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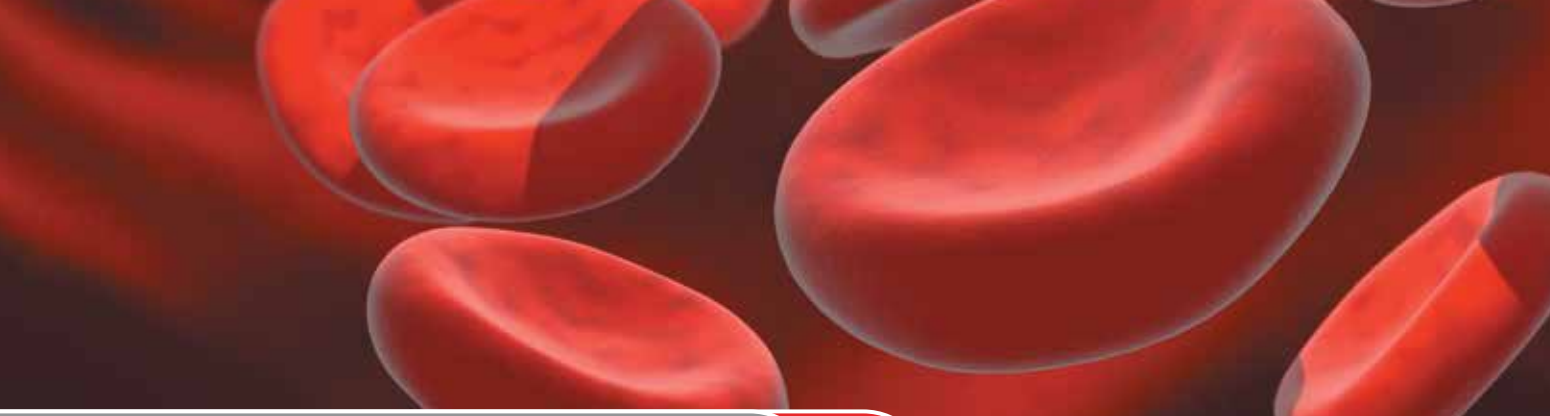

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Tabela1: Dane dotyczące zmniejszania dawki w przypadku MDS

Aktualna dawka	Zmniejszenie dawki
1,75 mg/kg	1,33 mg/kg
1,33 mg/kg	1mg/kg
1mg/kg	0,8 mg/kg

Jeżeli u pacjenta wystąpią utrzymujące się działania niepożądane stopnia 3 lub wyższego związane z leczeniem, leczenie powinno zostać opóźnione do momentu poprawy w zakresie toksyczności lub powrotu do stanu wyjściowego. Po opóźnieniu podania dawki pacjenci powinni ponownie rozpocząć leczenie od poprzedniej dawki lub zmniejszoną dawką zgodnie z wytycznymi dotyczącym i zmniejszania dawki. *Pominięcie dawek:* W przypadku pominięcia lub opóźnienia w stosunku do zaplanowanego podania leku pacjentowi należy jak najszybciej podać produkt leczniczy Reblozyl, a dawkowanie powinno być kontynuowane zgodnie z zaleceniami, z odstępem co najmniej 3 tygodni pomiędzy dawkami. *Pacjenci, u których nastąpiła utrata odpowiedzi:* Jeżeli u pacjentów nastąpi utrata odpowiedzi na leczenie z zastosowaniem produktu leczniczego Reblozyl, należy ocenić czynniki przyczynowe (np. epizod krwawienia). Jeżeli typowe przyczyny utraty odpowiedzi hematologicznej zostaną wykluczone, należy rozważyć zwiększenie dawki w sposób opisany powyżej dla konkretnego wskazania leczniczego. *Przerwanie stosowania produktu leczniczego*: Stosowanie produktu leczniczego Reblozyl należy przerwać, jeżeli u pacjenta nie nastąpi zmniejszenie zależności od transfuzji po 9 tygodniach leczenia (3 dawkach) przy maksymalnym poziomie dawki, jeżeli nie stwierdzono innych przyczyn wyjaśniających niepowodzenie odpowiedzi (np. krwawienie, zabieg chirurgiczny, inne choroby współistniejące)lub w przypadku wystąpienia niedopuszczalnej toksyczności. Szczególne populacje: *Pacjenci w podeszłym wieku*: Dostosowanie dawki początkowej nie jest wymagane w przypadku produktu leczniczego Reblozyl. *Pacjenci z zaburzeniami czynności wątroby* Dostosowanie dawki początkowej nie jest wymagane w przypadku pacjentów, u których poziom bilirubiny całkowitej (BIL) wynosi > górnej granicy normy (GGN) i (lub) aminotransferazy alaninowej (ALT) lub aminotransferazy asparaginianowej (AST) wynosi < 3 x GGN. Nie można sformułować konkretnych zaleceń dotyczących dawkowania w przypadku pacjentów z ALT lub AST ≥ 3xGGN lub uszkodzeniem wątroby stopnia ≥3 wg CTCAE z powodu braku danych. *Pacjenci z zaburzeniami czynności nerek:* Dostosowanie dawki początkowej nie jest wymagane w przypadku pacjentów z zaburzeniami czynności nerek o nasileniu łagodnym do umiarkowanego [szacunkowy współczynnik przesączania kłębuszkowego (ang. *estimated glomerular filtration rate*, eGFR) od < 90 do ≥ 30 ml/min/1,73 m^2]. Nie można sformułować konkretnych zaleceń dotyczących dawkowania w przypadku pacjentów z ciężkimi zaburzeniami czynności nerek (eGFR <30 ml/min/1,73 m^2) z powodu braku danych klinicznych. Pacjenci z zaburzeniami czynności nerek w punkcie wyjściowym powinni być uważnie monitorowani pod kątem czynności nerek w ramach leczenia standardowego. *Dzieci i młodzież* Stosowanie produktu leczniczego Reblozyl u dzieci i młodzieży we wskazaniu zespoły mielodysplastyczne nie jest właściwe. Sposób podawania: Podanie podskórne. Po rekonstytucji roztwór produktu leczniczego Reblozyl należy wstrzyknąć podskórnie w górną część ramienia, udo lub brzuch. Należy obliczyć dokładną całkowitą objętość sporządzonego roztworu wymaganego dla pacjenta i pobrać ją powoli z jednodawkowej fiolki/fiolek do strzykawki. Zalecana maksymalna objętość produktu leczniczego w miejscu wstrzyknięcia wynosi 1,2 ml. Jeśli wymagane jest podanie więcej niż 1,2 ml, całkowita objętość powinna zostać podzielona na oddzielne wstrzyknięcia o podobnej objętości i podawana w różne miejsca. Jeśli wymagane są wielokrotne wstrzyknięcia, do każdego wstrzyknięcia podskórnego należy użyć nowej strzykawki i igły. Z fiolki należy podać nie więcej niż jedną dawkę. Jeśli roztwór produktu leczniczego Reblozyl został schłodzony po rekonstytucji, należy go wyjąć z lodówki 15–30 minut przed wstrzyknięciem, aby umożliwić osiągnięcie temperatury pokojowej. Zwiększy to komfort wstrzyknięcia. **Przeciwwskazania:** Nadwrażliwość na substancję czynną lub na którąkolwiek substancję pomocniczą. Ciąża. **Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania** Identyfikowalność: W celu poprawienia identyfikowalności biologicznych produktów leczniczych należy czytelnie zapisać nazwę i numer serii podawanego produktu. Podwyższone ciśnienie krwi: W kontrolowanych badaniach klinicznych dotyczących MDS i β-talasemii u pacjentów leczonych luspatercept wykazano średni wzrost skurczowego i rozkurczowego ciśnienia krwi o 5 mm Hg w stosunku do wartości wyjściowej. Ciśnienie krwi należy monitorować przed każdym podaniem luspatercept. W przypadku utrzymującego się nadciśnienia lub zaostrzenia występującego wcześniej nadciśnienia pacjenci powinni otrzymywać leczenie nadciśnienia zgodnie z aktualnymi wytycznym i klinicznymi. Zawartość sodu Ten lek zawiera mniej niż 1 mmol (23 mg) sodu na dawkę, to znaczy lek uznaje się za „wolny od sodu". **Działania niepożądane:** Zarys profilu bezpieczeństwa: *Zespoły mielodysplastyczne:* Najczęściej zgłaszanymi działaniami niepożądanymi u pacjentów przyjmujących produkt leczniczy Reblozyl (u co najmniej 15% pacjentów) były zmęczenie, biegunka, osłabienie, nudności, zawroty głowy, ból pleców i ból głowy. Najczęściej zgłaszanymi działaniami niepożądanymi stopnia 3 lub wyższego (u co najmniej 2% pacjentów) były między innymi omdlenie/stan przedomdleniowy, zmęczenie, nadciśnienie tętnicze i osłabienie. Najczęściej zgłaszanymi ciężkimi działaniami niepożądanymi (u co najmniej 2% pacjentów) były zakażenie układu moczowego, ból pleców i omdlenie. Osłabienie, zmęczenie, zawroty głowy i ból głowy występowały częściej w trakcie pierwszych 3 miesięcy leczenia. Przerwanie leczenia z powodu działania niepożądanego nastąpiło u 2,0% pacjentów leczonych luspaterceptem. Działaniami niepożądanymi prowadzącymi do przerwania leczenia w grupie leczonej luspaterceptem były zmęczenie i ból głowy. Tabelaryczny wykaz działań niepożądanych Poniższa Tabela 2 zawiera dane dotyczące najwyższej częstotliwości występowania każdego działania niepożądanego, które zaobserwowano i zgłaszano w dwóch przed rejestracyjnych badaniach dotyczących MDS i β-talasemii. Działania niepożądane wymieniono poniżej według klasyfikacji układów i narządów i preferowanych terminów. Częstość występowania z definiowano w następujący sposób: 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) i bardzo rzadko(<1/10 000)

Tabela 2. Działania niepożądane u pacjentów leczonych produktem leczniczym Reblozylwprzypadku MDS

Klasyfikacja układów i narządów	Preferowany termin	Częstość (wszystkie stopnie)
Zakażenia i zarażenia pasożytnicze	zapalenie oskrzeli	Bardzo często
	zakażenie dróg moczowych	Bardzo często
	zakażenie górnych dróg oddechowych	Często
	grypa	Często
Zaburzenia układu immunologicznego	nadwrażliwość*	Często
Zaburzenia metabolizmu i odżywiania	hiperurykemia	Często
Zaburzenia układu nerwowego	zawroty głowy	Bardzo często
	ból głowy	Bardzo często
	omdlenie/stan przedomdleniowy	Często
Zaburzenia ucha i błędnika	zawroty głowy pochodzenia błędnikowego lub pozycyjne zawroty głowy pochodzenia błędnikowego	Często
Zaburzenia naczyniowe	nadciśnienie tętnicze~	Często
	zdarzenia zakrzepowo-zatorowe§	Często
Zaburzenia układu oddechowego, klatki piersiowej i śródpiersia	duszność	Bardzo często
Zaburzenia żołądka i jelit	biegunka	Bardzo często
	nudności	Bardzo często
Zaburzenia mięśniowo-szkieletowe i tkanki łącznej	ból pleców	Bardzo często
	bóle stawów	Często
	ból kości	Często
Zaburzenia ogólne i stany w miejscu podania	zmęczenie	Bardzo często
	osłabienie	Bardzo często
	reakcje w miejscu wstrzyknięcia#	Często

