. A protein called cysteine-rich protein 1 (CRIP1), produced abundantly in immune cells, may play a role in blood pressure regulation through its association with monocytes. CRIP1 mRNA expression in monocytes has been found to be related to blood pressure and to be influenced by proinflammatory changes.

Schweigert et al. [47] found that endogenous hormones, such as angiotensin II, might contribute to the inflammatory processes associated with hypertension, which involve CRIP1-positive circulating and splenic monocytes. These findings indicate that CRIP1 could potentially influence the interaction between the immune system, specifically monocytes, and the pathophysiology of hypertension [47]. These results indicate that hypertensive left ventricular hypertrophy (LVH) patients exhibit inflammation and a proinflammatory monocyte phenotype, characterized by increased expression of pro-inflammatory factors, and decreased expression of anti-inflammatory factors. Irbesartan appears to modulate the inflammatory state and monocyte phenotype in hypertensive LVH patients, which could contribute to its ability to reduce LVH through this previously unknown mechanism [48].

Recent research suggests that infiltrating macrophages, rather than neutrophils and proinflammatory monocytes, play a crucial role in angiotensin II-induced vascular dysfunction and the development of AH. This finding aligns with previous knowledge that monocytes infiltrate the vascular system in AH and contribute to the proliferation of connective tissue [49, 50].

Monocytes play a critical role in the inflammatory process of AH and offer potential targets for the development of antihypertensive medications. These targets include cytokines such as IL-1, IL-6, IL-12, and interferons (IFNs), which are either produced by, or act upon, myelomonocytic cells. Additionally, the MCP/CCR2 axis involved in chemokine signaling presents a promising target to prevent monocyte recruitment, adhesion, and infiltration into the vasculature. Modulating the activity of phagocyte-type NADPH oxidase or antioxidant enzymes is another potential approach. Excitingly, the pleiotropic effects of thrombin inhibition and other advanced anti-thrombotic therapies may also support the anti-inflammatory treatment of hypertension. By reducing the inflammatory burden imposed by myelomonocytic cells, it is possible to alleviate the global disease burden associated with AH [51].

Macrophages and their proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and IL-1, play a crucial role in the development of hypertension. These macrophages contribute to target organ damage and increased renal sodium retention by producing these M1 cytokines and reactive oxygen species, leading to hypertension. Human studies have supported this finding, showing higher levels of these cytokines in monocytes and serum of individuals with hypertension. Modifying macrophage function could potentially serve as a therapeutic approach for patients with resistant hypertension and end-organ damage. It has been observed that broad immune suppression can lead to a decrease in blood pressure in patients with rheumatological diseases, suggesting the potential efficacy of targeting macrophages as a class of therapy for hypertension [52].

Hence, additional research is being conducted to explore the blocking of macrophage functions or cytokines, particularly in patients with hypertension who exhibit M1 macrophage activation and indicators of cardiac or renal damage. Immunomodulation holds potential long-term benefits for these patients, outweighing any short-term risks. To develop more effective immunomodulatory treatments for this widespread disease, pre-clinical investigations should accurately identify the specific subpopulations of myeloid cells involved in hypertension development and its associated consequences. Furthermore, increased expression of transient receptor potential canonical type 3 (TRPC3) channels has been associated with enhanced monocyte migration in individuals with essential hypertension [53, 54].

Neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio

Liu et al.'s study [55] was the first to establish a strong association between higher levels of neutrophil-to-lymphocyte ratio and an increased risk of developing hypertension, providing insight into the underlying mechanisms of hypertension onset. Collectively, these findings indicate that NLR can serve as a useful indicator of organ damage, such as kidney dysfunction, in the hypertensive population undergoing normal health assessments. Moreover, an increase in MLR has been shown to probably be associated with declines in liver or kidney function, particularly in healthy populations [56].

Hou et al. [57] revealed elevated NLR levels in children with hypertension, which exhibited a positive correlation with office blood pressure measurements. Moreover, NLR showed potential as an indicator for evaluating left ventricular diastolic function in children with hypertension [57]. Also, a study by Sun et al. [58] showed that NLR may be useful in identifying the risk groups of older individuals with hypertension and informing treatment plans. When the participants were categorized, another study observed that older males in the higher NLR group tended to have higher blood pressure compared to those in the lower NLR group. However, there were no statistically significant differences observed among the female, younger, and BMI-specific groups [59]. Non-dipper status refers to individuals whose blood pressure does not significantly decrease during night-time sleep compared to daytime levels. It has been found that NLR and PLR can serve as cost-effective and easily accessible indicators of non-dipper status, particularly in individuals with hypertension [60].

Belen et al. [61] stated that compared to controlled hypertension and normotension (NT) patients, NLR and neutrophil count were considerably greater in resistant hypertension (RHT) patients. Increasing drug use and invasive procedures are the current standards of care for treating uncontrolled HT. More research is therefore required to ascertain the importance of the NLR in defining cardiovascular risk, particularly in individuals with uncontrolled HT and those who require intensive treatment and thorough monitoring. Additionally, larger-scale studies should be used to clarify how antihypertensive medication types affect NLRs [61]. Likewise, higher NLR hypertensives have been shown to be more susceptible to atherothrombotic and atherosclerotic events [62].

Platelet-to-lymphocyte ratio

Although the platelet-to-lymphocyte ratio (PLR) was found to be higher in a study group of hypertensive patients, the difference was not statistically significant [62]. A study conducted by Bayrakci et al. [63] indicated that a high PLR in individuals with hypertension might suggest an increased risk of atherosclerosis, and this could potentially have predictive value in the future. In contrast to other findings, patients with non-dipper hypertension exhibit significantly higher levels of NLR and PLR compared to those with dipper hypertension. Furthermore, a PLR above 107, but not NLR, has been found to be a reliable indicator of non-dipper status [64]. Another study also observed that non-dipper hypertensive individuals had significantly higher levels of PLR compared to dippers, suggesting that PLR could serve as a cost-effective and easily accessible biomarker [65].

Conclusions

Red blood cells, hematocrit, platelet count, white blood cells, lymphocytes, neutrophils, monocytes, neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, and platelet-to-lymphocyte ratio all play significant roles in the pathogenesis of hypertension, as explained in Figure 2. There are many other hematological parameters which have not been reported yet, a fact which underscores the need for additional research to elucidate the precise mechanism through which such parameters influence hypertension.

Article information and declarations

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Author contributions

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Conflict of interests

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None.

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Plenary survey on incidence of cardiac complications among transfusion-dependent thalassemia patients

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Abstract

Introduction: Cardiac complications are the leading cause of mortality amongst transfusion-dependent thalassemia (TDT) patients. The multifactorial etiology of cardiac disorders makes their management challenging. Therefore, in addition to evaluating the incidence of heart failure (HF) and pulmonary hypertension (PHT), we assessed the associated factors among 737 TDT patients, aiming to achieve a plenary perspective of their cardiac disorders and relative factors.

Material and methods: In this cross-sectional study, we evaluated the incidence of HF and PHT in 737 TDT patients while considering imperative factors such as endocrinopathies, iron status, and serum vitamin D level.

Results: The incidence of total heart failure and pulmonary hypertension were estimated at 12.3% among participants, although the rate of cardiac iron overload was c.40%. Splenectomy, serum vitamin D, low bone mass, age, gender, hypoparathyroidism, hypogonadism, and diabetes significantly impaired the cardiac function of our patients. In univariate analysis, only the frequency of blood transfusion proved to have a risk effect on left ventricle ejection fraction.

Conclusions: Cardiac iron overload has the highest impact on the incidence of cardiac disorders among TDT patients. We observed significant statistical associations between both HF and PHT with iron chelation regimen, endocrinopathies, splenectomy, serum vitamin D, and total body iron status in univariate analysis. Such results were not statistically significant in multiple logistic regression. However, in clinical practice, their effect could not be ignored. Further studies are required to achieve efficient management of thalassemia patients with cardiac disorders.

Key words: cardiac complications, heart failure, pulmonary hypertension, thalassemia

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Introduction

Nowadays, transfusion-dependent beta-thalassemia patients (TDT) need more medical attention due to increased survival rates and more disease-related complications threatening their quality of life [1]. Cardiac complications, one of the most studied subjects among TDT patients, are still a leading cause of mortality. Diastolic dysfunction, tricuspid regurgitation, pulmonary hypertension, heart failure, and arrhythmias are the most commonly recorded cardiac disorders [2]. In TDT, as in many other disorders such as osteoporosis and endocrinopathies, cardiac complications are triggered by iron overload as a result of frequent blood transfusions [3]. Despite iron chelation therapy and transfusion to improve anemia, cardiac complications still develop [4]. Heart failure (HF) is described as impaired ventricle function that results in decreased cardiac output. Therefore, measuring left ventricle ejection fraction (LVEF) is considered an appropriate parameter to detect HF [5, 6]. Pulmonary hypertension (PHT), another common cardiac complication of TDT, is a hemodynamic condition and is diagnosed when pulmonary artery pressure (PAP) is more than 20 mm Hg. The gold standard

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measurement of PHT is via right heart catheterization. However, this method is invasive, and transthoracic echocardiography is a favored method of detecting PHT probability. As a result, when PHT is suspected via echocardiography, further investigation such as cardiac magnetic resonance (CMR) help establish a definite diagnosis [7].

The multifactorial nature of the aforementioned cardiac disorders necessitates the evaluation of possible associated factors. As such, iron chelation regimen, splenectomy, and bone mass are associated factors that are still assessed in cardiac complications in addition to gender, age, amount of transfusion, vitamin D serum level, hemoglobin, and others. Measuring LVEF and assessing PH are precise factors for monitoring cardiac function. Assessment of cardiac disorders is advised via annual electrocardiogram, echocardiography, and T2* cardiac magnetic resonance (CMR) among thalassemia patients to provide better management [8]. CMR even provides predictive assessment for cardiac complications [9–13].

Below, we have compiled a review concerning HF and possible PHT by assessing 737 TDT patients. As well as reporting their incidence, we have focused on possible associated factors in addition to finding any correlation between low bone mass and cardiac complications, to determine their exact role to provide more accurate guidelines for assessing cardiac complications.

Material and methods

Patients

Seven hundred and seventy-eight transfusion-dependent thalassemia patients from the Dastgheib Comprehensive Thalassemia Center in Iran were enrolled in this historical cohort from September 2021 to August 2022.

Beta thalassemia was confirmed via hemoglobin electrophoresis, and patients were deemed transfusion-dependent if their pre-transfusion hemoglobin level was 9 g/dL. Those aged 16 or over with regular blood transfusions were included. Patients with a poor cardiology follow-up, a bone marrow transplant, those with active hepatitis B or C, human immunodeficiency virus (HIV) infection, liver cirrhosis, congenital cardiac complications, or incomplete medical records were excluded. In total, 41 patients were excluded and 737 participants remained in the study. Patients were on different iron chelation therapies (ICT) based on their total body iron and cardiac status.

We determined four groups of ICT regimens for our patients. The classifications were as follows: Group 1 patients used deferoxamine (DFO) with the dosage of 30–50 mg/kg daily 5–7 nights/week via a subcutaneous infusion pump; Group 2 used deferiprone (DFP) tablets with a dosage of 75 mg/kg daily; Group 3 (n = 71) took deferasirox (DFX) oral chelator with the dosage of 20–40 mg/kg daily; and Group 4 patients were prescribed a combination regimen of either DFP and DFO in the abovementioned dosages, or a combination of DFO and DFX. Patients who were suffering from low bone mass or vitamin D deficiency were prescribed vitamin D 50,000 IU weekly supplements for 6–8 weeks. Those with hypoparathyroidism were on calcitriol (0.25–2.0 µg/day). Levothyroxine was prescribed for TDT patients with hypothyroidism by an endocrinologist during their annual visit. Furthermore, the patients with low bone mass were on either alendronate 70 mg weekly or zoledronic acid in a 4 mg intravenous infusion over 45 minutes twice a year.

We collected data regarding splenectomy status, blood transfusion frequency, and endocrine status.

Splenectomy was considered when symptomatic splenomegaly, an increased amount of blood transfusion, impaired growth status, and thrombocytopenia were present.

Written informed consent was obtained from each individual, or their legal guardian, to participate in this study. This study was approved by the local Ethics Committee.

Cardiac assessment

An annual echocardiography was done by the same expert cardiologist, determining LVEF and PAP. Heart failure was considered if LVEF was below 50%. In addition, T2* magnetic resonance imaging (MRI) of the liver and heart (SIMENS, Germany, Avanta, 1.5 Tesla) was done for all patients, and iron loading was categorized as follows: cardiac T2*MRI; normal: >20, mild: 14–20, moderate: 10–14, or severe <10.

Biochemical laboratory data

Based on our center's routine protocol, 5 mL of venous blood was taken after 8 hours of fasting from each patient by a technician. Serum 25-OH vitamin D and ferritin levels were measured using electrochemiluminescence methods with Cobas 411 (Roche, Germany). Serum ferritin level was measured every three months, and hemoglobin level was assessed before and after blood transfusions. The last three documented hemoglobin and ferritin values were considered in the data analysis.

Bone mineral densitometry

Lumbar spine (L1–L4) and right femoral neck bone mineral density (BMD) were measured using the Hologic system dual energy X-ray absorptiometry (DXA) (Discovery QDR, USA). Data from DXA, which was obtained from the US Centers for Disease Control's National Health and Nutrition Examination Survey (NHANES), was used to interpret BMD Z-scores and normative data. Low bone mass (LBM) was diagnosed based on the definition of the International Society for Clinical Densitometry (ISCD) of a Z-score of −2 or lower as 'below the expected range for age' [14]. Based on the measurements of 15 patients, the coefficient of variation was 0.5% for the lumbar spine and the femoral neck in our center.