*Nadwrażliwość obejmuje obrzęk powiek, nadwrażliwość na lek, obrzęk twarzy, obrzęk około oczodołowy, obrzęk twarzy, obrzęk naczynioruchowy, obrzęk warg, wysypkę polekową. ~Reakcja nadciśnieniowa obejmuje samoistne nadciśnienie, nadciśnienie i przełom nadciśnieniowy. #Reakcje w miejscu wstrzyknięcia obejmują rumień w miejscu wstrzyknięcia, świąd w miejscu wstrzyknięcia, obrzęk w miejscu wstrzyknięcia i wysypkę w miejscu wstrzyknięcia. §Zdarzenia zakrzepowo-zatorowe obejmują zakrzepicę żył głębokich, zakrzepicę żył wrotnych, udar niedokrwienny i zatorowość płucną. Opis wybranych działań niepożądanych: *Ból kości*: Ból kości zgłoszono u 19,7% pacjentów z β-talasemią leczonych luspaterceptem (placebo 8,3%) oraz u 2,6% pacjentów z MDS leczonych luspaterceptem (placebo 3,9%). U pacjentów z β-talasemią leczonych luspaterceptem ból kości występował najczęściej w okresie pierwszych 3 miesięcy (16,6%) w porównaniu z miesiącami 4–6 (3,7%). Większość zdarzeń (41/44 zdarzeń) miała stopień nasilenia 1–2, przy czym 3 zdarzenia miały stopień nasilenia 3. Jedno z 44 zdarzeń było poważne, a 1 zdarzenie doprowadziło do przerwania leczenia. *Bóle stawów*: Bóle stawów zgłoszono u 19,3% pacjentów z β-talasemią leczonych luspaterceptem (placebo 11,9%) oraz u 5,2% pacjentów z MDS leczonych luspaterceptem (placebo 11,8%). W grupie pacjentów z β-talasemią leczonych luspaterceptem bóle stawów doprowadziły do przerwania leczenia u 2 pacjentów (0,9%). *Nadciśnienie tętnicze*: U pacjentów leczonych luspaterceptem wystąpił średni wzrost skurczowego i rozkurczowego ciśnienia krwi o 5 mm Hg w stosunku do punktu wyjściowego, którego nie zaobserwowano u pacjentów przyjmujących placebo. Nadciśnienie zgłoszono u 8,5% pacjentów z MDS leczonych luspaterceptem (placebo 9,2%) oraz u 8,1% pacjentów z β-talasemią leczonych luspaterceptem (placebo 2,8%). W grupie pacjentów z MDS zdarzenia o stopniu nasilenia 3 zgłoszono u 5 pacjentów (3,3%) leczonych luspaterceptem i u 3 pacjentów (3,9%) przyjmujących placebo. Nie przerwano leczenia w przypadku żadnego z pacjentów z powodu nadciśnienia. W grupie pacjentów z β-talasemią zdarzenia o stopniu nasilenia 3 zgłoszono u 4 pacjentów (1,8%) leczonych luspaterceptem (0,0% placebo).Nie przerwano leczenia w przypadku żadnego z pacjentów z powodu nadciśnienia. *Nadwrażliwość*: Reakcje typu nadwrażliwości (w tym obrzęk powiek, nadwrażliwość na lek, opuchlizna twarzy, obrzęk okołooczodołowy, obrzęk twarzy, obrzęk naczynioruchowy, obrzęk warg,wysypka polekowa) zgłoszono w przypadku 4,6% pacjentów z MDS (2,6% placebo) oraz 4,5% pacjentów z β-talasemią leczonych luspaterceptem (1,8% placebo). W badaniach klinicznych wszystkie zdarzenia miały stopień nasilenia 1/2. W grupie pacjentów z β-talasemią leczonych luspaterceptem nadwrażliwość doprowadziła do przerwania leczenia u 1 pacjenta (0,4%). *Reakcje w miejscu wstrzyknięcia*: Reakcje w miejscu wstrzyknięcia (w tym rumień w miejscu wstrzyknięcia, świąd w miejscu wstrzyknięcia, obrzęk w miejscu wstrzyknięcia i wysypka w miejscu wstrzyknięcia)zgłoszono w przypadku 3,9% pacjentów z MDS (placebo 0,0%) i u 2,2% pacjentów z β-talasemią otrzymujących luspatercept (placebo 1,8%). W badaniach klinicznych wszystkie zdarzenia miały stopień nasilenia 1, a żadne nie doprowadziło do przerwania leczenia. *Zdarzenia zakrzepowo-zatorowe*: Zdarzenia zakrzepowo-zatorowe (w tym zakrzepica żył głębokich, zakrzepica żył wrotnych, udar niedokrwienny i zatorowość płucna) wystąpiły u 3,6% pacjentów z β-talasemią otrzymujących luspatercept (placebo 0,9%). Wszystkie zdarzenia zgłoszono u pacjentów, którzy zostali poddani splenektomii, i u których występował co najmniej jeden inny czynnik ryzyka. Nie zaobserwowano różnic w zakresie zdarzeń zakrzepowo-zatorowych pomiędzy grupami otrzymującymi miluspatercept i placebo w przypadku pacjentów z MDS. *Immunogenność* W badaniach klinicznych dotyczących MDS analiza 260 pacjentów z MDS, którzy byli leczeni luspaterceptem i kwalifikowali się do oceny obecności przeciwciał przeciw luspaterceptowi, wykazała, że 23 (8,8%) pacjentów z MDS uzyskało dodatni wynik badania pod kątem obecności przeciwciał przeciw luspaterceptowi wytworzonych w toku leczenia, w tym u 9 (3,5%) pacjentów z MDS stwierdzono przeciwciała neutralizujące przeciw luspaterceptowi. W badaniach klinicznych dotyczących β-talasemi i analiza 284 pacjentów z β-talasemią, którzy byli leczeni luspaterceptem i kwalifikowali się do oceny obecności przeciwciał przeciw luspaterceptowi, wykazała, że 4 (1,4%) pacjentów z β-talasemią uzyskało dodatni wynik badania pod kątem obecności przeciwciał przeciw luspaterceptowi wytworzonych w toku leczenia, w tym u 2 (0,7%) pacjentów z β-talasemią stwierdzono przeciwciała neutralizujące przeciw luspaterceptowi. Stężenie luspaterceptu w surowicy wykazywało tendencję malejącą w obecności przeciwciał neutralizujących. Nie odnotowano ciężkich systemowych reakcji nadwrażliwości u pacjentów, u których występowały przeciwciała przeciw luspaterceptowi. Nie występował związek pomiędzy reakcjami typu nadwrażliwości lub reakcjami w miejscu wstrzyknięcia a obecnością przeciwciał przeciw luspaterceptowi.

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Incidence and disease prevalence for lymphoid neoplasms in Poland

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The incidence and prevalence of lymphoid neoplasms would appear to be on the increase due to population aging and the introduction of new treatment modalities in these diseases. However, finding support for such a general remark based on data from registers is very challenging, not only worldwide but specifically in Poland.

The aim of the authors of the article entitled "Incidence and prevalence of lymphatic neoplasms in Poland 2009–2015 determined on analysis of National Health Fund data used in the 'Maps of healthcare needs — database of systemic and implementation analyses' project" published in the current issue of "Acta Haematologica Polonica", was to analyze data from the Polish national healthcare provider (Narodowy Fundusz Zdrowia) [1]. This unique methodology may overcome some limitations inherent in the National Cancer Registry (Krajowy Rejestr Nowotworowy), which was created to collect and analyze data mainly from patients with solid tumors. The most common lymphoid malignancies were analyzed at national and regional levels. It was previously pointed out that there has been underrepresentation of the incidence of mantle cell lymphoma (MCL) and of follicular lymphoma (FL). For instance, in 2006, the calculated prevalence of MCL and FL was c.0.6 per 100,000 per year [2]. This figure is much lower than that found in other Western countries, and this has led experts to speculate as to possible differences in the prevalence between Poland and other European countries. Here, the calculated incidence rate for FL in 2014 was 1.74 per 100,000 per year, which is not much less than the 2.18 per 100,000 per year found in the European HAEMACARE study [3]. In the register of the British Hematological Malignancy Research Network (HMRN), the incidence rate of FL in 2004–2014 was 3.23 per 100,000 per year [4], and according to SEER (the Surveillance, Epidemiology and End Results program of the US National Cancer Institute), the standardized incidence rate was 2.7 per 100,000 per year [5]. Interestingly, in the US using statistical models for analysis, the age-adjusted rate for new FL cases fell by on average 1.9% per year between 2009 and 2018. The rate of new cases of diffuse large B-cell lymphoma (DLBCL) was 3.76 per 100,000 men and women in 2014 in Poland. Updated SEER results show DLBCL to have a higher incidence of 5.6 cases per 100,000 per year. Very interesting data has been generated for the incidence of chronic lymphocytic leukemia (CLL) in Poland. The 8.65 cases per 100,000 per year recorded in 2014 was much higher than that reported in recent years in the US (e.g. 4.6 per 100,000 per year in 2019) even though the number of CLL cases fell by on average 1.8% each year between 2009 and 2018. Age-adjusted death rates were stable over the same period. Globally, in contrast, the proportion of CLL cases more than doubled between 1990 and 2017 [6]. The greatest increase in CLL patients was detected in East Asia, followed by Southeast Asia and Eastern Europe. In Europe, the highest incidence was observed in the UK (5.27 per 100,000 per year). The incidence of multiple myeloma (MM) was 4.92 per 100,000 per year in 2014, with 1,900 new cases. Using a similar methodology, we identified more than 2,000 new patients in 2016 [7]. In SEER, the rate of new MM cases was 7.1 per 100,000 men and women per year. The numbers in the US seem to have been stable over the period 2009–2018, with age-adjusted death rates falling by on average 1.0% each year 2010–2019.

These differences in the incidences around the world are interesting, but significant discrepancies across Europe might also point to unmet medical needs in the proper registry of patients with hematological malignancies in Poland.

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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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Treatment recommendations of Polish Adult Leukemia Group (PALG) for management of myelodysplastic syndromes (MDS) and other MDS-related conditions in Poland

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Abstract

Myelodysplastic syndromes (MDS) comprise a heterogeneous group of malignant hematopoietic stem cell disorders that are characterized by ineffective blood cell production and a variable risk of transformation into acute myeloid leukemia. In recent years, significant progress in MDS biological research has allowed the addition of new drugs to the few existing therapeutic options.