Associated factors

A form filled out by an expert asked the patients subjectively to classify their physical activity into the three groups suggested by the American College of Sports Medicine: no physical activity, or one hour of physical activity less than three times a week, or at least one hour of physical activity more than three times a week. Body mass index (BMI) was measured and calculated by a trained health professional. Height was measured by a standard wall-mounted meter and rounded to the nearest 0.5 cm. Weight was assessed via a standard scale (Seca, Germany), while patients were wearing light clothing with no shoes. BMI was calculated using the standard formula BMI (kg/m^2) = weight (kg)/ /[height (m^2)] and classified into four groups: underweight (<18.5), healthy (18.5–24.9), overweight (25.0–29.9), or obese (>30) [15, 16].

All patients were prescribed to take calcium 500 mg and vitamin D 400 IU supplements, daily. Patients with vitamin D deficiency received a weekly 50,000-unit vitamin D pearl for eight weeks. Liver iron load classification was: normal (>6.3), mild (2.8–6.3), moderate (1.4–2.7), or severe (<1.4). Serum ferritin level was classified as mild (serum ferritin <1,000 ng/mL), moderate (serum ferritin 1,000–2,500 ng/mL), or severe (serum ferritin >2,500 ng/ /mL) [17].

Patients were classified into three groups according to their serum 25(OH) vitamin D level: sufficient (>50 nmol/ /L), insufficient (30–50 nmol/L), or deficient (<30 nmol/L) according to the Institute of Medicine (IOM) [18].

Statistical analysis

Data analysis was performed by SPSS software version 17 (SPSS Inc., Chicago, IL, USA). Descriptive results are presented as mean, standard deviation, frequency, and percentage. Correlation between quantitative variables was done by the Pearson Correlation test. Comparison of quantitative variables was done by student *t*-test between two groups and by ANOVA test among different groups. Qualitative variables were compared by Chi-square test among different groups. Variables with p value less than 0.2 in univariate analysis were entered into multivariate analysis. Multiple logistic regression analysis was done by the Enter method. P-values of less than 0.05 were considered to be statistically significant.

Results

The cardiac status of 737 TDT patients with a mean age of 28.02 ± 9.36 years was assessed over the course of 12 months of study. Gender distribution was almost equal (51% female) and patients' hemoglobin levels were 9.37 ± 1.17. The general characteristics of the studied patients are set out in Table I.

Table I. General characteristics of studied transfusion-dependent thalassemia patients

Variables	Value
Age (y) (mean ± SD)	28.02 ± 9.36
Gender n [%]:	
• female	376 (51.01)
• male	361 (48.99)
Splenectomy, n [%]	276 (37.4)
Splenectomized period [y] (mean ± SD)	19.09 ± 10.18
Blood transfusion/year	19.1 ± 6.66
Low bone mass [%]	59.8
Heart failure	38 (5.2)
Last 3 hemoglobin levels [g/dL] (mean ± SD)	9.7 ± 1.04
Last 3 serum ferritin mean levels [ng/mL] (mean ± SD)	3,027.21 ± 2,690.86
Mild [%]	26.7
Moderate [%]	31.6
Severe [%]	41.7
Physical activity [%]:	
• group 1	(16.7)
• group 2	(48.8)
• group 3	(34.5)
Bisphosphonate therapy, n [%]:	
• alendronate	154 (20.9)
• zoledronic acid	128 (17.4)
Cardiac complications, n [%]	91 (12.3)
Diabetes, n [%]	(81) 10.9
Hypoparathyroidism, n [%]	(67) 9
Hypothyroidism, n [%]	(35) 4.7
PHT, n [%]	(88) 11.9
Heart failure, n [%]	38 (5.2)
LVEF (mean ± SD)	58.89 ± 5.37
Vitamin D (mean ± SD):	27.77 ± 20.68
• <50 ng/mL [%]	86.8
• >50 ng/mL [%]	13.2
Cardiac T2 MRI (mean ± SD)	23.03 ± 11.06
Classification [%]:	
• normal	60.1
• mild	14.4
• moderate	9.5
• severe	16
Liver T2 MRI (mean ± SD)	6.58 ± 6.24
Classification [%]:	
• normal	28.6
• mild	49.5
• moderate	21.7
• severe	0.2

SD — standard deviation; PHT — pulmonary hypertension; LVEF — left ventricular ejection fraction; MRI — magnetic resonance imaging

Pulmonary hypertension

Overall cardiac complications based on heart failure and pulmonary hypertension were reported in 12.3% of patients, with a heart failure rate of 5.2%. It should be kept in mind that some patients suffer from both cardiac disorders.

Pulmonary hypertension (PHT), with a prevalence of 11.9%, was considered and assessed as another cardiac complication by analysis of possible associated factors. Splenectomy (p = 0.006), the number of transfusions/ /year (0.029), and physical activity (p = 0.034) were significantly related to PHT.

Multiple logistic regression with the Enter method was used to determine independent factors associated with cardiac complications. Variables with a P value of less than 0.2 in univariate analysis were entered into the regression model. The only significant covariate appears to be the number of transfusions per year with LVEF [p = 0.046, 95% odds ratio = 1.13 confidence interval (CI): 1.002–1.28]. ICT was also assessed in patients with heart failure and PHT, although the results were insignificant, and patients on a combination regimen had higher mean LVEF and lower incidence of PHT.

Discussion

In this cross-sectional study, we found 12.3% cardiac complications among 737 TDT patients, of whom 88 had possible PHT and 38 had suffered from HF. Regarding iron loading, almost half the patients had normal T2 MRI heart, but 40% had severe iron overload based on their serum ferritin level. Vitamin D serum level, splenectomy, serum ferritin, age, diabetes, hypoparathyroidism, and hypogonadism have been proven to statistically play a significant role. However, a regression analysis test did not confirm any of these latter-named factors to be significantly related.

Assessing the cardiac status of TDT patients is a continuous and mandatory undertaking, considering that it is a leading cause of mortality. Koohi et al. [2] reported a prevalence of cardiac complications at 42% with a cardiac iron overload of 25% among 26,893 beta-thalassemia major patients.

We focused on heart failure and pulmonary hypertension as cardiac complications. The prevalence was one-quarter of that found in the aforementioned large meta-analyses, but cardiac iron overload was almost twice as high. The differences between these figures could be explained by differences in the sizes of the studied populations; in addition, we must bear in mind that patients with cardiac iron overload are prone to develop cardiac complications [2]. There were several patients with cardiac iron overload in the region from which the patients studied by the authors of the present study came, similar to reports by Carpenter et al. [19], Aessopos et al. [20], and Ngim et al. [21], which highlight the importance of the region in this regard.

The multifactorial nature of TDT patients' cardiac complications is of interest to physicians regarding the associated factors. Cardiac iron overload is the main proven issue in inducing cardiac complications, which counts as a predictive criterion as well [22]. Of the indices revealing body iron status in TDT patients, we observed cardiac T2 MRI had the most association with relevant factors. We also observed patients with a higher cardiac iron load to be mostly combined ICT. The latter point is a result of following T2 MRI as an index of determining suitable ICT; in cardiac complications, combination therapy can provide better cardiac outcomes [23]. No significant correlation between ICT and cardiac T2 MRI (p = 0.001) was observed with the serum ferritin, liver T2 MRI or LVEF. This result could suggest that cardiac T2 MRI could be the most suitable and sensitive index for choosing an ICT regimen. Kwiatkowski et al. [24] provided a survey regarding the iron burden of thalassemia patients, and their results aligned with our current study.

On another iron overload-related issue, we found a significant correlation between the number of transfusions/ /year and PHT. In line with previous surveys, this result is understandable given that those with more frequent blood transfusions would suffer more from iron overload-related complications [25], although an insignificant number of patients with PHT were mostly on combined ICT regimens.

Alongside cardiac T2 MRI and iron burden, splenectomy appeared to play a prominent role in cardiac complications as well. The significant correlation between lower LVEF and a high rate of PHT and cardiac iron load with splenectomy is another concern regarding the cardiology status of TDT patients. Splenectomy is recommended only where necessary. In a previous study regarding endocrine disorders, we looked at the risk effect of splenectomy in developing or compromising low bone mass and endocrinopathies.

Now, given our current results, and based on previous and recent studies, we posit splenectomy as a serious predisposing factor in the cardiac status of TDT patients [21, 26]. Derchi et al. [27] reported ferritin and splenectomy as serious risks for developing cardiac complications in TDT patients in a study that included roughly half of our population. We reached such a conclusion as well, but serum ferritin was significantly associated with LVEF and cardiac T2 MRI.

Previously at the Shiraz University of Medical Sciences, our colleagues determined that serum ferritin could be an alternative index for determining iron status if T2 MRI was not available [28]. Based on our results, we suggest that relying on serum ferritin could provide a preliminary assessment, but might lead to missing several associated factors. Hiradfar et al. [29] conducted a study on the relevance of vitamin D serum level and cardiac T2 MRI, and followed LVEF changes of their 16 TDT patients following vitamin D treatment: improvement turned out to be significantly

related. Subsequently, we analyzed serum vitamin D levels with LVEF and cardiac T2 MRI, proving a significant correlation. Such a result was not obtained through serum ferritin and liver T2 MRI. Vitamin D deficiency impairs the myocardium by increasing serum parathyroid hormone, leading to heart failure. Despite close endocrinology monitoring, only 13.2% of our patients had optimal serum vitamin D levels, which highlights our patients' compliance and adherence, and reinforces the need for closer monitoring and follow-up to improve cardiac status, in addition to other vitamin D related endocrinopathies such as low bone mass and hypoparathyroidism.

Regarding endocrinopathies, later disorders as well as hypogonadism and diabetes were significantly associated with LVEF. Diabetes is a proven risk factor for cardiology status, regardless of whether or not there is an underlying disease. However it also happens to be a prominent risk factor in the cardiac status of TDT patients [30]. The negative correlation between LVEF and endocrinopathies calls for closer and more intensive endocrinopathy management among TDT patients with cardiac complications. Since the prevalence of endocrine disorders is more than 80% according to many surveys [3], it could prove challenging to provide acceptable management. We determined that LBM was the most prevalent endocrine disorder in TDT patients in our center, and found it adversely affected LVEF.

The risk of osteoporosis in cardiovascular disease is well established [31], yet the association of low bone mass and cardiac complications in TDT patients has been understudied. The basic etiology of both disorders remains iron overload, but there are differences as to when they developed. LBM can deteriorate the cardiac status of TDT patients. Kyriakou et al. showed that severe cardiac iron status is correlated with low bone mass [32]. We have determined a correlation with heart failure and we suggest the need for intensive bisphosphonate therapy for patients with both low bone mass and heart failure. Following the latter correlation, we evaluated the possible association of bisphosphonate therapy and cardiac status, which revealed no specific result. However, those who were taking zoledronic acid had more acceptable LVEF, so further assessments would provide more accurate results. Like many other TDT-related complications, age and gender were related to cardiac complications. As age increases, LVEF decreases significantly and males appeared to have more cardiac complications than females in our study, something which has previously been reported [33]. Therefore, closer cardiac observation is advisable in male TDT patients.

The fact that regression analysis did not provide any significant correlation could be explained by the multifactorial etiology of cardiac complications in TDT patients which calls for more comprehensive and prospective studies. Our study was conducted in a comprehensive thalassemia center on a large population. Our consideration of important associated factors counts as a prominent strength. Despite this, we acknowledge limitations such as a lack of data availability on arrhythmias and the fact that the study was retrospective.

A larger multi-center study is strongly recommended to provide more accurate data while considering more associated factors to deliver improved management guidelines.

Conclusion

We believe that 18 years of cardiology follow-up has led to lower cardiac complications in our center's patients. But the high rate of iron overload is an alarming fact that through data analysis was significantly related to the incidence of HF and possible PTH. This requires more thorough follow-up on the ICT regimen and patient compliance.

The clinical experience of our hematologist and cardiologist also implies that managing other associated factors such as endocrine disorders, splenectomy rate, and serum vitamin D level lowers the rate of cardiac disorders, and therefore the mortality rate.

Article information and declarations

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Author contributions

HB — main author, design of the study. SK — edited and prepared the manuscript, and was cardiologist involved with our participants. SH — main analyst, provided results, helped with editing. ORZ — helped design of the study, gathered data, edited manuscript.

Conflict of interests

The authors declare no conflict of interests.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Patient consent statement

A written consent form was obtained from all patients or their legal guardians.

Ethic statement

The study was approved by the local Ethics Committee of Shiraz University of Medical Sciences.

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ORIGINAL RESEARCH ARTICLE

VIA MEDICA

Early mortality, kidney failure, and venous thromboembolism in patients with multiple myeloma: a single-center analysis

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Abstract

Introduction: Our objectives were to assess early mortality, the prevalence of kidney failure, and venous thromboembolism (VTE), and to assess overall survival (OS), in patients with multiple myeloma (MM).

Material and methods: A retrospective analysis of clinical and laboratory parameters of 413 patients with MM treated between 2006 and 2017.

Results: The early mortality rate in the study group was 13% (57 of the 413 patients). Mortality rates were higher in men [odds ratio (OR) = 1.4] (p = 0.015), patients with kidney failure (OR = 9.1) (p = 0.001), and patients with significant proteinuria and immunoglobulin A secretion (OR = 1.3). Early mortality was not associated with age, lactate dehydrogenase levels, or hemoglobin levels at diagnosis. Patients with kidney failure at diagnosis of MM had lower total protein levels (p <0.001) and higher proteinuria levels (p <0.001) than the remaining patients. The 5-year OS in patients with kidney failure was 20% vs. 50% in those without kidney failure (p <0.001). VTE was reported in 38 patients (10.7%). There was no association between VTE and the patient's age, kidney failure, urinary protein levels, type of monoclonal protein, stage of MM according to the International Staging System, or type of induction therapy. The median OS in the study group was 4.08 years. There was no correlation between VTE and OS in patients undergoing autologous hematopoietic stem cell transplantation.

Conclusions: The use of novel drugs with a different mechanism of action in the treatment of MM has led to an improvement in survival rates, with an increase in median OS from 3–4 years to 5–7 years over the past 10 years. Even so, it is estimated that 25% of patients still die within two years after diagnosis.

Key words: early mortality, kidney failure, venous thromboembolism, overall survival, multiple myeloma

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Introduction

Multiple myeloma (MM) remains an incurable disease, although novel drugs with a different mechanism of action have considerably improved survival rates. Over the past 10 years, median overall survival (OS) has increased from 3–4 years to 5–7 years. Nevertheless, it is estimated that 25% of patients die within two years after diagnosis. In

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50–70% of patients, median survival is 5 years or longer, depending on response to treatment, treatment tolerance, and the possibility of using high-dose chemotherapy with autologous hematopoietic stem cell transplantation [1].

The rate of early (<6 months from diagnosis) mortality ranges from 10% to 14%, and still constitutes a significant challenge in clinical practice. Risk factors for early mortality include the patient's age, comorbidities, cancer stage, type of treatment, and biological characteristics of the disease. The identification of risk factors for early death might help reduce mortality rates and improve long-term outcomes of patients with MM [2, 3].

Kidney failure occurs in 50% of patients with MM, and is one of the most significant predictors of shorter survival. However, the median survival of patients with kidney disease in whom kidney function improved after treatment is similar to the median survival of patients with normal creatinine levels and estimated glomerular filtration rate at baseline. Bortezomib remains the first-line drug for the treatment of patients with MM and kidney failure. However, the use of immunomodulatory drugs (IMIDs) with dose reductions depending on creatinine clearance, or the use of monoclonal antibodies (anti-CD38, anti-BCMA, and anti-SLAMF7) without dose adjustments, may also be beneficial in this population [4–6].

Coagulation dysfunction in patients with MM has a complex pathogenesis. It develops due to plasma factors and platelet cell dysfunction, manifesting as bleeding and/or thromboembolic complications. Numerous factors increase the prothrombotic potential of plasma cells, including enhanced factor VII and von Willebrand factor activity, high P-selectin and fibrinogen levels, hyperfibrinolysis, acquired protein C resistance, reduced protein S levels, increased tissue factor and vascular endothelial growth factor expression, and increased thrombin formation and thrombin-activatable fibrinolysis inhibitor activity.

Risk factors for thrombosis are as follows: hyperviscosity syndrome; kidney failure; increased C-reactive protein levels; changes in the rheological properties of blood due to the presence of monoclonal protein; hypercalcemia; polychemotherapy regimens; treatment with IMIDs, anthracyclines, corticosteroids, or recombinant erythropoietin; age; immobilization; kidney failure; active infection; genetic predisposition; comorbidities; and previous surgery [7].

The lowest risk of thrombosis has been shown for monotherapy with IMIDs (<5%). The risk is higher in patients receiving IMIDs in combination with high-dose dexamethasone, and ranges from 11.5–26% [7]. The addition of doxorubicin increases the risk of thrombosis to 58% [7]. Zangari et al. [8] showed that the risk of thromboembolic complications is lower in patients treated with IMIDs and bortezomib vs patients treated with IMIDs alone. They suggested that bortezomib may have antihemostatic effects, thus reducing the high prothrombotic potential of IMIDs. This indicates that newly diagnosed patients referred for a high-dose chemotherapy regimen with bortezomib and IMIDs as induction therapy may benefit not only from the high probability of achieving a response to treatment, but also from a lower risk of thrombosis [8].

The objectives of this study were to assess the rates of early mortality (<6 months after diagnosis) as well as risk factors for early mortality in patients with MM, the prevalence of kidney failure and its effect on survival, and the prevalence of venous thromboembolism (VTE) and its association with selected parameters such as age, cancer stage according to the International Staging System, monoclonal protein class, and type of treatment, as well as to assess OS in patients with MM.

Material and methods

Characteristics of study group

This retrospective study included 413 consecutive patients with MM treated at the Department of Hematology in Rydygier Hospital in Kraków, Poland, between 2006 and 2017. The study group included 234 women (56.7%) and 179 men (43.3%) with a mean age of 66.9 years (range 27–89 years). All patients underwent diagnostic tests for MM. Moreover, cancer stage and prognostic factors were assessed. Patients received causative treatment as well as supportive therapies such as intravenous bisphosphonates, blood product transfusions, erythropoietin, pain medications, and clinical psychological counseling.

Clinical and laboratory parameters and associations assessed in study

The cause of death and early mortality (defined as death within <6 months from diagnosis) was assessed using a logistic regression model.

Kidney failure at diagnosis was defined as a creatinine level higher than 177 μmol/L or creatinine clearance lower than 40 mL/min/m^2 according to the 2014 International Myeloma Working Group criteria. Associations between kidney failure and total protein and urinary monoclonal protein levels at diagnosis were assessed. In addition, the association between kidney failure at diagnosis and OS was assessed.

A venous thromboembolism was diagnosed on the basis of clinical symptoms confirmed by compression ultrasound or computed tomography angiography.

OS rates (OS defined as time from diagnosis to death or being lost to follow-up) and time to progression (defined as time from the first and subsequent treatment lines to disease progression) were also assessed.

Statistical analysis

Qualitative variables such as selected laboratory parameters were presented as mean and standard deviation

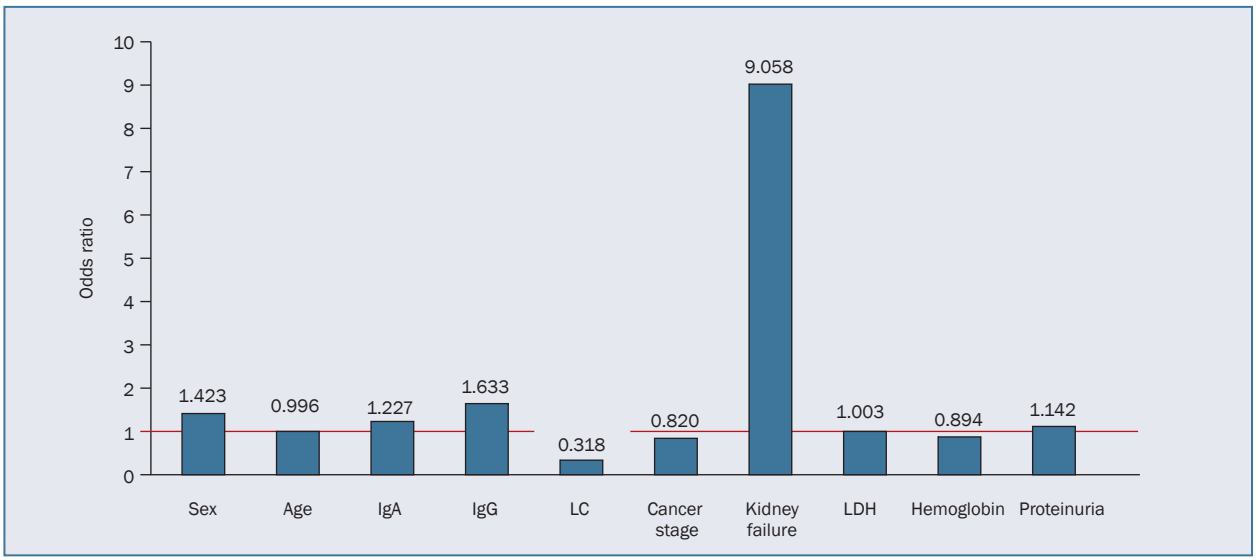

Figure 1. Odds ratio in logistic regression model for predicting early mortality; IgA — immunoglobulin A; IgG — immunoglobulin G; LC — light chains; LDH — lactate dehydrogenase

(SD), median, and minimum-maximum values. Variables were compared between subgroups divided according to risk, treatment, or selected clinical parameters (such as disease severity) using a nonparametric Mann-Whitney test for comparisons between two variables and a Wilcoxon test for comparisons between two or more variables.

Ranked or qualitative variables were presented as number and percentage of patients. Survival analysis was used to compare OS depending on selected risk factors, type of treatment, treatment outcomes after each line of chemotherapy, and selected clinical parameters. The independent χ^2 test was used in this subgroup to assess OS depending on selected factors as well as to assess the effect of selected risk factors on OS shorter or longer than 5 years. The Kaplan–Meier method was used to assess survival curves.

Results with a *p* value of 0.05 or lower were considered significant. Statistical analysis was conducted using Statistica 13 PL (StatSoft, Kraków, Poland).

Results

Causes of early death

In our study, death was reported in 204 of the 413 patients, including 57 early deaths (27.9%). The most common causes of death were infectious complications, progression of primary disease, and multi-organ failure. The early mortality rate in the study group was 13% (57 of the 413 patients). Mortality rates were higher in men [odds ratio (OR) = 1.4] ($p = 0.015$), in patients with kidney failure ($p = 0.001$), and in patients with significant proteinuria and immunoglobulin A secretion (OR = 1.3) (Figure 1).

Logistic regression analysis of ORs showed that kidney failure was a significant predictor of early death ($p = 0.004$). Kidney failure was associated with a 9-fold higher risk of early death (OR = 9.1) (Figure 1).

Early mortality was not associated with the patient's age, lactate dehydrogenase levels, or hemoglobin levels at diagnosis (Figure 1).

Kidney failure

Total protein levels in patients with kidney failure were higher than in patients without kidney failure ($p < 0.001$). The presence of kidney failure was associated with urinary protein levels ($p < 0.001$). Urinary protein levels lower than 1 g/L were noted in 69.73% of patients without kidney failure vs. 26.76% of patients with kidney failure. Despite higher proteinuria occurring in patients with kidney failure, there were not any amyloidosis cases (assessed by Red Kongo staining of bone marrow).

Kidney failure was associated with lower OS ($p < 0.001$). The 5-year OS rate in patients with kidney failure at diagnosis was 20% vs. 50% in those without kidney failure (Figure 2).

Venous thromboembolism

A VTE was reported in 38 patients (10.7%). The presence of a VTE was not associated with the patient's age, kidney failure, urinary protein levels, type of monoclonal protein, stage of MM according to the International Staging System, or the type of induction therapy (standard chemotherapy, bortezomib, thalidomide).

Overall survival

The median OS in the study group was 4.08 years (Figure 3).

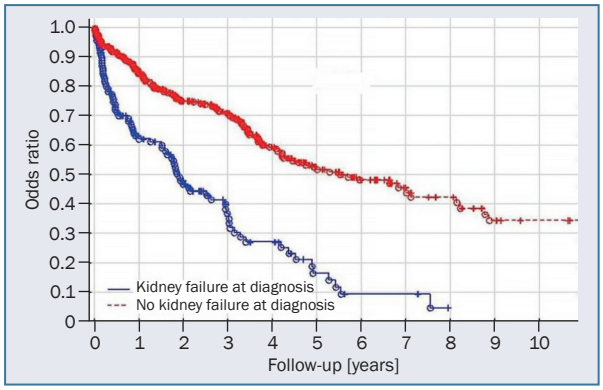

Figure 2. Overall survival rates depending on presence of kidney failure at diagnosis of multiple myeloma; p <0.001

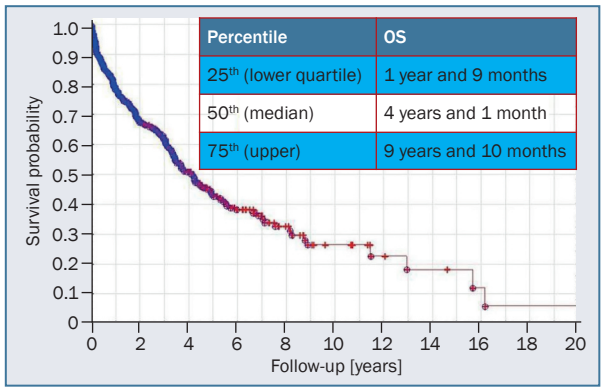

Figure 3. Overall survival (OS) in whole study group

Discussion

Recent years have seen significant advances in the treatment of MM due to the introduction of novel therapies, including IMIDs, proteosome inhibitors [1], as well as monoclonal antibodies, signaling pathways inhibitors, and CAR T-cell therapy (immune therapy with genetically modified autologous T cells) [9].

Our study showed that kidney failure and significant proteinuria are associated with lower OS. Early mortality rates were significantly higher in men, in patients with kidney failure, and in patients with significant proteinuria. These findings are in line with literature data [2, 3]. It is noteworthy that in our study, kidney failure was associated with a 9-fold higher risk of early death. Therefore, efforts should be made to restore normal kidney function, and patients should be referred for renal replacement therapy early enough to prevent further kidney damage during initial therapy, and to increase the chances of improving kidney function. Infectious complications are the most common direct cause of death in MM. Therefore, prevention of bacterial infections (with sulfamethoxazole + trimethoprim or levofloxacine) as well as of viral infections is important [3].

Venous thromboembolism, either deep vein thrombosis or pulmonary embolism, is a common complication of cancer, and is associated with a higher mortality risk. Cancer-related risk factors for VTE include the type of cancer, chemotherapy, the surgical treatment, the use of central venous catheters, older age, and immobilization [10]. The approach to VTE treatment has evolved in recent years, and randomized clinical trials provide evidence to guide clinicians in making appropriate decisions on treatment [11]. The risk of VTE is 4- to 7-fold higher in patients with cancer vs those without cancer, with an annual incidence of up to 15% [12, 13]. In our patients, VTE was reported in 10.7% of cases. The risk of VTE in patients at an older age, with comorbidities, with more advanced disease, and those treated with IMIDs was similar to that in the remaining patients, which may be explained by the widespread and regular use of antiplatelet drugs (acetylsalicylic acid), low-molecular-weight heparin (LMWH), or non-vitamin K antagonist oral anticoagulants (NOACs; particularly edoxaban and rivaroxaban) for thrombosis treatment and prevention in these patients [11].