This article presents the recommendations of MDS experts of the Polish Adult Leukemia Group for the treatment of myelodysplastic syndromes, and for the management of conditions that are particularly common in patients with MDS i.e. infections, iron overload, and disease recurrence after hematopoietic cell transplantation. The aim of this study was to present a clear therapeutic algorithm to facilitate decision-making in everyday practice.

Key words: myelodysplastic syndromes, treatment, recommendations

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Introduction

The choice of treatment for patients with myelodysplastic syndromes (MDS) is determined by the level of risk of transformation into acute myeloid leukemia (AML), as well as by the predicted overall survival time according to the prognostic scoring systems International Prognostic Scoring System (IPSS) and Revised International Prognostic Scoring System (IPSS-R):

- the lower-risk group (MDS-LR) consists of patients with low and intermediate-1 risk according to IPSS, or very low, low, and intermediate risk with scores ≤3.5 according to IPSS-R;
- the higher-risk group (MDS-LR) consists of patients with intermediate-2 or high risk according to IPSS, or intermediate with scores ≥4.0, high, or very high risk according to IPSS-R [1, 2].

The goal of treatment in lower-risk patients is to obtain hematological improvement, and the quality of life (QoL) improvement that comes with that. Taking into account the relatively favorable prognosis, and the toxicity of therapy, aggressive treatment is not usually used in this population (Figure 1).

In higher-risk patients, depending on their general condition and the biological characteristics of the underlying disease, palliative or disease-modifying treatments (i.e. hypomethylating agents, chemotherapy) are used with the intention of prolonging survival and improving QoL or even as curative treatment [e.g. allogeneic hematopoietic stem cell transplantation (allo-HSCT)] (Figure 2).

Treatment response criteria

Treatment response is assessed according to the International Working Group (IWG) 2006 criteria, modified in 2018 for MDS-LR patients. Such responses include increases in blood cell count, reductions in the number of transfusions or transfusion independence, and reductions in bone marrow blasts percentages (Tables I and II) [3, 4].

Treatment of lower-risk patients

Blood product transfusions

Red blood cell (RBC) transfusions are given to prevent the serious complications of anemia, including heart failure and myocardial infarction. Chronic persistence of anemia, with hemoglobin (Hb) levels <9 g/dL in men and <8 g/dL in women, contributes to an increased risk of death and cardiovascular events [5, 6]. However, there is no data on the optimal time at which to start transfusions in MDS-LR patients, and the decision to transfuse RBC is based on clinical symptoms and Hb level.

Although the severity of anemia has a significant impact on the QoL of MDS patients, the Hb level at which RBC should be transfused has not been determined [7]. The only randomized study in MDS-LR patients comparing two thresholds for transfusion e.g. restrictive (8.0 g/dL, maintaining Hb level 8.5–10.0 g/dL) versus liberal (10.5 g/dL, maintaining Hb level 11.0–12.5 g/dL) favored the liberal versus the restrictive policy in relation to improvements in the five main QoL components [8].

The concept of RBC transfusion dependence (TD) is not clearly defined. The consensus is that patients who require two RBC concentrate units/month are transfusion-dependent. According to the 2018 IWG criteria, patients with red blood cell transfusion dependency (RBC-TD) are those who require a transfusion of ≥3 units/16 weeks [4]. RBC-TD is associated with shorter survival and faster transformation into AML [9]. However, an European MDS Registry (EU-MDS Registry) analysis found that even transfusion <3 units/16 weeks was associated with an increased risk of MDS progression [10]. Accordingly, it may be that we should consider all patients receiving regular transfusions as TD. Recommendations for transfusion of RBC and platelet concentrates (PC) are set out in Tables III [11–14] and IV [15–21]. Recommended platelets (PLT) level when performing invasive procedures are presented in Table V.

Erythropoiesis-stimulating agents

Erythropoiesis-stimulating agents (ESAs) are recommended as first-line treatment in MDS-LR patients with symptomatic anemia and Hb levels below 10 g/dL [2, 15]. Erythropoietin alpha has been registered in the European Union in this indication, and darbepoetin (approved only in the Unites States) is widely used in Poland and other European countries [22, 23]. The use of ESAs in patients with symptoms of anemia and higher Hb levels depends on individual clinician decision. Appropriate patient qualification determines the success of treatment. The validated and preferred predictive response model is the Nordic index.

The benefits of ESA treatment have been observed in patients with erythropoietin (EPO) levels below 500 U/L and a transfusion requirement of less than 2 RBC units/month (see Table VI) [24]. However, the greatest benefit is derived from starting ESA treatment before the patient becomes dependent on RBC transfusions. Initiating ESA treatment within 6 months of diagnosis improves response rates and delays the need for transfusion [25, 26].

Detailed information on the dosing and treatment regimen of ESA is provided in Figure 3. Treatment failure should only be considered after 24 weeks of ESA administration, with or without granulocyte colony-stimulating factor (G-CSF).

The response rate to ESA treatment is 38–60%, median time to response to ESA is 2–3 months, and median duration of response is 18–24 months [22–24, 27]. For non-responders,

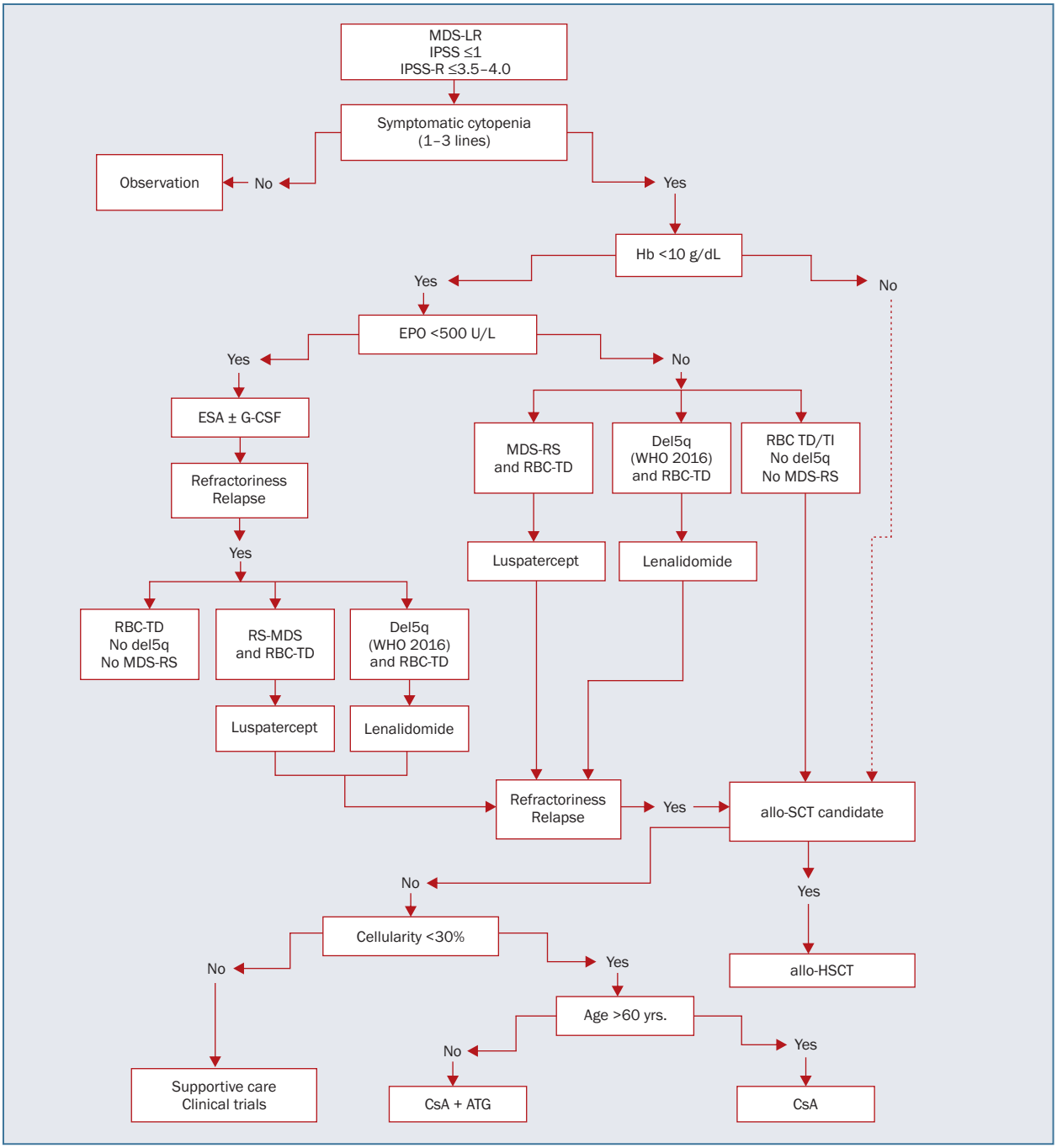

Figure 1. Therapeutic algorithm in patients with low-risk myelodysplastic syndromes (MDS); allo-HSCT — allogeneic hematopoietic stem cell transplantation; CsA — cyclosporine; ATG — anti-thymocyte globulin; ESA — erythropoiesis stimulating agent; G-CSF — granulocyte colony-stimulating factor; Hb — hemoglobin level; IPSS — International Prognostic Scoring System; IPSS-R — Revised International Prognostic Scoring System; MDS-LR — low-risk myelodysplastic syndrome; MDS-RS — MDS with ring sideroblasts; RBC-TD — red blood cell transfusion dependency

increasing the ESA dose and adding G-CSF allows a response to be obtained in an additional c.20% of patients [28, 29]. Patients who achieve complete (Hb >11.5 g/dL) or partial (Hb elevation >1.5 g/dL and RBC independence but Hb <11.5 g/dL) RBC response should continue treatment at the lowest dose needed to maintain the response [24].

There is no clinical data describing the management of only a minor RBC response according to IWG 2018 (reduction in the number of RBC transfusions by half). However, it seems justified to continue treatment at the current doses or, if possible, with increased ESA doses or in combination with G-CSF.

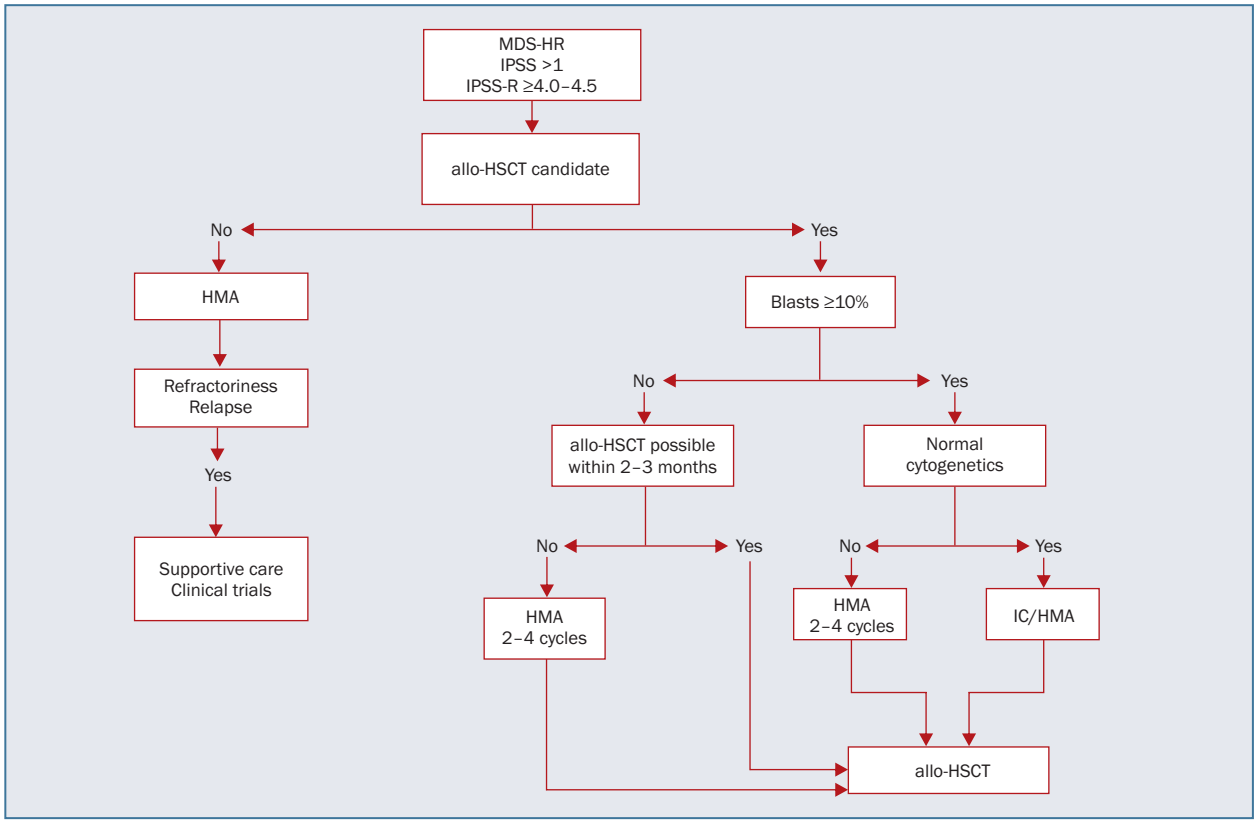

Figure 2. Therapeutic algorithm in patients with high-risk myelodysplastic syndromes (MDS); allo-HSCT — allogeneic hematopoietic stem cell transplantation; HMA — hypomethylating agent; IC — intensive chemotherapy; IPSS — International Prognostic Scoring System; IPSS-R — Revised International Prognostic Scoring System; MDS-HR — high-risk myelodysplastic syndrome

Although the risk of thromboembolic complications in MDS patients treated with ESA is less than 2%, it seems appropriate to temporarily discontinue treatment if a rapid increase in hematocrit is observed, or if Hb level increases above 12 g/dL [22, 23, 30]. ESA can be re-started in a reduced dose, and responses should be carefully monitored [15].

The Polish Adult Leukemia Group (PALG) MDS working group's indications for the treatment of ESA ± G-CSF are as follows patients in MDS LR group according to IPSS with:

- symptomatic anemia (regardless of RBC-TD although it is optimal to start treatment before RBC transfusion demand is ≥2 units/month) and
- EPO level <500 U/L

In non-responding patients or after loss of response to ESA some efficacy is shown by: lenalidomide, immunosuppressants, hypomethylating agents (HMA), luspatercept, and allogeneic hematopoietic stem cell transplantation (allo-HSCT) in selected cases.

Thrombopoietin receptor agonists

Thrombopoietin receptor agonists (TPO-RAs), romiplostim and eltrombopag are not approved for the treatment of thrombocytopenia in MDS-LR patients. Romiplostim at a dose of 500 to 1,500 µg weekly has increased platelet count in 36–65% of patients [31–33]. Eltrombopag at a dose of 150–300 mg/day has increased platelet count in 47% of MDS LR patients [34]. The use of both drugs allows for a significant reduction in the frequency of bleeding complications, and a reduction in the number of platelet transfusions. Some concerns have been raised by the impact of TPO-RA on the increased risk of transformation into AML. A transient increase in blasts percentage that resolves after drug discontinuation has been observed in 15% of patients, and a long-term follow-up did not confirm a higher transformation risk or increased mortality in patients receiving romiplostim [35]. The efficacy and safety of TPO-RA has not been confirmed in phase III studies, and therefore these drugs should be used with caution in clinical trials in patients with a blast percentage below 5%.

No phase III study has been conducted so far that would confirm the efficacy and safety of TPO-RA, and these drugs have not been approved for the treatment of patients with myelodysplastic syndromes in either the United States or Europe. Therefore they are not recommended by Polish experts in routine clinical practice.

It is worth noting however that TPO-RA may be a valuable therapeutic option in MDS-LR patients with severe

Table I. 2006 International Working Group (IWG) myelodysplastic syndrome (MDS) response criteria (based on [3])

Category	Response criterion (must last at least 4 weeks)
Complete remission (CR)	Bone marrow: ≤5% myeloblasts with normal maturation of all cell lines Persistent dysplasia permissible Hb: ≥11 g/dL, platelets: ≥100 G/L, neutrophils: ≥1.0 G/L, blasts: 0%
Partial remission (PR)	All CR criteria if abnormal before treatment, except bone marrow blasts decreased by ≥50% over pretreatment but still >5%
Marrow complete remission (mCR)	Bone marrow: ≤5% myeloblasts and decreased by ≥50% over pretreatment regardless of peripheral blood response
Stable disease (SD)	Failure to achieve CR and PR, but no evidence of progression for >8 weeks
Progressive disease (PD)	For patients with: • less than 5% blasts: 50% increase in blasts to 5% blasts • 5–10% blasts: 50% increase to 10% blasts • 10–20% blasts: 50% increase to 20% blasts • 20–30% blasts: 50% increase to 30% blasts Any of the following: • at least 50% decrement from maximum remission/response in granulocytes or platelets • reduction in Hb by 2 g/dL • transfusion dependence
Relapse after CR or PR	At least one of the following: Return to pretreatment bone marrow blast percentage Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets Reduction in Hb concentration by ≥1.5 g/dL or transfusion dependence
Hematological improvement (HI)	Response criteria (responses must last at least 8 weeks):
Erythroid response (HI-E) (pretreatment, <11 g/dL)	• Hb increase by ≥1.5 g/dL • relevant reduction of units of RBC transfusions by ≥4 RBC transfusions/8 weeks
Platelet response (HI-PLT) (pretreatment PLT <100 G/L)	• absolute increase of ≥30 G/L for patients starting with <20 G/L platelets • increase from <20 G/L to ≥20 G/L and by at least 100%
Neutrophil response (HI-G) (pretreatment <1.0 G/L)	• at least 100% increase and an absolute increase >0.5 G/L

Hb — hemoglobin level; RBC — red blood cells

Table II. Revised International Working Group (IWG) 2018 hematological response criteria in patients with myelodysplastic syndrome (MDS) (based on [4])

Line	Pretreatment criteria	Response criteria
HI-E	NTD = (0 RBC in 16 weeks) [1] Transfusion independent anemia: 0 RBC in 16 weeks LTB: 3–7 RBC in 16 weeks in at least 2 TRSFN episodes max 3 in 8 weeks HTB: ≥8 RBC in 16 weeks ≥4 in 8 weeks	HI-E response: at least 2 consecutive Hb measurements with increase of ≥1.5 g/dL for minimum of 8 weeks in observation period of 16–24 weeks HI-E response: TRSFN independence for minimum of 8 weeks in an observation period of 16–24 weeks Major HI-E response: TRSFN independent over a period of a minimum of 8 weeks in an observation period of 16–24 weeks Minor HI-E: reduction by at least 50% of RBC over a minimum of 16 weeks
Platelet response	20 G/L <PLT <100 G/L 0 <PLT < 20 G/L	Absolute increase of ≥30 G/L Increase to >20 G/L and by at least 100%
Neutrophil response	NEU <1.0 G/L	At least 100% increase and absolute increase >0.5 G/L

Hb — hemoglobin level; HI-E — hematological improvement-erythroid response; HTB — high transfusion burden; LTB — low transfusion burden; NEU — neutrophils; NTD — not transfusion dependent; PLT — platelet count; RBC — red blood cells; TRSFN — transfusion

Table III. Recommendations for red blood cell (RBC) transfusion in patients with low-risk myelodysplastic syndrome (MDS-LR) (based on [11–14])

Hb threshold for RBC transfusion should be individualized depending on:
• comorbidities
• symptoms at a given Hb level
• observed clinical benefits after previous transfusions
• patient preferences
No specific Hb level can be recommended as a threshold for RBC transfusion. But in asymptomatic patients with chronic anemia, Hb transfusion should be considered when Hb level is <8 g/dL
No single target Hb level can be recommended, but it should be taken into account that chronic anemia with Hb <8–9 g/dL significantly increases risk of cardiovascular disease and death
No limit on frequency or total number of units transfused lifelong into MDS patient
Frequency of transfusions should reflect duration of clinical benefit between transfusions
Routine RBC phenotypic selection is not recommended for all MDS patients treated with transfusions, but may be considered for patients with little improvement after RBC transfusions
Multiple recipients should be transfused with leukocyte-depleted preparations

Hb — hemoglobin level

Table IV. Recommendations for platelets (PLT) transfusion in patients with low-risk myelodysplastic syndrome (MDS-LR) (based on [15–21]

Prophylactic PLT transfusion is not recommended in asymptomatic patients not receiving MDS modifying therapy
Preventive PLT transfusions (routinely transfuse only one PLT package (1 unit/10 kg bw):
• in patients receiving intensive chemotherapy/hypomethylating drugs or undergoing allo-HSCT to maintain PLT levels ≥10 G/L, even without clinically significant bleeding (grade 0–1 and not requiring invasive procedures)
• in patients in serious condition/seriously ill, even if there is no active bleeding or no invasive procedure planned
• individual assessment of patients with chronic bleeding of WHO grade ≥2 according to symptoms severity and establishing strategies for prophylactic PLT transfusions, e.g. twice a week
In patients with bleeding, use of anti-fibrinolytic agents such as tranexamic acid should be considered [21]

allo-HSCT — allogeneic hematopoietic stem cell transplantation; WHO — World Health Organization

thrombocytopenia in whom other therapeutic options (azacitidine, allo-HSCT) are not considered. Neither of these drugs is reimbursed in Poland for this indication.