For many years, LMWH was the first-line treatment in cancer patients with VTE and a low recurrence rate [relative risk (RR) 0.6], without an increased risk of major bleeding (RR 1.07) compared to vitamin K antagonists.

As for NOACs, they were initially used in patients without cancer, but two recent randomized clinical trials that compared the efficacy of NOACs vs LMWH in cancer-associated VTE have provided new evidence to support NOAC use in this population. Kraaijpoel et al. [14] randomized 1,050 patients with cancer either to a group treated with oral edoxaban, a direct factor Xa inhibitor, or to a group treated with subcutaneous dalteparin for 6–12 months. Edoxaban was shown to be non-inferior to dalteparin: the risk of VTE recurrence was lower by 3.4% hazard ratio [hazard ratio (HR) 0.71] and the risk of major bleeding was higher by 2.9% (HR 1.77) in patients treated with edoxaban versus those receiving dalteparin [14].

In the SELECT-D study including 406 patients with cancer, 6-month treatment with rivaroxaban, an oral factor Xa inhibitor, was compared to treatment with dalteparin. The cumulative risk of recurrent VTE was 4% in the rivaroxaban group vs. 11% in the dalteparin group. The risks of major bleeding were 6% and 4%, respectively.

Therefore, the use of NOACs seems to be an acceptable alternative to LMWH due to their efficacy, safety, and a convenient route of administration. In addition to the patient's own preference, potential interactions between NOACs and anticancer drugs should be considered. Inhibitors and activators of P-glycoprotein and cytochrome p450 3A4 affect the metabolism of NOACs, as well as their efficacy and safety profile.

The most recent guidelines of the Scientific and Standardization Committee of the International Society on

Thrombosis and Haemostasis have recommended NOAC use in patients with cancer and newly diagnosed VTE, low bleeding risk, and no risk of drug-drug interactions. On the other hand, LMWH is recommended in patients at high bleeding risk, especially in the case of thrombocytopenia [15, 16].

Clinical trials in cancer patients have confirmed the efficacy of NOACs for thromboprophylaxis [9]. It seems justified to use them as an alternative option for thrombosis prevention and treatment in patients with cancer, including those with MM.

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Author contributions
MPR — study concept and design, manuscript writing. MAR, MMR — data collection and analysis, literature search and critical review, revision of manuscript and paper design, editorial preparation of manuscript, language edition. All authors — critical revision and final approval.

Conflict of interests
The authors declare no conflict of interests.

Data availability statement
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethic statement
The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; uniform requirements for manuscripts submitted to biomedical journals.

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Effectiveness of blood utilization across departments in a tertiary health institution

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Abstract

Introduction: The limited availability of blood makes it imperative that hospitals and transfusion centers employ blood utilization indicators to ensure effective and efficient use. This study is a review of the transfusion practices and blood utilization indicators in the largest tertiary health center in South East Nigeria.

Material and methods: This study was a retrospective cross-sectional hospital-based type. Bio-demographic data, clinical diagnosis, and blood bank information such as patient and donor blood types from a 3-year period (January 2018 to January 2021) was reviewed. The total number of units crossmatched, issued, transfused, or returned was extracted. Utilization indicators such as crossmatch-to-transfusion ratio (C/T ratio), transfusion probability (TP), and transfusion index (TI) were calculated, and our findings were compared to those of similar studies performed in centers in India, Ethiopia and Saudi Arabia.

Results: A total of 2,919 blood units were cross-matched, of which 2,212 units were transfused to 1,953 patients. The study reported an overall C/T ratio of 1.3, a TP of 71%, and a TI of 1.1. These figures compare favorably with findings reported from studies done in other low and middle income countries. The department of medicine, with a C/T ratio of 1.1, had the most efficient blood ordering practices.

Conclusion: Our study shows that the quality indicators on the utilization of blood in our tertiary health institution are in keeping with international best practice. The implementation of policies like the maximum surgical blood ordering schedule could further strengthen the practice and improve the results of the surgical disciplines.

Key words: blood utilization indicators, crossmatch-to-transfusion ratio, transfusion probability, transfusion index, South East Nigeria

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Introduction

Blood utilization refers to the relationship between the number of units of blood requested and the quantity used or transfused as this relates to the different departments and units in a hospital. Blood is the most frequently transferred body tissue in clinical practice, and it requires significant input in terms of human and material resources for the provision of safe blood. Ensuring an adequate supply of blood demands that the available blood be properly dispensed to avoid wastage. The basic aim of an effective blood utilization program is to ensure a rational use of blood [1].

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Blood transfusion, despite being a life-saving procedure, is well known to be associated with risks that can result in morbidity and mortality.

Blood utilization audits guarantee the appropriateness of blood use, reduce wastage and unnecessary transfusions, and subsequently improve quality outcomes. Effective blood utilization can help reduce transfusion risk as unnecessary transfusion is avoided, and the risk-to-benefit outcome of every single unit of blood is properly determined for an individual patient [1]. Overall quality is improved by effective blood utilization as the burden on blood supply is lessened because unnecessary blood units are not transfused, and the improvement of the stability of blood supply is a quality indicator. Reducing non-beneficial transfusions means less is spent on reagents and consumables, and more time is made available for other blood bank processes [1, 2].

The efficiency of blood utilization is calculated using the crossmatch-to-transfusion (C/T) ratio, the probability of transfusion (TP), and the transfusion index (TI) [3]. Effective blood utilization has been used as a term to describe the C/T ratio whose target should be 1.0, implying that all crossmatched blood is actually used. Different studies have shown the C/T ratio to be 2.3 in Ethiopia [3], 1.08 in Turkey [4], and an average of 1.85 in the United States of America [5]. Boral and Henry et al. [6], in coining this term, noted that the desired value is <2.5. This ratio is useful in estimating the over-ordering of blood, but it does not actually assess whether the number of units of blood crossmatched was appropriate for the procedures to be carried out, nor the probability that a transfusion will be required for a particular procedure. Many surgical units demand more than is in fact needed for a surgical procedure to allow a safety margin for transfusions, which may be needed if and when emergencies occur.

Other transfusion indicators include TP and TI. The TP is calculated as the number of patients transfused/number of patients cross matched × 100 (values of more than 30% being thought to be appropriate) [7]. TPs of 20%, 36.9% and 47% have been reported in Zambia, Egypt, and Ethiopia respectively [8–10]. The TI is the average number of units of blood used per patient who was crossmatched. Here, more than 0.5 is regarded as optimal. Various studies have shown the TI to be 0.4, 0.69, and 0.77 in Zambia, Egypt, and Ethiopia respectively [8–10]. These findings are relevant as these are countries with significant similarities in terms of their cultural, political and socioeconomic experiences to Nigeria.

An assessment of these transfusion parameters to determine the efficacy of blood utilization across the different departments of our tertiary health institution will provide information to target intervention and changes in policy aimed at limiting the wastage of this highly valuable resource.

These transfusion parameters provide reliable measures for the efficient and effective management of blood transfusion. Assessing these measures across various departments and sections in clinical practice will enable targeted intervention in terms of awareness campaigns and continued medical education for clinicians to reduce wastage with regard to blood transfusion. This study serves to showcase these utilization measures across the clinical departments of our hospital.

Materials and methods

This was a retrospective study of blood donation and blood bank data from the University of Nigeria Teaching Hospital (a 500-bed multi-specialty hospital located at Ituku-Ozalla, Enugu state) over three years (January 2018 to January 2021). The data was extracted from Excel and analyzed using IBM SPSS version 25.0. Inferential statistics are presented in figures and tables. Statistical analysis included the estimation of median values, frequencies, cross-tabulation, and Chi-Square (Fishers exact test) to estimate statistical differences across various groups. All calculations were done without assuming equal variance, and any *p*-value of less than 0.05 was assumed to be significant.

The overall effectiveness of blood utilization was determined using these blood product utilization quality indicators.

Packed red cells were the most common red cell preparation issued, and is subsequently used interchangeably with the word “blood” in this work.

Crossmatch-to-transfusion ratio

This was calculated using the formula: the total number of units of blood crossmatched/total number of units of blood transfused.

Transfusion probability

This was calculated using the formula: the number of patients transfused/number of patients cross-matched × 100.

Transfusion index

This was calculated using the formula: the number of units of blood transfused/total number of patients crossmatched.

Results

With respect to the various departments, the numbers of recipients were: internal medicine department — 304 (12.8%); surgical departments — 536 (22.6%); obstetrics and gynecology — 434 (18.3%); pediatrics — 238 (10%); emergency (adult and pediatric) — 508 (21.4%); oncology — 153 (6.5%); and others [including intensive care unit (ICU), hematology, special care ward, and radiotherapy/

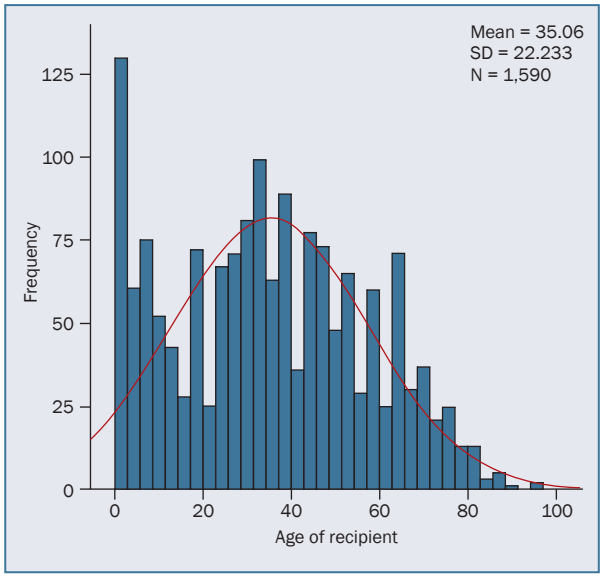

Figure 1. Histogram showing age distribution of blood recipients; SD — standard deviation

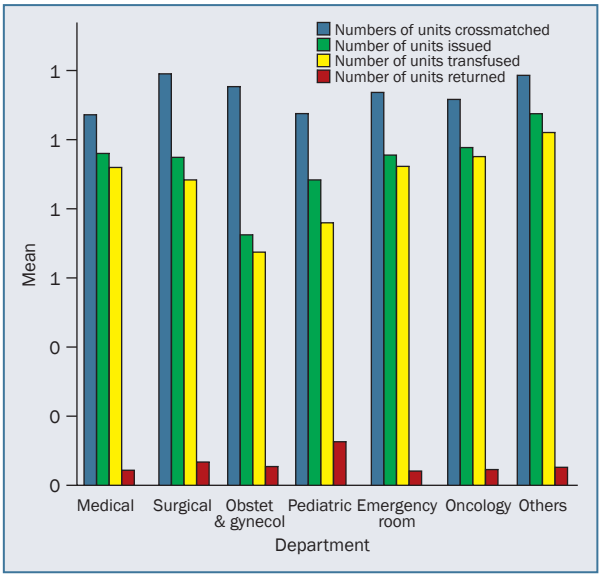

Figure 2. Numbers of units crossmatched, issued, transfused, and returned across various departments; Obstet & gynecol — obstetrics & gynecology

Table I. Transfusion parameters across various departments

Department	Crossmatch-to-transfusion ratio[a]	Transfusion probability[b]	Transfusion index[c]
All departments	2,919/2,212 (**1.32**)	1,953/2,565 (**76.1%**)	2,212/1,953 (**1.13**)
Internal medicine	326/292 (**1.12**)	274/304 (**90.1%**)	292/274 (**1.07**)
Surgery	638/474 (**1.35**)	399/536 (**74.4%**)	474/399 (**1.19**)
Obstetrics and gynecology	502/292 (**1.72**)	242/433 (**55.9%**)	292/242 (**1.21**)
Pediatrics	255/179 (**1.42**)	170/238 (**71.4%**)	179/170 (**1.05**)
Emergency (adults and children)	577/470 (**1.23**)	415/508 (**81.7%**)	470/415 (**1.13**)
Oncology	171/146 (**1.17**)	133/155 (**88.1%**)	146/133 (**1.10**)
Others*	235/207 (**1.14**)	171/198 (**86.4%**)	207/171 (**1.21**)

[a]Crossmatch-to-transfusion ratio (C/T ratio) — number of units crossmatched/number of units transfused; [b]transfusion probability (TP) — number of patients transfused/number of patients crossmatched × 100; [c]transfusion index (TI) — number of units transfused/number of patients crossmatched; *radiotherapy, hematology, special care ward, intensive care unit, eye ward

/radio-oncology] — 198 (8.4%). The average age of the recipients was 34 years (range 0–96). Figure 1 shows the age distribution of recipients. The CT ratio, TP, and TI are shown in Table I, while Figure 2 shows a histogram of the various departments with regard to the number of units of blood crossmatched, issued, transfused, and returned.

Figure 1 shows two peaks, with the pediatric and the 30–40 age groups showing the highest frequencies of transfusions.

Cumulatively, the adult patient population had higher numbers of transfusions. There were 1,213 individuals (588 females and 625 males) presenting at different clinical specialties (age range 18 to 96 years, median age 42) who were booked for possible transfusion during this period. A total of 946 units of blood was transfused out of the 1,213 units of blood initially crossmatched. The overall adult blood utilization indices were therefore estimated to be a C/T ratio of 1.28, a transfusion probability (TP) of 77.9%, and a TI of 1.15.