Table V. Recommended platelets (PLT) level when performing invasive procedures [17–20]

Procedure	Recommended PLT level [G/L]
Placement of central catheters:	>20–30
• tunneled	
• non-tunneled	
Major surgery	>50
Lumbar puncture	≥40
Epidural catheter insertion/removal	≥80
Percutaneous liver biopsy	>50
Neurosurgery	>100
Ophthalmic surgery for posterior segment of eye	

Table VI. Predictive model of response to erythropoiesis-stimulating agents (ESA) treatments

Need for transfusions, point	EPO level [IU/L], point
<2 RBC unit/month, 0	<500, 0
≥2 RBC unit/month, 1	≥500, 1
Anticipated response to ESA treatment:	
score 0 = 74%, score 1 = 23%, score 2 = 7%	

RBC — red blood cells

Granulocyte colony-stimulating factors

Neutropenia occurs in 15–20% of MDS-LR patients [36]. Although the use of G-CSFs increases the number of neutrophils in 60–75% of patients with neutropenia, chronic use of G-CSF is not recommended because it does not prolong survival in these patients. In addition, the possibility of transformation into AML, or progression to more advanced MDS, in patients treated with G-CSF has not been absolutely ruled out [37, 38]. G-CSFs are currently recommended in MDS LR patients with dominant neutropenia, but only with recurrent or severe infections [2, 39].

Lenalidomide

Lenalidomide at a dose of 10 mg for 21 days in 28-day cycles is recommended in MDS-LR patients with del5(q) who have lost a response or who are not candidates for ESA treatment [4, 5]. Erythroid response is achieved after 4–5 weeks in 61–76% of patients, RBC independence in 56–67% of patients, and 50–73% of patients achieve a cytogenetic response, including 29–45% of complete responses [40, 41]. Median overall survival in lenalidomide-treated patients is 3.5–4 years, and 5.7 years in patients who achieved transfusion independence.

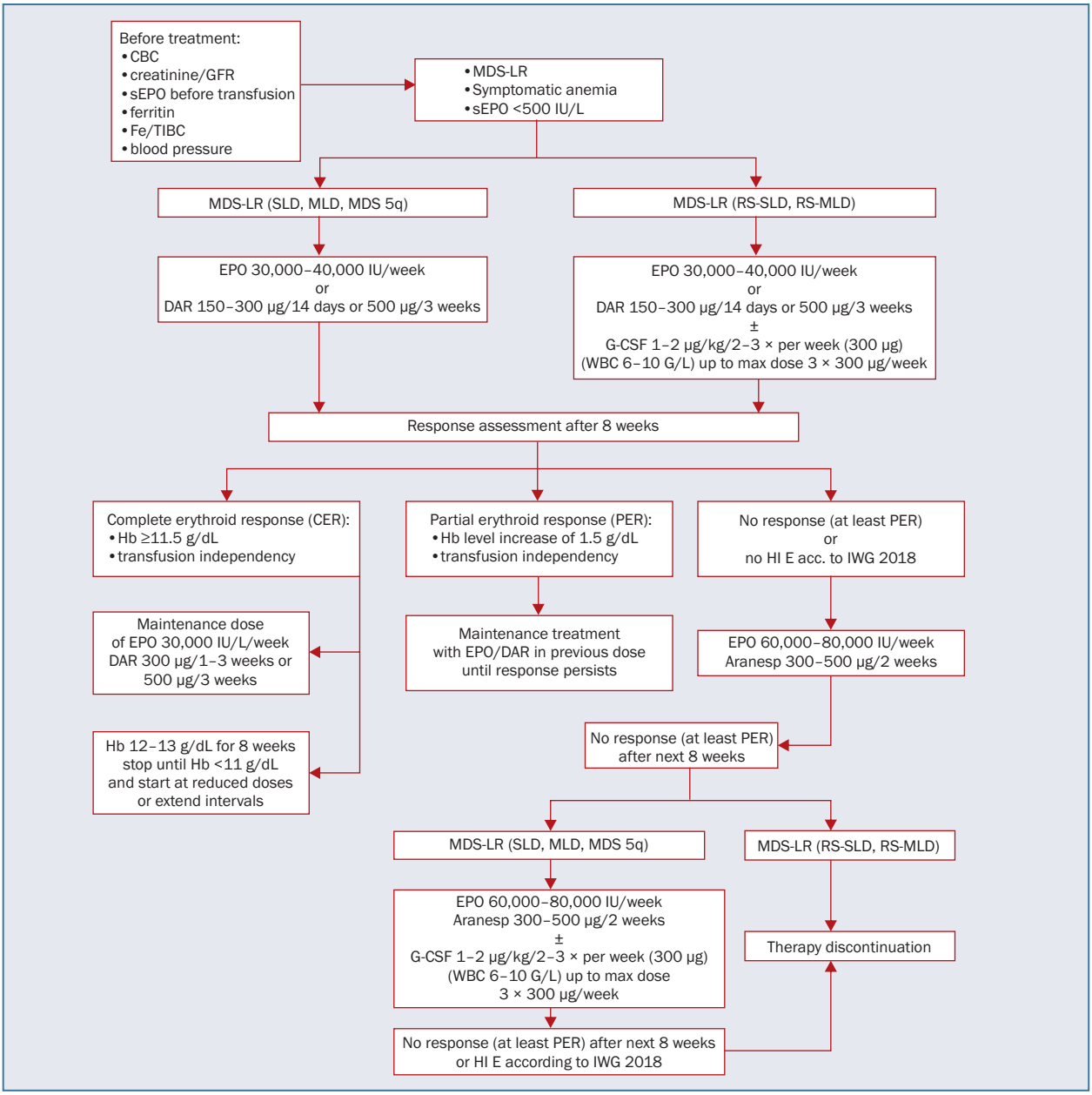

Figure 3. Algorithm of treatment with erythropoiesis stimulating proteins in patients with myelodysplastic syndromes (MDS); CBC — complete blood count; DAR — darbepoetin; EPO — erythropoietin; Fe — ferrum; G-CSF — granulocyte colony-stimulating factor; GFR — glomerular filtration rate; Hb — hemoglobin level; HI-E according to IWG 2018 — hematological improvement-erythroid response according to revised International Working Group (IWG) 2018 hematological response criteria; MDS-LR — low-risk myelodysplastic syndrome; MLD — multilineage dysplasia; N — normal level; PER — partial erythroid response; RS — ring sideroblasts; sEPO — serum erythropoietin; SLD — single lineage dysplasia; TIBC — total iron binding capacity; WBC — white blood cells

The most common side effects of lenalidomide are neutropenia (75%) and thrombocytopenia (40%), with 70% of patients requiring drug discontinuation in the first month of treatment and subsequent dose reduction to 5 mg when restarted [42]. In recurrent neutropenia, 1–2 injections of G-CSF weekly should be considered. In cases of renal failure, the dose of lenalidomide should be reduced to a minimum of 2.5 mg every other day. Due to the increased risk of thromboembolic events with lenalidomide, it is reasonable to use anticoagulation prophylaxis, especially when additional risk factors are present.

In Poland, lenalidomide is reimbursed only in patients with an isolated del5(q) and RBC dependence, although the National Comprehensive Cancer Network (NCCN) recommends the use of lenalidomide before the need for transfusion and in patients with an isolated chromosome

5 deletion. According to the European LeukemiaNet (ELN) guidelines, patients may have an additional cytogenetic aberration except chromosome 7 disorder or deletion 17. The *TP53* gene mutation is found in c.20% of MDS patients with del5q and is a negative prognostic and predictive factor for response to lenalidomide, although the chance of RBC independence is comparable to that in patients without *TP53* gene mutation.

In patients without del5(q) and transfusion dependence treated with lenalidomide, hematological improvement-erythroid (HI-E) is achieved in 43% of patients, and RBC independence in 27% of patients, with a response duration of 8 months [43]. Treatment with lenalidomide in combination with ESA does not significantly alter treatment outcome: HI-E is achieved by 39% of patients, and RBC independence in 24% of patients with a response duration of 15 months [44]. Lenalidomide is not approved for the treatment of anemia in patients without del(5q), and its use is associated with the possibility of developing or worsening of neutropenia and thrombocytopenia.

Indications for lenalidomide treatment (all criteria must be met):

- low-risk or intermediate-low-risk MDS according to IPSS;
- isolated del5 (+ possibly an additional abnormality except chromosome 7 disorder or del 17);
- symptomatic anemia and RBC independence (Hb 8–10 g/dL): dose of 5 mg or patients with RBC-TD: dose of 10 mg.

Luspatercept

Luspatercept was registered in 2020 in the European Union (EU) based on MEDALIST, a randomized phase III trial for the treatment of patients with (myelodysplastic syndrome with ring sideroblasts) MDS-RS subtype with RBC-TD who failed or were not eligible for ESA treatment. Luspatercept, a transforming growth factor beta (TGF-β) receptor inhibitor, unblocks the proper erythroblasts maturation and differentiation, acting synergistically with erythropoietin on the proliferation of immature red blood cells. In the MEDALIST [A Study of Luspatercept (ACE-536) to Treat Anemia Due to Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes] study, luspatercept administered subcutaneously at a dose of 1.0–1.75 mg/kg every 3 weeks resulted in RBC independence for at least 8 weeks in 47% of patients, and HI-E according to IWG 2006 criteria in 53% of patients. The median duration of transfusion independence was 30 weeks, and the median duration of HI-E was 83.6 weeks. The most common side effects in patients treated with luspatercept were weakness, diarrhea, nausea, and chills. Treatment was discontinued in 8% of patients due to grade 3 or more adverse events [45]. In patients with ring sideroblasts percentage <15%, luspatercept is slightly less effective, although the response rate is still 29–43% [46].

Immunosuppressive treatment

Immunosuppressive therapy (IST) can be used in MDS-LR patients with symptomatic cytopenia, with thrombocytopenia or neutropenia even in the first line [37], and in the case of anemia only after the failure of first and/or second line treatment. Although hypocellular bone marrow, the presence of HLA-DR 15, age less than 60 years, normal karyotype or trisomy 8, the presence of paroxysmal nocturnal hemoglobinuria (PNH) clone, and short RBC dependence duration are often considered to be predictors of a favorable response to IST, a study by Sloand et al. [47], and Stahl et al. [48] showed that none of these factors had predictive value for achieving ed blood cell transfusion dependency (RBC-TD), except for hypocellular bone marrow <20%.

Anti-thymocyte globulin (ATG) with or without cyclosporin is used for IST; horse ATG (h-ATG) is more effective, but it is only available in the United States [49]. A meta-analysis of trials with IST in MDS-LR patients showed 42% of responses and 33% of RBC independence. In the elderly, cyclosporine can be used as monotherapy, and the chances of achieving overall response (OR), HI-E, and transfusion independency (TI) are 47%, 50%, and 45%, respectively [48].

Other agents

HMA are not approved in the EU for use in MDS-LR patients, although 20–30% of ESA and/or lenalidomide failures achieve response [50, 51]. In patients with MDS LR, the use of 5-day treatment regimens allows for comparable efficacy as the 7-day courses, and with less toxicity [52]. Patients who have failed treatment with ESA and/or lenalidomide should be offered available clinical trials with new drugs whenever possible.