The surgical departments had the highest blood usage, with 638 units being crossmatched while 474 units were transfused. While the medical departments had the most efficient blood utilization parameters, with a C/T ratio of 1.12, a TP of 90.1%, and a TI of 1.07, the department with the lowest tendency to transfuse blood that had already been crossmatched was obstetrics & gynecology, with a C/T ratio of 1.72, a TP of 55.9%, and a TI of 1.21. The Chi-square value showed a significant difference across the departments with regards to the numbers of units crossmatched ($r = 22.52$, $p = 0.001$), the number of units issued ($r = = 21.569$, $p = 0.001$), the number of units transfused ($r = 18.809$, $p = 0.004$), and the number of units returned ($r = 30.752$, $p = 0.0001$).

The results presented above are mainly for packed red cells and the occasional whole blood transfusions, representing the most common type of blood products requested in our center. Furthermore, whole blood centrifugation at room temperature (an initial light spin followed by a heavy spin) produces platelet concentrate and fresh plasma, which are issued.

Discussion

Blood is indispensable for life and is thus listed in the World Health Organization (WHO) list of essential medications [11]. Research has shown that transfusion therapy is associated with one in ten hospital admissions [12] and is ranked among the top five most commonly used therapies [13].

Juxtaposing this fact with that of the scarcity and limited blood supply often encountered especially in Sub-Saharan Africa [14] creates a need for the implementation of transfusion programs that will promote effective and efficient utilization of blood products. These programs require periodic audits to further strengthen existing patient blood management (PBM) programs by revealing deficiencies in blood transfusion practice and areas that require improvement.

In the University of Nigeria Teaching Hospital, PBM programs are improving clinical outcomes while discouraging unnecessary use of blood products. Adherence to PBM practices varies across the different specialties of the hospital, with obstetrics & gynecology, other surgical units, and the hemostasis units usually the most compliant. Representatives from these specialties are active members of the Hospital's Transfusion Committee which serves as a 'think tank' on blood transfusion practices.

Analysis of the bio-demographic data from our work reveals a median age of 34 years. Most (63.7%) recipients of the transfused blood components were female. This aligns with studies done in Northern India [15] and Ethiopia [16]. This imbalance can be explained by the high transfusion demand for labour and other particular hemorrhagic conditions, both in the antepartum and post-partum periods. Conversely, some other researchers have reported a preponderance of male recipients [17]. This could be explained by greater occupational exposure, as well as the higher possibility of trauma requiring surgery or transfusion in males.

The C/T ratio is greatest in operative (surgical) disciplines relative to other departments in the hospital. This is predominantly in the departments of general surgery and obstetrics & gynecology. this may be ascribed to vestiges of the age-old surgical practice of estimated blood ordering done to forestall any peri-operative eventualities. Unchecked, this readily leads to material and financial waste, with increased work hours [18, 19]. This also highlights the need for hospital transfusion committees to implement the maximum surgical blood ordering schedule (MSBOS) as a means of limiting wastage. This is a program where the average agreed maximum quantity of blood units required for each specific surgical procedure is documented and consistently used, with no allowances made for individual preferences. This negates the tendency of some surgical teams to request far more blood than they actually require.

Transfusion practice has devised various quality indicators over the years to encourage efficient and effective patient blood management practices by preventing excessive ordering and inappropriate use of blood and blood products [6, 7, 20]. In interpreting the C/T ratio as a blood utilization quality indicator, a ratio of 1:1 is deemed ideal, meaning that all crossmatched units are actually transfused. In practice, a C/T ratio of less than 2:1 [21] is most desirable and portrays efficient and appropriate blood usage, while a C/T ratio of >2.5 indicates inappropriate blood usage.

This study has reported an overall C/T ratio of 1.3. This implies an appropriate and efficient blood ordering practice, and is similar to the C/T ratio of 1.5 reported for Saudi Arabia [2] and of 1.5 and 1.4 respectively for two centers in India [15, 20]. Our reported values are significantly lower than the C/T ratios of 7.6, 3.9, and 3.7 respectively noted in studies performed in Ethiopia [3], Egypt [10], and Tanzania [22].

In our study, the different hospital specialties all had a C/T ratio of <2; the department of internal medicine with a C/T ratio of 1.14:1 had the most efficient blood ordering practices, followed closely by the oncology department. This may be explained by the chronicity of the diseases managed in these departments. Reversal of blood transfusion orders there is unlikely. Relatively, surgical patients with surgical emergencies are more prone to preemptive blood ordering with extra units requested. This practice of requesting blood as 'back up' in case it is needed may explain why most surgical units have higher C/T ratios, as demonstrated in previous studies.

Another quality indicator, the TP, was initially traditionally applied to surgical disciplines [3, 7]. It refers to the probability of the use of transfusion therapy for a particular surgical procedure or the definite number of transfusions done out of all that were crossmatched for such procedures. A value of 30% and above indicates efficient blood usage. Our study found an overall TP of 74.1%. internal medicine had a TP of 90.1%, oncology 88.1%, and surgery 71.1%.

The TI is a reflection of how appropriate is the number of units of blood crossmatched for a particular clinical condition [3, 23]. It is mathematically derived by calculating the average number of units used per patient crossmatched. A value of greater than 0.5 indicates efficient blood usage. The overall TI in our study was 1.1 and this is in keeping with the results of Yasmeen et al. [15] with a value of 1.1, and Trisal et al. [20] with a value of 1.2. A higher value of 2.5 was reported by Shash et al. [2] in Saudi Arabia.

By inference, our reported overall study TI, and the TI values for the various departments, indicate blood ordering policy and transfusion practices that are within acceptable standards.

Our findings thus compare favorably with reported TP and other utilization indicators seen in low and middle income countries (LMIC) as mentioned above. This implies that most units in our hospital are very intentional when ordering blood or have been adequately trained with respect to the use of clinically relevant 'transfusion triggers'.

In contrast, significant differences exist between transfusion practices in LMIC and high-income countries (HIC). These include differences in transfusion indicators, donor rates, the availability and use of components therapy, transfusion rates, and the capacity for comprehensive testing for infectious markers [24]. Also, high income countries use computerized medical records and electronic transfusion requests with automated decision systems on the appropriateness of blood transfusion. Consequently, audits of blood utilization in HIC are based on these systems, making it difficult to compare our work to findings in these areas. Although Zachee and Vanderkerckhove [25] reported a TI of 2.72, significantly greater than values in this study and in other LMICs, there is a shortage of reports on other blood utilization indicators in HIC.

Conclusions

The quality indicators on utilization of blood noted in this study are all within acceptable reference limits. However, it is important to further interrogate the increased C/T ratios noted in the surgical disciplines when compared to other departments in our Hospital.

To that effect, policies such as MSBOS should be implemented for specific surgical procedures that are associated with excessive ordering, so as to further improve our indices and overall patient blood management.

Article information and declarations

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Author contributions

IOA participated in conceptualization, study design, and drafting, also data collection, interpretation and manuscript reviews. AM participated in conceptualization, study design and drafting, in aaddition to data interpretation and statistical analysis. EM participated in conceptualization, study design, and drafting, also data collection, interpretation and manuscript reviews. CN, HO, AU, AD, CE participated in the study design, data collection and Interpretation. All authors participated in the final approval of the manuscript.

Conflict of interests

The authors declare no conflict of interests.

Data availability statement

Data sets and other study documents are appropriately secured and will be made available on request.

Ethics statement

Ethical approval for our study was obtained from the University of Nigeria Teaching Hospital Health Research and Ethical Review Board.

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Acquired hemophilia A as rare complication in course of myeloproliferative syndrome

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Introduction

Acquired hemophilia A (AHA) is an autoimmune disorder in which antibodies against factor VIII (FVIII) are produced, decreasing its activity. This leads to massive bleeding. AHA often affects people over 60 years of age, in 11% of cases it accompanies solid tumors, while hematological malignancies and predominant lymphoproliferative malignancies account for 3.8% of cases. The clinical manifestation is spontaneous bleeding, and the mortality rate reaches 20% [1]. AHA has been estimated to occur in 1.5 per 1,000,000 people, although the latest research suggests that this percentage may in fact be 2–3 times higher [2]. Clinically, AHA manifests as sudden bleeding; laboratory tests show isolated prolongation of activated partial thromboplastin time (APTT), a decrease in FVIII activity, and the presence of an inhibitor [measured in Bethesda units (BU)] [2, 3]. A 1-to-1 plasma mixing test is used in diagnostics, wherein incomplete or no correction is observed [4]. Myeloproliferative neoplasms (MPN) include essential thrombocythemia (ET), polycythemia vera (PV), primary myelofibrosis (PMF), and pre-fibrotic PMF (pre-PMF). MPN are characterized by the presence of the JAK2 *V617F* mutation [5, 6]. MPN is a rare disease (2.17 cases/100,000) [7], and the coexistence of AHA in the course of MPN has only rarely been described in the literature. This report focuses on the diagnostic dilemmas of AHA in a patient with massive bleeding and a history of polycythemia vera.

Case report

A 76-year-old man with polycythemia vera being treated with hydroxycarbamide and anagrelide visited his family doctor because of a subcutaneous and intramuscular hemorrhage on the right side of his trunk. Due to enlargement of the hematoma, the patient was referred to the emergency department of his district hospital, where imaging tests were performed. Chest tomography showed hyperdense thickening (max. 6–7 cm) of the soft tissues, i.e. lateral and posterior parts of the chest, abdominal cavity, and pelvis. The image suggested the presence of an extensive intramuscular and subcutaneous hematoma.

The patient began to become anemic, despite numerous transfusions of red blood cell concentrate and plasma, demonstrating resistance to the transfusions, and the growth of clinical bleeding symptoms with a further decrease in hemoglobin (data in the table) and extending the time to APTT to 60 s. A control chest tomography showed (Figure 1) enlargement of the dimensions of the hematoma. In addition, the patient presented hepatosplenomegaly. Laboratory tests showed reduced FVIII activity with an inhibitor titer of 0.6 BU, allowing the AHA diagnosis.

The patient was treated with inhibitor eradication therapy: cyclophosphamide at 1 mg/kg body weight and prednisone at 1 mg/kg body weight. Due to thrombocytosis and a history of a stroke, activated prothrombin complex concentrate (aPCC), which is associated with a slightly higher prothrombotic risk, was not administered. Treatment with

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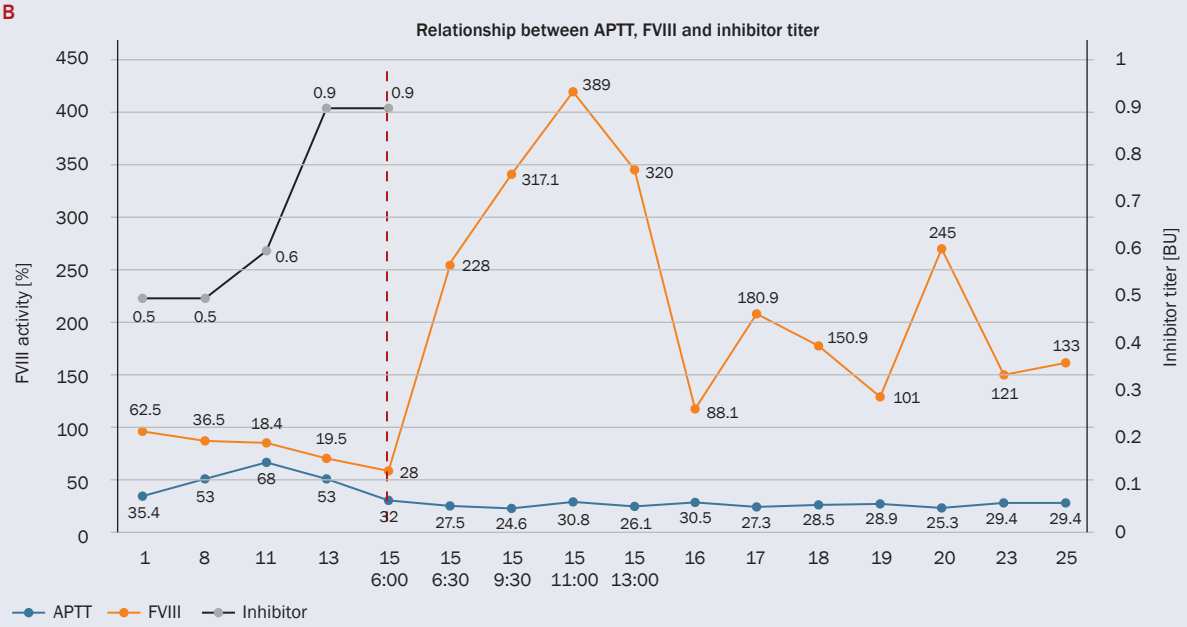
A

Day	WBC [10^9/L]	Hb [mmol]	PLT [10^9/L]	FFP [U]	RBCC [U]
1	35.36	6.1	733		
2	32.07	6.0	741		
3	27.23	5.5	623		2
4	27.00	6.3	647		
5	28.34	5.8	679		
6	30.19	4.5	701	2	4
7	34.17	4.2	678	2	4
8	33.57	5.1	708		
9	31.67	4.7	701	2	3
11	32.87	4.4	687	2	2
13	30.00	5.5	699	4	