Iron chelating agents

Iron overload resulting from RBC transfusions (1 unit contains 200–250 mg of iron), and significant hyperferritinemia associated with e.g. ineffective iron metabolism, adversely affect overall survival in MDS patients [53–55]. Ferritin levels should be measured in MDS-LR patients every 12 weeks [15]. Chelation therapy should be started after an infusion of 20–25 units of RBC concentrate or when ferritin levels exceed 1,000 µg/L with the proviso that the patient's non-MDS-related life expectancy exceeds 3 years, and always in HSCT candidates with iron overload regardless of IPSS risk score [56–58].

Deferoxamine is used at a dose of 30–40 mg/kg/day in infusions lasting many hours (e.g. 10–12 h) (subcutaneously or intravenously), at least 5 days a week, until the ferritin level drops below 1,000 µg/L. Deferasirox at a dose of 20–30 mg/kg can be used to obtain a ferritin concentration below 500 µg/L, but this drug is not reimbursed in Poland in adult patients.

In the prospective, randomized TELESTO [Myelodysplastic Syndromes (MDS) Event Free Survival With Iron Chelation Therapy] study, oral deferasirox (20–30 mg/kg) prolonged (2:1) the time to onset of hepatic and heart failure compared to a placebo [59].

Phlebotomy should be considered in patients after allogeneic hematopoietic cell transplantation who are still iron overloaded and no longer anemic.

The Polish experts recommend the use of iron chelators in patients with MDS with low or intermediate-1 risk score according to IPSS and:

- with serum ferritin level >1,000 µg/L
  and/or
- who received over 25 units of RBC concentrate;
- with two patient-related factors (not related to MDS) that could shorten survival to less than 3 years.

Treatment of higher risk MDS patients

Chemotherapy (intensive and low-dose)

Anthracyclines and cytarne-based intensive chemotherapy (IC) in high-risk myelodysplastic syndrome (MDS-HR) patients has limited indications due to low efficacy and high toxicity. The complete remission (CR) rate is 36–60%, and is particularly low in patients with unfavorable prognostic karyotype. The duration of remission is short (10–12 months), and prolonged periods of aplasia are more common than in AML patients [60, 61].

Low doses of cytarne, e.g. 20 mg/m^2/day for 14–21 days in 4-week cycles, make it possible to achieve CR/partial remission (PR) in 15–20% of patients, although their use is associated with a shorter overall survival compared to HMA, and therefore this treatment regimen is not recommended.

Intensive chemotherapy is recommended in patients:

- with MDS-HR (>10% bone marrow blasts) without severe comorbidities, up to 65–69 years without unfavorable prognostic cytogenetics according to IPSS and IPSS-R and/or *TP53* mutations/deletions
- and who
- are candidates for allo-HSCT (for remission).

The use of IC in patients who do not have a donor, or do not agree to allo-HSCT, is debatable.

Hypomethylating agents

Patients at higher risk according to IPSS who are not eligible for allo-HSCT are candidates for azacitidine treatment according to the Summary of Product Characteristics (SmPC). It should be noted however that some patients qualified for an allo-HSCT procedure may benefit from azacitidine as first-line treatment. According to the SmPC, the use of azacitidine in this group of patients is possible because at the time of commencing this drug the patient may not be eligible for allo-HSCT due to high MDS activity, and after several treatment cycles remission could be achieved, allowing for the transplantation. The dose of azacitidine is 75 mg/m^2 administered subcutaneously for 7 days on/21 days off (28-day cycle). For organizational reasons, the drug can be administered within a 5-day schedule with a 2-day break (weekend) and then two consecutive days of drug administration (i.e. 5 + 2 + 2). The treatment results are similar to those of the 7-day regimen.

In patients treated with azacytidine, CR rate is 17%, PR rate 12%, and hematological improvement (HI) including possible CR and PR is 49%.

The median time to response is four treatment cycles, so it is important that the patient is able to receive at least three; 24–37% of patients receive up to three [62]. The response duration is 9–15 months, but much shorter (4 months) in patients with complex karyotype [63]. Patients who have achieved CR, PR, or hematological response (e.g. RBC, PLT transfusion independence) should receive the drug until disease progression or unacceptable toxicity. Discontinuation of azacitidine treatment leads to rapid progression.

The most common adverse reactions are grade 3–4 peripheral cytopenias: neutropenia (84%), thrombocytopenia (74%), anemia (54%), and grade 3–4 infections (30–60%). It is worth noting that, if possible, doses/intervals should not be modified due to hematological toxicity during the first three treatment cycles.

Decitne increases progression-free survival (PFS) but does not extend overall survival compared to best supportive care (BSC), so is not approved in the EU.

The prognosis of patients after the failure of azacitidine treatment is poor, with median survival of c.6 months.

Indications for treatment with azacitidine:

- intermediate-2 and high-risk myelodysplastic syndromes according to the IPSS in patients not eligible for IC;
- chronic myelomonocytic leukemia (CMML) with 10–29% bone marrow blasts without myeloproliferative disorder (WBC <13 G/L), in patients not eligible for IC;
- acute myeloid leukemia with 20–30% blasts with multi-lineage dysplasia, according to World Health Organization (WHO) classification, in patients not eligible for IC;
- AML with >30% bone marrow blasts according to WHO classification, in patients not eligible for IC;
- bridging therapy in selected patients prior to allo-HSCT (in patients with unfavorable karyotype or aged >65);
- higher-risk patients who have undergone allo-HSCT as relapse treatment, pre-treatment, or maintenance treatment.

Allogeneic hematopoietic stem cells transplantation in treatment of MDS

Despite the undoubted progress in the treatment of patients with MDS in recent years, allo-HSCT remains the only potentially curative method [64].

Patient-related and disease-related factors should be taken into account in the decision-making process of qualifying an MDS patient for allo-HSCT [56, 64–66]. Patient-related factors include: age, performance status according to Karnofsky performance scale (KPS), comorbidities (according to the augmented HCT-CI scale), psychosocial status, and patient preferences. The mean age of developing MDS is c.70, so it is particularly important to consider the qualification of some patients >65 years to allo-HSCT. Currently, it is believed that the chronological age (previously accepted upper age limit 65–75) is slightly less important than the biological age [assessment based, among others, on Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI), KPS, geriatric scales] [67].

'Fit' patients, i.e. those in whom an allo-HSCT procedure can be performed, are defined by the following parameters: KPS ≥70–80 and HCT-CI ≤3 (ELN 2020) [56].

High-risk patients with bone marrow blasts <10% and no medical contraindications for transplantation should be eligible for allo-HSCT as first-line therapy provided they have an available donor. Best long-term results were achieved when pre-transplant blasts <5%. Conversely, when bone marrow blasts are 10% or greater, the patient should receive cytoreduction therapy prior to transplantation. The clinical outcomes of the use of azacitidine or intensive chemotherapy as cytoreduction are comparable [68].

Hematopoietic stem cells transplantation is a potential option for 'fit' patients from the higher risk group according to IPSS or IPSS-R, and in lower risk (IPSS) or moderate/lower risk (IPSS-R) patients with:

- unfavorable cytogenetic disorders;
- a 50% increase in blasts or bone marrow blasts >15%;
- life-threatening cytopenias defined as:
  - absolute neutrophil count (ANC) <0.3 G/L,
  - PLT <30 G/L,
  - RBC-TD of at least 2 units/month for 6 months.

The long-term outcome of allo-HSCT in MDS patients and the peri-transplant risk have been assessed in several prognostic indices, among which the predictive model by Della Porta et al. (based on age, HCT-CI, karyotype, IPSS-R and response to induction chemotherapy) and the so-called European Group for Blood and Marrow Transplantation (EBMT) transplant-specific risk score for MDS, are the most widely used [65, 69].

When qualifying an MDS patient for a transplant procedure, the optimal preparation method should be considered, i.e. conditioning. The choice of myeloablative conditioning (MAC) versus reduced intensity conditioning (RIC) depends primarily on the patient's age and the presence of comorbidities. In the randomized, multicenter EBMT clinical trial, the results of RIC versus MAC use were comparable, with 2-year survival rates of 76.3% and 63.2%, respectively [70]. In this study, patients >60 years accounted for only 4%. The decision to select specific conditioning regimens is generally based on site preferences and experience [70–73]. In recent years, a fludarne/treosulfan regimen with relatively low toxicity has been successfully used. In Wedge et al.'s study [74], 3-year overall survival rate after fludarne/treosulfan-based conditioning was 71%. In the group receiving the standard MAC regimen [total body irradiation (TBI)/cyclophosphamide or busulfan/cyclophosphamide] it was 52.8%, and in the group receiving RIC it was 62% (p = 0.075) [74].

Today, for the vast majority of patients, it is possible to match a donor of hematopoietic cells: the first choice is a related donor fully matched with human leukocyte antigen (HLA) antigens, the second choice is a fully matched or other acceptable unrelated donor, and the next best is a haploidentical donor.

Azacitidine in patients after allo-HSCT

The most common cause of allo-HSCT failure in patients with MDS and AML is disease relapse (30–70% of patients) [75]. Survival rate in patients with relapse after allo-HSCT is low, e.g. 2-year survival rate below 10–20%.

Recent reports indicate that in a selected population of MDS patients with relapse after transplantation, the treatment strategy may be even more important for overall survival than pre-transplant cytoreduction [76].

Due to the genetic heterogeneity of AML/MDS and the risk of clonal evolution after transplantation, it is helpful to simultaneously use several assessment methods for remission monitoring. Standard recommendations regarding optimal minimal residual disease (MRD) measurement intervals after transplantation have not yet been established.

The following are relapse definitions [77–81]:

- cytometric, according to ELN AML 2017, is defined at MRD cut-off level >0.1%;
- molecular: an increase in MRD level of ≥1 log10 between 2 positive samples in a previously negative patient;
- hematological relapse of MDS after alloHSCT: bone marrow blasts 5–20% and/or reappearance of myelodysplastic features associated with cytopenia or autologous regeneration in chimerism testing;
- hematological relapse of MDS with progression to AML: bone marrow blasts exceeding 20%;
- hematological relapse of AML after allo-HSCT: bone marrow blasts equal to or greater than 5%, peripheral blood blasts or extramedullary leukemia.