FIX	FXI
99.80%	62.80%
N: 63–150	N: 65–150

B



C

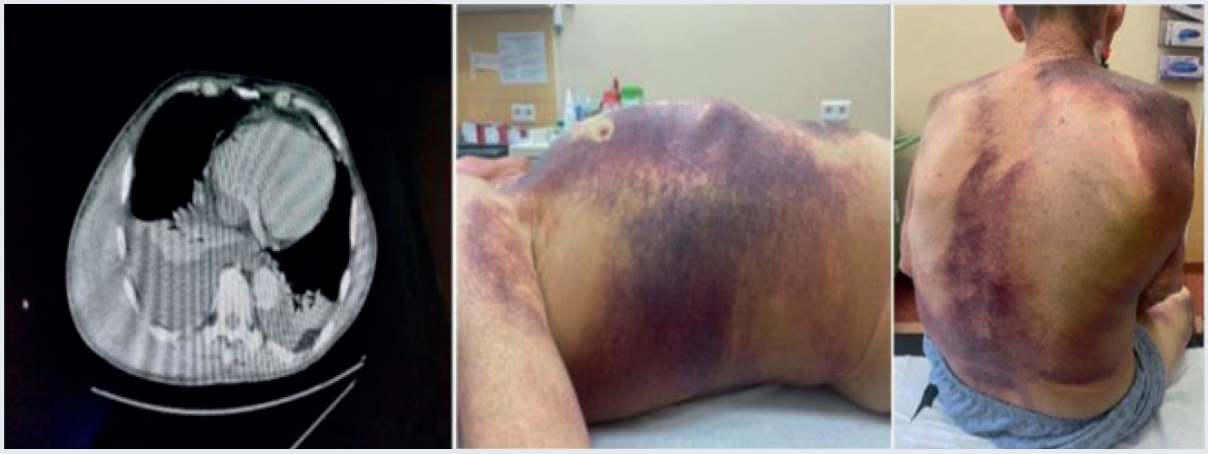


Figure 1A–C. Relationship between activated partial thromboplastin time (APTT), factor VIII (FVIII) activity, and inhibitor titer. Tables show test results (morphology, factor activity and number of transfusions); WBC — white blood cells; Hb — hemoglobin; PLT — platelets; FFP — fresh frozen plasma; RBCC — red blood cell concentrate; FIX — factor IX; FXI — factor XI; rpFVIII — porcine factor VIII

recombinant factor VII (FVII) was initiated via injection — repeated doses of 90 µg/kg body weight were introduced as life-saving therapy. Before recombinant porcine factor VIII administration, the anti-recombinant porcine factor VIII (anti-rpFVIII) inhibitor titer was determined to be 0.9 BU. Then, rpFVIII was presented at an initial dose of 200 U/kg

body weight. Finally, we adjusted the quantity to 80 U/kg body weight depending on factor VIII activity above 100%, as preparation for invasive surgery, obtaining a gradual increase in FVIII activity. The imagefrom a trepanobiopsy confirmed the presence of post-PV myelofibrosis. The presence of JAK2 mutations was demonstrated. In the course of hospitalization, gradual absorption of the hematoma was observed, and the inhibitor-eradicating treatment was reduced.

RpVIII has high hemostatic efficiency and a low risk of thromboembolic complications. Therefore, rpVIII is used as rescue therapy in AHA patients, regardless of age and comorbidities [8]. Due to the patient's progression, a ruxolitinib treatment program has been included in the treatment, and the inhibitor is improving, gaining improvement in the field of bleeding control.

Discussion

Single cases of AHA in the course of a myeloproliferative syndrome have been reported in literature reviews. Biss et al. [9] described the case of a 71-year-old patient with acquired FVIII inhibitor with an inhibitor titer of 9 BU and manifesting massive bleeding. The accompanying myeloproliferative syndrome was characterized by splenomegaly and erythropoiesis disorders [9]. Vener et al. [10] described the case of a 42-year-old patient with diagnosed PV and AHA who had intramuscular bleeding and a massive hematoma of the retroperitoneal space. Studies showed an uncorrected APTT prolongation in the mixed plasma test and an inhibitor titer of 90 BU [10]. Epidemiological data shows that PV, ET, and primary myelofibrosis occur in 0.84, 1.03, and 0.47 cases per 100,000, respectively [7].

On the basis of the diagnostic difficulties in the presented, rarely reported, case of AHA in the course of post-PV myelofibrosis, the successful preparation of the rpVIII before trepanobiopsy allowed us to confirm the diagnosis of Philadelphia-negative myeloproliferative neoplasm.

Article information and declarations

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Author contributions
PG — manuscript preparation. EW — data collection, laboratory tests. JRM — study design, coordination, conceptualization, language edition, final approval. MS — data collection.

Conflict of interests
The authors declare no conflict of interests.

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SKRÓCONA INFORMACJA O LEKU

IMBRUVICA® (ibrutynib), 140 mg tabletki powlekane, 280 mg tabletki powlekane, 420 mg tabletki powlekane, 560 mg tabletki powlekane, 140 mg kapsułki twarde.

SKŁAD I POSTAĆ FARMACEUTYCZNA: IMBRUVICA 140 mg kapsułki twarde. Każda kapsułka twarda zawiera 140 mg ibrutynibu. Kapsułka twarda. Biała, nieprzezroczysta kapsułka twarda, o długości 22 mm, z czarnym nadrukiem "ibr 140 mg". IMBRUVICA 140 mg tabletki powlekane. Każda tabletka powlekana zawiera 140 mg ibrutynibu. Substancja pomocnicza o znanym działaniu. Każda tabletka powlekana 140 mg zawiera 28 mg laktozy jednowodnej. IMBRUVICA 280 mg tabletki powlekane. Każda tabletka powlekana zawiera 280 mg ibrutynibu. Substancja pomocnicza o znanym działaniu. Każda tabletka powlekana 280 mg zawiera 56 mg laktozy jednowodnej. IMBRUVICA 420 mg tabletki powlekane. Każda tabletka powlekana zawiera 420 mg ibrutynibu. Substancja pomocnicza o znanym działaniu. Każda tabletka powlekana 420 mg zawiera 84 mg laktozy jednowodnej. IMBRUVICA 560 mg tabletki powlekane. Każda tabletka powlekana zawiera 560 mg ibrutynibu. Każda tabletka powlekana 560 mg zawiera 112 mg laktozy jednowodnej.IMBRUVICA 140 mg tabletki powlekane. Żółtozielone do zielonych, okrągłe tabletki (9 mm), z wytłoczonym napisem „ibr" z jednej strony i „140" z drugiej strony. IMBRUVICA 280 mg tabletki powlekane. Fioletowe, podłużne tabletki (długości 15 mm i szerokości 7 mm), z wytłoczonym napisem „ibr" z jednej strony i „280" z drugiej strony. IMBRUVICA 420 mg tabletki powlekane. Żółtozielone do zielonych, podłużne tabletki (długości 17,5 mm i szerokości 7,4 mm), z wytłoczonym napisem „ibr" z jednej strony i „420" z drugiej strony. IMBRUVICA 560 mg tabletki powlekane. Żółte do pomarańczowych, podłużne tabletki (długości 19 mm i szerokości 8,1 mm), z wytłoczonym napisem „ibr" z jednej strony i „560" z drugiej strony.

WSKAZANIA: Produkt leczniczy IMBRUVICA w monoterapii jest wskazany do leczenia dorosłych pacjentów z nawracającym lub opornym na leczenie **chłoniakiem z komórek płaszcza** (ang. *mantle cell lymphoma,* MCL). Produkt leczniczy IMBRUVICA w monoterapii lub w skojarzeniu z rytuksymabem, lub obinutuzumabem, lub wenetoklaksem jest wskazany do leczenia dorosłych pacjentów z wcześniej nieleczoną **przewlekłą białaczką limfocytową** (ang. *chronic lymphocytic leukaemia,* CLL). Produkt leczniczy IMBRUVICA w w monoterapii lub w skojarzeniu z bendamustyną i rytuksymabem (BR) jest wskazany do leczenia dorosłych pacjentów z CLL, którzy otrzymali co najmniej jedną wcześniejszą terapię. Produkt leczniczy IMBRUVICA w monoterapii jest wskazany do leczenia dorosłych pacjentów z **makroglobulinemią Waldenströma (WM)**, którzy otrzymali co najmniej jedną wcześniejszą terapię lub pacjentów leczonych po raz pierwszy, u których nie jest odpowiednie zastosowanie chemioimmunoterapii. Produkt leczniczy IMBRUVICA w skojarzeniu z rytuksymabem jest wskazany do leczenia dorosłych pacjentów z WM.

DAWKOWANIE: Leczenie tym produktem powinno być rozpoczynane i nadzorowane przez lekarza z doświadczeniem w stosowaniu przeciwnowotworowych produktów leczniczych. **Chłoniak z komórek płaszcza:** Zalecana dawka w leczeniu MCL to 560 mg raz na dobę. **Przewlekła białaczka limfocytowa i makroglobulinemia Waldenströma:** Zalecana dawka w leczeniu CLL i WM w monoterapii jak i w terapii skojarzonej to 420 mg raz na dobę. Leczenie produktem IMBRUVICA należy kontynuować do czasu progresji choroby lub utraty tolerancji przez pacjenta. W skojarzeniu z wenetoklaksem w leczeniu CLL, produkt IMBRUVICA należy podawać jako pojedynczy lek przez 3 cykle (1 cykl trwa 28 dni), a następnie przez 12 cykli produkt IMBRUVICA z wenetoklaksem. Pełne informacje na temat dawkowania wenetoklaksu, patrz Charakterystyka Produktu Leczniczego (ChPL) wenetoklaksu. Podczas podawania produktu leczniczego IMBRUVICA w skojarzeniu z terapią anty-CD20, zaleca się podawanie produktu leczniczego IMBRUVICA przed terapią anty-CD20, gdy jest podawana tego samego dnia. **Dostosowanie dawki:** Umiarkowane i silne inhibitory CYP3A4 zwiększają ekspozycję na ibrutynib. Należy zmniejszyć dawkę ibrutynibu do 280 mg raz na dobę w przypadku jednoczesnego stosowania z umiarkowanymi inhibitorami CYP3A4. Należy zmniejszyć dawkę produktu leczniczego IMBRUVICA do 140 mg raz na dobę lub wstrzymać podawanie na okres 7 dni w przypadku jednoczesnego stosowania z silnymi inhibitorami CYP3A4. Należy przerwać stosowanie produktu leczniczego IMBRUVICA w razie nowego wystąpienia lub nasilenia: niewydolności serca stopnia 2., zaburzeń rytmu serca stopnia 3., toksyczności niehematologicznych stopnia ≥3., neutropenii stopnia 3. lub większego, z zakażeniem lub gorączką, lub toksyczności hematologicznych stopnia 4. Gdy objawy toksyczności zmniejszą się do stopnia 1. lub ustąpią, można wznowić leczenie produktem leczniczym IMBRUVICA w zalecanej dawce zgodnie z poniższymi tabelami.

Zalecane modyfikacje dawki dla zdarzeń niekardiologicznych przedstawiono poniżej:

Zdarzenia	Wystąpienie toksyczności	MCL modyfikacja dawki po ustąpieniu	CLL/WM modyfikacja dawki po ustąpieniu
Toksyczność niehematologiczna stopnia 3. lub 4.	Pierwsze*	wznowić leczenie w dawce 560 mg na dobę	wznowić leczenie w dawce 420 mg na dobę
	Drugie	wznowić leczenie w dawce 420 mg na dobę	wznowić leczenie w dawce 280 mg na dobę
Neutropenia stopnia 3. lub 4. z zakażeniem lub gorączką	Trzecie	wznowić leczenie w dawce 280 mg na dobę	wznowić leczenie w dawce 140 mg na dobę
Toksyczność hematologiczna stopnia 4.	Czwarte	odstawić produkt IMBRUVICA	odstawić produkt IMBRUVICA

** Podczas wznawiania leczenia należy ponownie rozpocząć je od tej samej lub mniejszej dawki w oparciu o ocenę korzyści i ryzyka. W przypadku ponownego wystąpienia toksyczności należy zmniejszyć dawkę dobową o 140 mg.*

Zalecane modyfikacje dawki w przypadku wystąpienia zdarzeń związanych z niewydolnością serca lub zaburzeniami rytmu serca opisano poniżej:

Zdarzenia	Wystąpienie toksyczności	MCL modyfikacja dawki po ustąpieniu	CLL/WM modyfikacja dawki po ustąpieniu
Niewydolność serca stopnia 2.	Pierwsze	wznowić leczenie w dawce 420 mg na dobę	wznowić leczenie w dawce 280 mg na dobę
	Drugie	wznowić leczenie w dawce 280 mg na dobę	wznowić leczenie w dawce 140 mg na dobę
	Trzecie	odstawić produkt IMBRUVICA	odstawić produkt IMBRUVICA
Zaburzenia rytmu serca stopnia 3.	Pierwsze	wznowić leczenie w dawce 420 mg na dobę†	wznowić leczenie w dawce 280 mg na dobę†
	Drugie	odstawić produkt IMBRUVICA	odstawić produkt IMBRUVICA
Niewydolność serca stopnia 3. lub 4. Zaburzenia rytmu serca stopnia 4.	Pierwsze	odstawić produkt IMBRUVICA	odstawić produkt IMBRUVICA

†Ocenić bilans korzyści do ryzyka przed wznowieniem leczenia.