Complete chimerism (CC) and mixed chimerism (MC) means >95% and ≤95, respectively, of donor cells in the selected fraction of tested cells [82]. Currently, the most

Table VII. Principles of azacitidine (AZA) treatment after allogeneic hematopoietic stem cell transplantation (allo-HSCT) (based on [83–92])

Consolidation treatment	
General guidelines	Heterogeneous group due to limitations of MRD diagnostics
Indications	Patients in complete remission and with full chimerism with **high risk of recurrence:**
	• high-risk cytogenetic features — complex karyotypes and/or *TP53* mutations
	• initially advanced disease (except for CR1 before transplantation)
	• history of treatment-resistant disease
	• no possibility of using targeted therapy (e.g. FLT3 inhibitors, IDH)
	• application of RIC conditioning
Dose	32 mg/m^2/d for 5 days, 28-day regimen
Initiation treatment time	30–100 days after allo-HSCT
Treatment duration	Not established, 4 to 12 cycles were used
Summary	Treatment not routinely recommended
Preemptive treatment	
General guidelines	Systematic MRD monitoring recommended
Indications	Patients with MRD, molecular relapse, and/or progressive mixed chimerism
Dose	75 mg/m^2/d for 7 days, 28-day regimen
Initiation treatment time	Early disease detection and immediate treatment initiation from day 30 after allo-HSCT
Treatment duration	Not established, from 6 to 12 or even 24 cycles
	DLI administration to be considered every other cycle
Summary	Standard management
Treatment of hematological relapse	
General guidelines	Combination with cell therapy (DLI) or targeted therapy indicated
Indications	Patients with hematological relapse
Dose	75 mg/m^2/d for 7 days, 28-day regimen
Initiation treatment time	Early detection of disease and immediate initiation of treatment is essential
Treatment duration	Administered chronically, discontinuation of treatment is associated with disease relapse
Summary	Transient treatment effect
	This may be a bridge strategy to II allo-HSCT

MRD — minimal residual disease; CR1 — first complete remission; FLT3 — Fms related receptor tyrosine kinase 3; IDH — isocitrate dehydrogenase; RIC — reduced intensity conditioning; DLI — donor lymphocyte infusions

commonly used treatments of MDS/AML relapse after allo-HSCT are hypomethylating agents, especially azacitidine, often in combination with donor lymphocyte infusions (DLI). The principles of maintenance treatment, pre-treatment and relapse treatment are summarized in Table VII [83–92].

Hypoplastic myelodysplastic syndromes

Decreased bone marrow cellularity is found in 10–20% of MDS patients, and this is the basis for the diagnosis of the hypoplastic form of this disease [hypoplastic MDS (h-MDS)]. To date, no precise definition of h-MDS has been developed, but the usual borderline value is bone marrow cellularity below 20–30%. According to the WHO classification, h-MDS is not a separate subtype of myelodysplastic syndrome. Patients with h-MDS are younger, with less severe anemia, but with deeper neutropenia and thrombocytopenia compared to patients with normo-/hypercellular bone marrow. The distribution of particular prognostic groups according to IPSS does not differ depending on the marrow cellularity. The clinical course of this disease is characterized by greater effectiveness of immunosuppressive treatment and a better prognosis compared to typical MDS.

Primarily, aplastic anemia (AA) should be considered in the differential diagnosis [93, 94].

Myelodysplastic syndromes with bone marrow fibrosis

According to the WHO 2016 classification, myelodysplastic syndrome with bone marrow fibrosis (MDS-F) is not a separate subtype of MDS, although a provisional subtype has

been distinguished: myelodysplastic syndromes with excess of blasts and fibrosis, known as MDS-EB-F or MDS-F [95]. Most patients with MDS-F have an increased percentage of bone marrow blasts. Unlike primary myelofibrosis, patients with MDS-F usually do not have splenomegaly or leukoerythroblastosis. MDS-F includes patients with grade 2 or more fibrosis (10–15% of MDS).

The presence of advanced fibrosis worsens the prognosis, increases mortality [96] and shortens the time to transformation into AML [97]. Due to the difficulties in obtaining a reliable bone marrow for cytological examination, trephine biopsy is a valuable supplementary test in assessing the percentage of blasts. It has been shown that in MDS-F, grade 3 fibrosis correlates with an increased percentage of blasts, increased lactate dehydrogenase (LDH) activity, lower number of platelets, greater RBC dependence, multilinear dysplasia, complex karyotype, and the presence of molecular disorders (in *TP53*, *SETBP1* genes). *JAK2* gene mutation has not been found to be more frequent, which may help differential diagnosis.

Advanced fibrosis (BMF 3) has been shown not to worsen the response to hypomethylating agents and lenalidomide, but it has not yet been established whether their use in low-risk groups reduces fibrosis [96].

Fibrosis worsens transplantation outcomes by delaying cell reconstitution and increasing the risk of graft failure. The probability of 3-year overall survival in MDS patients with stage 3 fibrosis is only 21%, compared to 40–49% in patients with grade 0–2 fibrosis. Fibrosis does not influence the risk and course of graft-versus-host disease (GvHD) [98].

Therapy-related myelodysplastic syndromes

Therapy-related myelodysplastic syndromes (t-MDS) are a group of diseases that are a late complication after chemo- and/or radiotherapy used in the treatment of neoplastic and non-neoplastic diseases [95]. t-MDS accounts for c.10–20% of all myelodysplastic syndromes [99]. Among neoplastic diseases, 70% of newly diagnosed t-MDS are preceded by therapy of solid tumors, and 30% by treatment of hematological malignancies [95]. The incidence of t-MDS after treatment with conventional chemotherapy is 0.8–6.3% over 20 years, and after high-dose chemotherapy with autologous hematopoietic stem cell transplantation (auto-HSCT) is 1.1–24.3% over 5 years [100]. The prognosis in patients with t-MDS is worse than in patients with pMDS, with overall survival of 5–34 months [101].

Therapy of t-MDS includes hypomethylating agents, conventional chemotherapy, adjuvant therapy, and allo-HSCT, which remains the only potentially curative form of therapy [102].

Prevention and treatment of infections in myelodysplastic syndromes

The risk of infections in MDS patients is the result of immune disorders occurring in the course of disease, general condition, comorbidities and treatment complications [103–106]. Infectious complications account for 30–38% of all death causes [107].

The most common infectious complications in the course of MDS are febrile neutropenia (36–47%), pneumonia (21–50%) and sepsis (14%) [108, 109]. The most common is bacterial etiology, accounting for 80% of infections (caused by both Gram-positive and Gram-negative bacteria), but they are usually diagnosed clinically, and microbiological confirmation is achieved only in c.30% of patients.

In recent years, attention has turned to the increased incidence of invasive mycoses, including mucormycosis, in this group of patients. Viral infections [except for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)] are rare in conventionally treated patients, although influenza can have a severe course in patients with myelodysplastic syndromes.

The risk of infection depends on the severity of the underlying disease; in MDS-LR patients treated with azacitidine, the risk of grade 3–4 infections is c.9.5–26% and is significantly lower than in MDS-HR patients (43–71%) [110, 111]. Infections most often occur within the first three treatment cycles of azacitidine (66% of all infections).

Based on a retrospective analysis of 298 patients performed by the PALG MDS Working Group, a model of infection risk in patients treated with azacitidine has been developed with the following risk factors identified: RBC-TD, neutropenia <0.8 G/L, thrombocytopenia <50 G/L, hypoalbuminemia <3.5 g/dL, and Eastern Co-operative Oncology Group Performance Status (ECOG PS) ≥2.

Patients with three, four, or all five of the abovementioned factors had a significantly higher risk of infection (73%) compared to patients with 0–2 risk factors (25%) [108]. In this study, mortality in patients with sepsis, pneumonia, and febrile neutropenia was 45%, 26%, and 15%, respectively. Based on preliminary data, SARS-CoV-2 infection in MDS patients is associated with a very high risk of death, reaching 42–47% [112].

Although there is no clear indication for pharmacological prophylaxis in all patients treated with azacitidine, it should be considered in specific risk groups [113]. The efficacy of fluoroquinolone-based antibacterial prophylaxis has been confirmed in patients treated with decitne [114]. It remains unclear which antifungal agents should be used in this group of patients, and in particular whether to use azoles with proven efficacy against molds [115]. Recommendations regarding the prevention of infection in MDS patients for whom treatment is planned are set out in Table VIII.

Table VIII. Recommendations for infection prophylaxis in myelodysplastic syndrome (MDS) patients with planned treatment

Infection type	Diagnostic tests	Prophylaxis
Hepatitis B, C	HBsAg, anti-HCV	
	Anti-HBc, (HBV DNA), anti-HBsAg, (HCV RNA) — optionally	
HIV	HIV combi	
Tuberculosis	IGRA, tuberculin test — optional	
Colonization with MRB (ESBL, VRE, MBL)	Outpatient — no	No
	Hospitalized — yes (rectal swab with culture)	
Invasive mycoses	Galactomannan antigen	Only in patients treated with IC-posaconazole
		In patients undergoing allo-HSCT: same procedure as in other transplant patients
Bacteria		Primary: only at high risk Secondary: quinolones
		G-CSF: to be considered only when infection with neutropenia
Immunization		*Streptococus pneumoniae*, Flu, SARS CoV-2 — yes
HSV, CMV, EBV, parvovirus B19	Routinely not	Acyclovir only in case of recurrent HSV reactivation

HBsAg — hepatitis B surface antigen; anti-HCV — antibodies against hepatitis C virus; anti-HBc — antibodies against core antigen of hepatitis B virus; HBV DNA — hepatitis B virus deoxyribonucleic acid; HCV RNA — hepatitis C virus ribonucleic acid; HIV — human immunodeficiency virus; IGRA — gamma interferon secretion tests; MRB — multiresistant bacteria; ESBL — extended-spectrum beta-lactamase; VRE — vancomycin-resistant enterococci; MBL — metallo-beta-lactamase; IC — intensive chemotherapy; allo-HSCT — allogeneic hematopoietic stem-cell transplantation; G-CSF — granulocyte colony-stimulating growth factors; SARS-CoV-2 — severe acute respiratory syndrome coronavirus 2; HSV — herpes simplex virus; CMV — cytomegalovirus; EBV — Epstein-Bárr virus

New agents in myelodysplastic syndrome treatment

In recent years, many clinical trials with the use of new molecules have been conducted in patients with myelodysplastic syndromes. After many years without new effective drugs, the latest results of phase II and III studies are generating optimism regarding the addition of new agents to what is still a relatively modest armamentarium (Table IX).

Authors' contributions

Conception and design: KM, JDT. Manuscript writing, final approval of the manuscript: all authors.

Conflict of interest

None.

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None.

Ethics

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.