Pominięcie dawki: W razie pominięcia przyjęcia dawki w zaplanowanym czasie, należy przyjąć ją niezwłocznie tego samego dnia i kontynuować przyjmowanie następnego dnia, według dotychczasowego schematu. Nie należy przyjmować dodatkowych kapsułek/tabletek w celu uzupełnienia pominiętej dawki. **Szczególne grupy:** ***Osoby w podeszłym wieku*** Nie jest konieczne specjalne dostosowanie dawki u pacjentów w podeszłym wieku (≥65 lat). ***Zaburzenia czynności nerek:*** Nie przeprowadzano szczególnych badań klinicznych u pacjentów z zaburzeniami czynności nerek. W badaniach klinicznych produktu leczniczego IMBRUVICA leczono pacjentów z łagodnymi lub umiarkowanymi zaburzeniami czynności nerek. Nie ma konieczności dostosowania dawki u pacjentów z łagodnymi lub umiarkowanymi zaburzeniami czynności nerek (klirens kreatyniny większy niż 30 ml/min). Należy utrzymywać nawodnienie i okresowo monitorować stężenie kreatyniny w surowicy. Produkt leczniczy IMBRUVICA można podawać pacjentom z ciężkimi zaburzeniami czynności nerek (klirens kreatyniny <30 ml/min) tylko gdy korzyści przeważają nad ryzykiem i należy dokładnie obserwować pacjentów w celu wykrycia objawów toksyczności. Brak danych u pacjentów z ciężkimi zaburzeniami czynności nerek lub pacjentów dializowanych. ***Zaburzenia czynności wątroby:*** Ibrutynib jest metabolizowany w wątrobie. W badaniu u pacjentów z zaburzeniami czynności wątroby, dane wykazały zwiększenie ekspozycji na ibrutynib. U pacjentów z łagodnymi zaburzeniami czynności wątroby (klasa A wg Child-Pugh), zalecaną dawką jest 280 mg na dobę (jedna tabletka 280mg lub dwie kapsułki 140mg). U pacjentów z umiarkowanymi zaburzeniami czynności wątroby (klasa B wg Child-Pugh), zalecaną dawką jest 140 mg na dobę. Należy obserwować pacjentów w celu wykrycia objawów toksyczności produktu IMBRUVICA i w razie potrzeby zastosować się do wytycznych modyfikacji dawki. Nie zaleca się podawania produktu IMBRUVICA pacjentom z ciężkimi zaburzeniami czynności wątroby (klasa C wg Child-Pugh). ***Ciężkie choroby serca:*** Do badań klinicznych produktu IMBRUVICA nie włączano pacjentów z ciężką chorobą układu sercowo-naczyniowego. ***Dzieci i młodzież:*** Nie zaleca się stosowania produktu IMBRUVICA u dzieci i młodzieży w wieku od 0 do 18 lat, ponieważ nie ustalono skuteczności. Obecnie dostępne dane u pacjentów z dojrzałym chłoniakiem nieziarniczym z komórek B zostały opisane w punktach 4.8, 5.1 i 5.2 ChPL.

SPOSÓB PODAWANIA: Produkt IMBRUVICA należy podawać doustnie raz na dobę, popijając szklanką wody, o tej samej porze każdego dnia. Kapsułki/tabletki należy połykać w całości popijając wodą i nie należy ich otwierać, łamać ani żuć. Nie wolno przyjmować produktu IMBRUVICA razem z sokiem grejpfrutowym lub gorzkimi pomarańczami. Przeciwwskazania: Nadwrażliwość na substancję czynną lub na którąkolwiek substancję pomocniczą. Stosowanie preparatów zawierających ziele dziurawca zwyczajnego jest przeciwskazane u pacjentów leczonych produktem leczniczym IMBRUVICA.

SPECJALNE OSTRZEŻENIA I ŚRODKI OSTROŻNOŚCI: Zdarzenia związane z krwawieniem. Zgłaszano przypadki zdarzeń krwotocznych u pacjentów leczonych produktem leczniczym IMBRUVICA, zarówno z małopłytkowością jak i bez małopłytkowości. Obejmowały one niewielkie zdarzenia krwotoczne, takie jak uraz, krwawienie z nosa i wybroczyny; i duże zdarzenia krwotoczne, niektóre ze skutkiem śmiertelnym, obejmujące krwawienie z żołądka lub jelit, krwotok wewnątrzczaszkowy, krwiomocz. Nie należy stosować warfaryny ani innych antagonistów witaminy K jednocześnie z produktem IMBRUVICA. Stosowanie leków przeciwzakrzepowych lub produktów leczniczych hamujących czynność płytek krwi (leki przeciwpłytkowe) jednocześnie z produktem IMBRUVICA zwiększa ryzyko poważnych krwawień. Większe ryzyko poważnych krwawień obserwowano w przypadku leków przeciwzakrzepowych, niż w przypadku leków przeciwpłytkowych. Należy rozważyć ryzyko i korzyści z leczenia przeciwzakrzepowego lub przeciwpłytkowego podczas jednoczesnego stosowania z produktem IMBRUVICA. Należy obserwować objawy przedmiotowe i podmiotowe krwawienia. Należy unikać stosowania suplementów takich jak olej rybi i witamina E. Należy wstrzymać stosowanie produktu leczniczego IMBRUVICA przez co najmniej 3 do 7 dni przed i po zabiegu chirurgicznym, w zależności od rodzaju zabiegu i ryzyka krwawienia. Mechanizm zdarzeń krwotocznych nie został w pełni poznany. Nie badano pacjentów z wrodzoną skazą krwotoczną. Leukostaza: Stwierdzono kilka przypadków leukostazy u pacjentów leczonych produktem leczniczym IMBRUVICA. Duża liczba krążących limfocytów (>400 000/µl) może powodować zwiększone ryzyko. Należy rozważyć czasowe wstrzymanie podawania produktu IMBRUVICA. Należy dokładnie obserwować pacjentów. W razie potrzeby zastosować leczenie wspomagające obejmujące nawodnienie i (lub) leczenie cytoredukcyjne. Pęknięcie śledziony: Zgłaszano przypadki pęknięcia śledziony po przerwaniu terapii produktem leczniczym IMBRUVICA. Stan choroby i wielkość śledziony należy dokładnie monitorować (np. badaniem klinicznym, USG), gdy terapia produktem leczniczym IMBRUVICA zostanie przerwana lub zakończona. Pacjenci, u których wystąpią bóle lewego górnego odcinka jamy brzusznej lub barku powinni zostać zbadani i należy rozważyć możliwość pęknięcia śledziony. Zakażenia: U pacjentów leczonych produktem leczniczym IMBRUVICA stwierdzano zakażenia (w tym posocznicę, posocznicę neutropeniczną, zakażenia bakteryjne, wirusowe lub grzybicze). Niektóre z tych zakażeń skutkowały hospitalizacją i śmiercią. U większości pacjentów z zakażeniami prowadzącymi do zgonu stwierdzono neutropenię. Należy obserwować pacjentów w celu wykrycia gorączki, nieprawidłowych wyników badań czynności wątroby, neutropenii i zakażeń i w razie potrzeby wdrożyć odpowiednie leczenie przeciwinfekcyjne. U pacjentów ze zwiększonym ryzykiem zakażeń oportunistycznych należy rozważyć profilaktykę, wg. standardów postępowania. Po zastosowaniu ibrutynibu zgłaszano przypadki inwazyjnych zakażeń grzybiczych, w tym zakażeń *Aspergillus, Cryptococcus i Pneumocystis jiroveci.* Zgłoszone przypadki inwazyjnych zakażeń grzybiczych wiązały się ze skutkami śmiertelnymi. Zgłaszano przypadki postępującej leukoencefalopatii wieloogniskowej (ang. *progressive multifocal leukoencephalopathy,* PML), w tym zakończone zgonem po stosowaniu ibrutynibu podczas wcześniejszej lub jednoczesnej terapii immunosupresyjnej. W diagnozie różnicowej należy rozważyć możliwość wystąpienia PML u pacjentów z nowymi neurologicznymi, poznawczymi lub behawioralnymi objawami przedmiotowymi lub podmiotowymi, lub nasileniem istniejących. W razie podejrzewania PML należy wykonać odpowiednie badania i przerwać leczenie, do czasu wykluczenia PML. W razie jakichkolwiek wątpliwości należy rozważyć konsultację neurologiczną oraz przeprowadzenie badań diagnostycznych w kierunku PML, w tym obrazowanie metodą rezonansu magnetycznego, najlepiej z kontrastem, badanie płynu mózgowo-rdzeniowego na obecność DNA wirusa JC oraz powtórne badania neurologiczne. Zdarzenia dotyczące wątroby: U pacjentów leczonych produktem leczniczym IMBRUVICA występowały przypadki działania toksycznego na wątrobę, reaktywacji wirusowego zapalenia wątroby typu B oraz przypadki wirusowego zapalenia wątroby typu E, które mogą być przewlekłe. U pacjentów leczonych produktem leczniczym IMBRUVICA występowała niewydolność wątroby, w tym zdarzenia zakończone zgonem. Przed rozpoczęciem leczenia produktem leczniczym IMBRUVICA należy ocenić czynność wątroby i stan wirusowego zapalenia wątroby. W trakcie leczenia pacjenci powinni być okresowo monitorowani w celu wykrycia zmian parametrów czynności wątroby. W zależności od wskazań klinicznych, należy wykonać badania wiremii i badania serologiczne w kierunku wirusowego zapalenia wątroby,

zgodnie z lokalnymi wytycznymi medycznymi. W przypadku pacjentów, u których zdiagnozowano zdarzenia dotyczące wątroby, należy rozważyć konsultację z ekspertem w dziedzinie chorób wątroby w celu podjęcia odpowiedniego postępowania. Cytopenie: U pacjentów leczonych produktem leczniczym IMBRUVICA stwierdzano związane z leczeniem cytopenie stopnia 3. lub 4. (neutropenia, małopłytkowość i niedokrwistość). Należy badać morfologię krwi raz w miesiącu. Śródmiąższowa choroba płuc: U pacjentów leczonych produktem leczniczym IMBRUVICA zgłaszano przypadki śródmiąższowej choroby płuc. Należy obserwować pacjentów czy nie występują objawy płucne, wskazujące na śródmiąższową chorobę płuc. W razie wystąpienia objawów należy przerwać stosowanie produktu IMBRUVICA i zastosować odpowiednie leczenie śródmiąższowej choroby płuc. Jeśli objawy będą utrzymywać się należy ocenić ryzyko i korzyści terapii produktem IMBRUVICA i zastosować zalecenia dotyczące modyfikacji dawki. Zaburzenia rytmu serca i niewydolność serca: U pacjentów leczonych produktem IMBRUVICA występowały zakończone zgonem i ciężkie zaburzenia rytmu serca oraz niewydolność serca. Pacjenci w zaawansowanym wieku, w stanie sprawności ≥2 wg Eastern Cooperative Oncology Group (ECOG) lub ze współistniejącymi chorobami serca mogą być bardziej narażeni na ryzyko wystąpienia zdarzeń, w tym nagłych zdarzeń sercowych ze skutkiem śmiertelnym. Stwierdzano migotanie przedsionków, trzepotanie przedsionków, tachyarytmię komorową oraz niewydolność serca szczególnie u pacjentów z ostrymi zakażeniami lub z czynnikami ryzyka sercowego, takimi jak: nadciśnienie tętnicze, cukrzyca i zaburzenia rytmu serca w wywiadzie. Przed rozpoczęciem stosowania produktu leczniczego IMBRUVICA należy przeprowadzić odpowiednią ocenę kliniczną wywiadu i czynności serca. Pacjenci powinni być uważnie monitorowani w trakcie leczenia, w celu wykrycia objawów klinicznego pogorszenia czynności serca i powinni być prowadzeni klinicznie. U pacjentów, u których istnieją zagrożenia sercowo-naczyniowe, należy rozważyć dalszą ocenę (np. EKG, echokardiogram), jeśli jest to wskazane. U pacjentów z istotnymi czynnikami ryzyka zdarzeń sercowych, przed rozpoczęciem leczenia produktem leczniczym IMBRUVICA należy starannie ocenić stosunek korzyści do ryzyka; można rozważyć zastosowanie alternatywnego leczenia. U pacjentów, u których wystąpią objawy przedmiotowe i (lub) podmiotowe tachyarytmii komorowej, należy czasowo odstawić produkt leczniczy IMBRUVICA i dokonać dokładnej oceny klinicznej korzyści do ryzyka przed ewentualnym wznowieniem leczenia. U pacjentów z wcześniej występującym migotaniem przedsionków wymagających leczenia przeciwzakrzepowego, należy rozważyć alternatywne leczenie do produktu IMBRUVICA. U pacjentów, u których wystąpi migotanie przedsionków podczas terapii produktem leczniczym IMBRUVICA należy dokonać szczegółowej oceny ryzyka choroby zakrzepowo-zatorowej. U pacjentów z wysokim ryzykiem oraz gdy nie ma odpowiedniego alternatywnego leczenia do produktu IMBRUVICA, należy rozważyć dokładnie kontrolowane leczenie przeciwzakrzepowe. Pacjenci powinni być monitorowani w celu wykrycia objawów przedmiotowych i podmiotowych niewydolności serca podczas stosowania produktu leczniczego IMBRUVICA. W niektórych z tych przypadków niewydolność serca ustąpiła lub uległa poprawie po odstawieniu produktu leczniczego IMBRUVICA lub zmniejszeniu dawki. Incydenty naczyniowo-mózgowe: U pacjentów leczonych produktem IMBRUVICA zgłaszano występowanie incydentów naczyniowo-mózgowych, przemijających napadów niedokrwiennych mózgu i udaru niedokrwiennego, w tym także zakończonych zgonem, z jednoczesnym migotaniem przedsionków i (lub) nadciśnieniem tętniczym oraz bez nich. Wśród przypadków ze zgłoszonym opóźnieniem, od czasu rozpoczęcia leczenia produktem IMBRUVICA do wystąpienia niedokrwiennych zmian naczyniowych w ośrodkowym układzie nerwowym w większości przypadków upływało kilka miesięcy (ponad 1 miesiąc w 78% i ponad 6 miesięcy w 44% przypadków), co podkreśla konieczność regularnego kontrolowania stanu pacjentów. Zespół rozpadu guza: Podczas leczenia produktem IMBRUVICA stwierdzano występowanie zespołu rozpadu guza (ang. *tumour lysis syndrome*, TLS). Pacjentom z dużym obciążeniem nowotworem przed leczeniem zagraża wystąpienie zespołu rozpadu guza. Należy dokładnie obserwować pacjentów i stosować odpowiednie środki ostrożności. Rak skóry niebędący czerniakiem: Raki skóry niebędące czerniakiem zgłaszano częściej u pacjentów leczonych produktem IMBRUVICA niż u pacjentów otrzymujących komparatory w zbiorczych porównawczych randomizowanych badaniach fazy 3. Należy obserwować pacjentów w celu wykrycia raka skóry niebędącego czerniakiem. Nadciśnienie: U pacjentów leczonych produktem IMBRUVICA stwierdzano nadciśnienie tętnicze (patrz punkt 4.8 ChPL). Należy regularnie monitorować ciśnienie tętnicze u pacjentów leczonych produktem IMBRUVICA i jeśli zajdzie taka potrzeba, włączyć lub dostosować leczenie przeciwnadciśnieniowe w trakcie terapii produktem IMBRUVICA. Limfohistiocytoza hemofagocytarna (ang. *Haemophagocytic lymphohistiocytosis*, HLH): U pacjentów leczonych produktem IMBRUVICA zgłaszano przypadki HLH (w tym przypadki śmiertelne). Limfohistiocytoza hemofagocytarna jest zagrażającym życiu zespołem patologicznej aktywacji immunologicznej, charakteryzującym się objawami klinicznymi i objawami skrajnego uogólnionego stanu zapalnego. Limfohistiocytoza hemofagocytarna charakteryzuje się gorączką, hepatosplenomegalią, hipertriglicerydemią, wysokim stężeniem ferrytyny w surowicy i cytopeniami. Pacjenci powinni być informowani o objawach HLH. Pacjenci, u których występują wczesne objawy patologicznej aktywacji immunologicznej, powinni być natychmiast poddani ocenie klinicznej i należy rozważyć rozpoznanie HLH. Interakcje lekowe: Jednoczesne stosowanie silnych lub umiarkowanych inhibitorów CYP3A4 z produktem leczniczym IMBRUVICA może prowadzić do zwiększonej ekspozycji na ibrutynib a tym samym zwiększyć ryzyko wystąpienia toksyczności. Jednakże, jednoczesne stosowanie induktorów CYP3A4 może prowadzić do zmniejszenia ekspozycji na produkt leczniczy IMBRUVICA a w konsekwencji do braku skuteczności leczenia. Należy unikać, jeśli tylko to możliwe jednoczesnego stosowania produktu IMBRUVICA z silnymi inhibitorami CYP3A4 i z silnymi lub umiarkowanymi induktorami CYP3A4, a jednoczesne stosowanie należy rozważyć jedynie wtedy, gdy potencjalne korzyści przeważają znacznie nad ryzykiem. Należy uważnie obserwować pacjentów w celu wykrycia objawów toksyczności produktu IMBRUVICA, jeśli musi być zastosowany inhibitor CYP3A4. W przypadku konieczności stosowania induktora CYP3A4, należy uważnie monitorować pacjentów w celu wykrycia utraty skuteczności produktu leczniczego IMBRUVICA. Kobiety w wieku rozrodczym: Kobiety w wieku rozrodczym muszą stosować wysoce skuteczną metodę antykoncepcji podczas stosowania produktu IMBRUVICA. **Substancje pomocnicze o znanym działaniu (kapsułki):** Każda kapsułka zawiera mniej niż 1 mmol sodu (23 mg) i jest zasadniczo wolna od sodu. **Substancje pomocnicze o znanym działaniu (tabletki):** Produktu leczniczego nie należy stosować u pacjentów z rzadko występującą dziedziczną nietolerancją galaktozy, całkowitym brakiem laktazy lub zespołem złego wchłaniania glukozy-galaktozy. Każda tabletka powlekana zawiera mniej niż 1 mmol sodu (23 mg) i jest zasadniczo wolna od sodu.

DZIAŁANIA NIEPOŻĄDANE. Podsumowanie profilu bezpieczeństwa. Najczęściej występującymi działaniami niepożądanymi (≥20%) były biegunka, neutropenia, bóle mięśniowo-szkieletowe, krwotok (np. siniaki), wysypka, nudności, trombocytopenia, ból stawów i zakażenia górnych dróg oddechowych. Najczęstszymi działaniami niepożądanymi stopnia 3./4. (≥5%) były neutropenia, limfocytoza, trombocytopenia, nadciśnienie i zapalenie płuc. Profil bezpieczeństwa określono na podstawie zbiorczych danych z udziału 1981 pacjentów przyjmujących produkt IMBRUVICA, w czterech badaniach klinicznych 2 fazy i ośmiu randomizowanych badaniach 3 fazy oraz raportów po wprowadzeniu produktu do obrotu. Pacjenci leczeni z powodu MCL, w badaniach klinicznych otrzymywali produkt IMBRUVICA w dawce 560 mg raz na dobę, a pacjenci leczeni z powodu CLL lub WM, w badaniach klinicznych otrzymywali produkt IMBRUVICA w dawce 420 mg raz na dobę. Wszyscy pacjenci w badaniach klinicznych otrzymywali produkt IMBRUVICA do czasu progresji choroby lub utraty tolerancji przez pacjenta z wyjątkiem badań z zastosowaniem produktu IMBRUVICA w skojarzeniu z wenetoklaksem, w których pacjenci otrzymywali leczenie o ustalonym czasie trwania (badania CLL3011 i PCYC-1142-CA). Mediana czasu trwania leczenia produktem IMBRUVICA w zbiorczym zestawie danych wynosiła 14,7 miesięcy. Mediana czasu trwania leczenia w przypadku CLL/SLL wynosiła 14,7 miesięcy (do 52 miesięcy); MCL - 11,7 miesięcy (do 28 miesięcy); WM - 21,6 miesięcy (do 37 miesięcy). Działania niepożądane stwierdzone u pacjentów z nowotworami B-komórkowymi oraz działania niepożądane stwierdzone po wprowadzeniu produktu do obrotu, zostały wymienione poniżej według klasyfikacji układów i narządów oraz częstości występowania. Częstość występowania zdefiniowano następująco: bardzo często (≥1/10), często (≥1/100 do <1/10), niezbyt często (≥1/1 000 do <1/100), rzadko (≥1/10 000 do <1/1 000), częstość nieznana (nie można określić częstości na podstawie dostępnych danych). W obrębie każdej grupy o określonej częstości występowania objawy niepożądane są wymienione zgodnie ze zmniejszającym się nasileniem. Zakażenia i zarażenia pasożytnicze: Bardzo często: zapalenie płuc, zakażenie górnych dróg oddechowych, zakażenie skóry. Często: posocznica, zakażenie dróg moczowych, zapalenie zatok. Niezbyt często: zakażenia Cryptococcus, zakażenia Pneumocystis, zakażenia Aspergillus, reaktywacja wirusa WZW B. Nowotwory łagodne i złośliwe (w tym torbiele i polipy): Często: rak skóry niebędący czerniakiem, rak podstawnokomórkowy, rak kolczystokomórkowy. Zaburzenia krwi i układu chłonnego: Bardzo często: neutropenia, trombocytopenia, limfocytoza. Często: gorączka neutropeniczna, leukocytoza. Rzadko: leukostaza, Zaburzenia układu immunologicznego: Często: śródmiąższowa choroba płuc. Zaburzenia metabolizmu i odżywiania: Często: hiperurykemia. Niezbyt często: zespół rozpadu guza. Zaburzenia układu nerwowego: Bardzo często: zawroty głowy, ból głowy. Często: neuropatia obwodowa. Niezbyt często: incydent naczyniowo-mózgowy, przemijający napad niedokrwienny, udar niedokrwienny. Zaburzenia oka: Często: niewyraźne widzenie. Niezbyt często: krwotok w gałce ocznej. Zaburzenia serca: Często: niewydolność serca, migotanie przedsionków. Niezbyt często: tachyarytmia komorowa, zatrzymanie akcji serca. Zaburzenia naczyniowe: Bardzo często: krwotok, siniaczenie, nadciśnienie. Często: krwawienie z nosa, wybroczyny. Niezbyt często: krwiak podtwardówkowy. Zaburzenia żołądka i jelit: Bardzo często: biegunka, wymioty, zapalenie jamy ustnej, nudności, zaparcia, dyspepsja. Zaburzenia wątroby i dróg żółciowych: Niezbyt często: niewydolność wątroby. Zaburzenia skóry i tkanki podskórnej: Bardzo często: wysypka, Często: pokrzywka, rumień, łamliwość paznokci. Niezbyt często: obrzęk naczynioruchowy, zapalenie podskórnej tkanki tłuszczowej, dermatozy neutrofilowe, zianiniak naczyniowy. Rzadko: Zespół Stevensa-Johnsona. Zaburzenia mięśniowo-szkieletowe i tkanki łącznej: Bardzo często: ból stawów, skurcze mięśniowe, ból mięśniowo-szkieletowy. Zaburzenia nerek i dróg moczowych: Często: ostre uszkodzenie nerek. Zaburzenia ogólne i stany w miejscu podania: Bardzo często: gorączka, obrzęk obwodowy. Badania diagnostyczne: Bardzo często: zwiększone stężenie kreatyniny we krwi. **Opis wybranych działań niepożądanych** *Przerwanie leczenia i zmniejszenie dawki z powodu działań niepożądanych:* z 1981 pacjentów leczonych produktem leczniczym IMBRUVICA z powodu nowotworów B komórkowych, 6% pacjentów przerwało leczenie, głównie z powodu działań niepożądanych. Obejmowały one zapalenie płuc, migotanie przedsionków, neutropenię, wysypkę, trombocytopenię i krwotok. Działania niepożądane prowadzące do zmniejszenia dawki wystąpiły u około 8% pacjentów. ***Pacjenci w podeszłym wieku:*** Z 1981 pacjentów leczonych produktem leczniczym IMBRUVICA, 50% pacjentów miało co najmniej 65 lat. Zapalenie płuc stopnia 3. lub wyższego (11% pacjentów w wieku co najmniej 65 lat vs. 4% pacjentów w wieku poniżej 65 lat) i trombocytopenia (11% pacjentów w wieku co najmniej 65 lat vs. 5% pacjentów w wieku poniżej 65 lat) występowały częściej u osób w podeszłym wieku leczonych produktem IMBRUVICA. ***Bezpieczeństwo długoterminowe*** Przeanalizowano dane dotyczące bezpieczeństwa z długoterminowej terapii produktem IMBRUVICA, trwającej ponad 5 lat, od 1284 pacjentów (wcześniej nieleczeni z CLL/SLL n = 162 i z nawrotową/lekooporną CLL/SLL n = 646, nawrotowym/lekoopornym MCL n=370 i WM n=106). Mediana czasu trwania leczenia CLL/SLL wynosiła 51 miesięcy (zakres od 0,2 do 98 miesięcy), przy czym 70% i 52% pacjentów otrzymywało leczenie, odpowiednio, przez ponad 2 lata i 4 lata. Mediana czasu trwania leczenia MCL wynosiła 11 miesięcy (zakres od 0 do 87 miesięcy), przy czym 31% i 17% pacjentów otrzymywało leczenie, odpowiednio, przez ponad 2 lata i 4 lata. Mediana czasu trwania leczenia WM wynosiła 47 miesięcy (zakres od 0,3 do 61 miesięcy), przy czym 78% i 46% pacjentów było leczonych, odpowiednio, przez ponad 2 lata i 4 lata. Ogólny znany profil bezpieczeństwa pacjentów narażonych na produkt IMBRUVICA pozostał stały, z wyjątkiem rosnącej częstości występowania nadciśnienia, bez żadnych nowych obaw dotyczących bezpieczeństwa. Częstość występowania nadciśnienia stopnia 3. lub wyższego wynosiła 4% (rok 0-1), 7% (rok 1-2), 9% (rok 2-3), 9% (rok 3-4) i 9% (rok 4-5); całkowita częstość występowania w okresie 5 lat wynosiła 11%. ***Dzieci i młodzież*** Ocena bezpieczeństwa opiera się na danych z badania 3. fazy, w którym stosowano produkt IMBRUVICA w skojarzeniu ze schematem zawierającym rytuksymab, ifosfamid, karboplatynę, etopozyd i deksametazon (RICE) lub schematem zawierającym rytuksymab, winkrystynę, ifosfamid, karboplatynę, idarubicynę i deksametazon (RVICI), jako terapia podstawowa lub sama terapia podstawowa u dzieci i młodzieży (w wieku od 3 do 19 lat) z nawrotowym lub opornym na leczenie, dojrzałym chłoniakiem nieziarniczym z komórek B. W tym badaniu nie zaobserwowano żadnych nowych działań niepożądanych. **Zgłaszanie podejrzewanych działań niepożądanych** Po dopuszczeniu produktu leczniczego do obrotu istotne jest zgłaszanie podejrzewanych działań niepożądanych. Umożliwia to nieprzerwane monitorowanie stosunku korzyści do ryzyka stosowania produktu leczniczego. Osoby należące do fachowego personelu medycznego powinny zgłaszać wszelkie podejrzewane działania niepożądane za pośrednictwem Departamentu Monitorowania Niepożądanych Działań Produktów Leczniczych Urzędu Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych, Al. Jerozolimskie 181C, PL02222 Warszawa, Tel.: +4822 4921301, Faks: +4822 4921309, Strona internetowa: https://smz.ezdrowie.gov.pl, Działania niepożądane można zgłaszać również podmiotowi odpowiedzialnemu.

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KATEGORIA DOSTĘPNOŚCI: Produkt leczniczy wydawany z przepisu lekarza - Rpz. Przed podaniem należy zapoznać się z zatwierdzoną Charakterystyką Produktu Leczniczego.

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