Table IX. Clinical trials with selected new agents for myelodysplastic syndrome (MDS) treatment

Agent	MoA	Studied cohort	Phase	Results	Reference
Imetelstat	Telomerase inhibitor	LR-MDS RBC-TD, r/r ESA	II	RBC-TI 42% (HI-E 68%)	[116]
		or EPO >500 U/L	III	Ongoing (2023)	
Roxadustat	Inhibition of HIFα degradation	LR-MDS RBC-TD LTB, non-del 5q, EPO <400 U/L	III (OL)	RBC-TI 38% (HI-E 63%)	[117]
			III	Ongoing (2021)	
Venetoclax	BCL-2 inhibitor	HR MDS: venetoclax + AZA (I line) HMA r/r	Ib	OR 79% (CR 39.7%)	[118, 119]
		Venetoclax + AZA (II line)	III	OR 39% (CR 7%)	
Pevonedistat	Neddylation inhibitor	HR-MDS HMA r/r Pevonedistat + AZA	II	OR 42% (CR, mCR, HI)	[120, 121]
		Pevonedistat + AZA (I line)	III	OR 79% (CR, PR, HI)	
Magrolimab	CD47 inhibitor	MDS-HR (I line) Magrolimab + AZA	Ib	OR 100% (CR 53%)	[122]
			III	Ongoing	
Eprenetapopt APR-246	Restoring p53 function	HR MDS with *TP53* mutation (+ AZA)	Ib/II	OR 73% (CR 50%, CCR 58%)	[123]
			III	Ongoing	
Rigosertib	RAS pathway affector inhibitor: PI3K and PLK	HR MDS Rigosertib + AZA (I line)	II	OR 92% (CR 34%)	[124]
		HMA r/r Rigosertib ± AZA (I line)	III	OR 54% (CR 4%) Ongoing	

AZA — azacitidine; CCR — complete cytogenetic response; CR — complete response; EPO — erythropoietin; ESA — erythropoiesis-stimulating agent; HI-E — hematological improvement-erythroid; HIFα — hypoxia inducible factor; HMA — hypomethylating agent; HR — high-risk; LR — low-risk; LTB — low transfusion burden (1–4 red blood cell units/8 weeks); mCR — marrow complete remission; MoA — mechanism of action; OL — open label; OR — overall response; PI3K — phosphoinositide 3-kinase; PLK – polo-like kinase; PR — partial remission; RBC-TD — red blood cell transfusion dependency; RBC-TI — red blood cell transfusion independence; r/r — relapsed/refractory

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REVIEW ARTICLE

Chronic lymphocytic leukemia following venetoclax treatment failure

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Abstract

Venetoclax (ABT-199) is a highly selective and potent inhibitor of BCL-2, capable of inducing deep remission in chronic lymphocytic leukemia (CLL). The introduction of this compound to the treatment armamentarium of CLL represented a real breakthrough, as the drug is effective in high-risk CLL patients and in the setting of Bruton's tyrosine kinase inhibitors (BTKi) failure. Nevertheless, treatment failure or progression following venetoclax treatment occurs over time. Potential mechanisms of refractoriness, including BCL-2 mutations or activation of alternative anti-apoptotic pathways, have been identified. So far, questions regarding patient management after venetoclax and venetoclax-based regimen failure have yet to be answered, and only a few studies have addressed this problem. With increasing use of venetoclax-based treatment, the optimal sequencing and the most suitable next line treatment should be addressed in upcoming guidelines. In this review, we summarize the possible mechanism of resistance to venetoclax, and explore possible therapeutic options in cases of venetoclax failure.

Key words: chronic lymphocytic leukemia, immunochemotherapy, ibrutinib, venetoclax, resistance

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Introduction

Chronic lymphocytic leukemia (CLL) is an incurable clonal proliferation of CD5/CD19 lymphocytes accumulating in the blood, bone marrow, and lymphoid tissues [1]. It is the most commonly diagnosed leukemia, with an annual age-adjusted incidence of 3–5 per 100,000 persons. It is mostly encountered in older people, with a median age at diagnosis of 72 years [1, 2]. In the last decade, new treatment options have emerged, of which the most notable have been Bruton's tyrosine kinase (BTK) inhibitors (ibrutinib and acalabrutinib), selective phosphatidylinositol-3-kinase (PI3K) inhibitors (idelalisib and duvelisib), the Bcl-2 antagonist venetoclax, and the new anti-CD20 antibodies (obinutuzumab) [1, 3]. Ibrutinib and idelalisib combined with rituximab have shown remarkable efficacy in high-risk patients with defects in the p53 pathway (deletion 17p13 and/or *TP53* mutation) [4–6]. Despite treatment with these agents, clonal evolution with the selection of resistant clones can lead to therapy failure with possibly rapid progression [6–11]. Venetoclax was hailed as a breakthrough in CLL therapy due to the high activity of this small molecule in high-risk CLL patients, as well as in the setting of therapy failure with BTK and PI3K inhibitors [12–22]. Venetoclax is an attractive therapy option in treatment-naïve as well as relapse and refractory settings when combined with anti-CD20 antibodies due to its highly effective, predictable adverse event profile, and the possibility of a time limited therapy as opposed to BTK and PI3K inhibitors [23, 24]. With a broad range of venetoclax use in CLL patients, the development of treatment strategies in case of its failure as therapy is of the utmost importance. In this review, we summarize the current efficacy of venetoclax in CLL and potential future directions in this clinical setting.

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Venetoclax mechanism of action and clinical efficacy

Proteins of the B-cell lymphoma 2 (BCL-2) are capable of regulating the intrinsic apoptosis pathway and, depending on the protein type, may act as proapoptotic or antiapoptotic factors. In normal, stable conditions the impact of both types of proteins is in balance. However, in stress conditions, the balance may be shifted towards the initiation of the apoptotic program [25]. The BCL-2 family of proteins is characterized by the presence of B-cell homology domain (BH) in all of its members. The antiapoptotic members include BCL-2, BCL-X_L, MCL-1, BCL-W, and BFL-1/A1 which poses four BH domains (BH1-4). The proapoptotic members include BAD, BIK, NOXA, HRK, PUMA, BMF, BID, and BIM which are bound to be the antiapoptotic BCL-2 subfamily members (including BCL-2). Once the proapoptotic members are unbound from the antiapoptotic members, they activate the proapoptotic effectors BAK and BAX, which due to allosteric structural changes form hetero- and homodimeric channels leading to mitochondrial outer membrane permeabilization (MOMP), cytochrome C release, and eventually caspase cascade activation [25–27].

BCL-2 is overexpressed in c. 95% of CLL cells. Interestingly, the proportion is higher in lymph node-derived cells than in ones isolated from peripheral blood [28, 29]. In parallel, CLL cells overexpress the proapoptotic BIM protein, which is bound by overexpressed BCL-2. However, such balance renders clonal lymphocytes prone to apoptosis [26, 27]. The use of anti-BCL-2 compounds such as venetoclax shifts the balance towards apoptosis via the activation of the intrinsic apoptosis pathway independently of the p53 pathway status [30, 31].

Venetoclax (ABT-199) is a highly selective and potent inhibitor of BCL-2, capable of neutralizing the antiapoptotic effect in subnanomolar concentrations [32]. Early phase as well as phase III clinical trials have shown that venetoclax can achieve fast, deep, and durable remissions in both treatment-naïve (TN) and relapse and refractory (RR) CLL cases. Its combination with anti-CD20 antibodies has established its importance in international guidelines [1, 33, 34]. A recent metanalysis of 14 clinical trials and real-life observations in RR-CLL showed a pooled overall response rate (ORR) of 82% [95% confidence interval (CI) 77–87%] for venetoclax monotherapy, 89% (95% CI 83–94%) for a combination of venetoclax and anti-CD20 antibody, and 86% (95%CI 78–92%) for a venetoclax-ibrutinib combination [35]. The recently published results of the phase III CLL14 trial showed that a 1-year fixed duration of venetoclax and obinutuzumab (Ven-Obi) treatment of TN-CLL led to an ORR of 86% in patients with coexisting comorbidities [36]. The Ven-Obi protocol showed achievement of durable remissions and at a median follow-up of 52.4 months the median progression-free survival (PFS) was not reached and the estimated 4-year PFS rate was 74.0%. Nevertheless, the analysis of minimal residual disease (MRD) dynamics indicates that disease progression is inevitable over time [37].

Resistance to venetoclax therapy

Data from clinical trials and real-world observations show that venetoclax discontinuation is attributable in most cases to disease progression, while discontinuation due to adverse events is rare [13–18, 21, 36–41]. The retrospective analyses identified that heavy (more than three lines of therapy) pretreatment, previous therapy with BTK inhibitor, fludarabine resistance, bulky disease, complex karyotype, 17p deletion, mutations of *TP53, SF3B1 NOTCH1*, and unmutated *IGHV* status were associated with shorter responses [41–43]. So far, several mechanisms of venetoclax resistance have been identified, although the mutation of target protein and activation of alternative anti-apoptotic or survival pathways seem to be the most important.

Mutation in the binding site of the BH3 grove of BCL-2 protein has been shown to diminish venetoclax binding affinity. Analysis of paired samples before venetoclax initiation and at disease progression in 15 CLL cases identified the presence of *BCL2*p.Gly101Val mutation in seven patients [44]. The mutation was firstly detectable after 19 to 42 months of therapy, but was not present in the pretreatment samples. Its emergence anticipated clinical disease progression by several months, and in the analyzed samples the median time to disease progression was 36 months. Gly101Val mutation reduces the affinity of BCL2 for venetoclax by approximately 180-fold, and prevents the drug from displacing proapoptotic mediators from BCL-2 in CLL cells stopping the apoptosis [44]. Additional mutations in residues 103, 104, 107–110, 113 and 129 of *BCL2* have been detected in patients resistant to venetoclax [45, 46].

The activation of alternative pathways and kinases such as BTK, PI3K, spleen tyrosine kinase (SYK), or B-Raf protooncogene (BRAF) may foster activation of alternative anti-apoptotic signaling independently of BCL-2, shifting the balance by upregulating other anti-apoptotic BCL-2 family members such as MCL-1 and BCL-XL [47–51]. Amplification of CD274 (PD-L1), loss of CDKN2A/B, and/or mutation in *BTG1* have also been observed in patients refractory to venetoclax [51]. In addition, amplification of 1q also confers venetoclax resistance by upregulating MCL-1 expression [49].

The accumulated data indicates that the proper identification of a potential resistance mechanism is important in order to tailor treatment at disease progression under venetoclax treatment.

Efficacy of treatment regimens following venetoclax failure

Questions regarding patient management after venetoclax and venetoclax-based regimen failure have not yet been answered, and only a few studies have addressed this problem (Table I). Treatment of CLL relapse after venetoclax therapy remains to be determined [43, 52].

Immunochemotherapy

Only limited data concerns the use of immunochemotherapy after venetoclax treatment. In one of the first reports of the clinicopathological features and outcomes of patients with CLL progression during venetoclax treatment, only 1 of 8 patients received FCR (fludarabine, cyclophosphamide, rituximab) immunochemotherapy after post-venetoclax relapse, and the response to the treatment is unknown [41]. In their retrospective analysis, Mato et al. [43] identified 41 CLL patients who discontinued venetoclax, just over half, 21 of them, because of disease progression. Three patients treated with anthracycline-based regimens were described, however none of them responded [43]. In the updated analysis of the MURANO trial, 15 patients received immunochemotherapy after a venetoclax-rituximab regimen, although the outcomes of these patients were not presented [53, 54].

The use of anti-CD20 monoclonal antibody monotherapy after venetoclax discontinuation has been mentioned in only one study concerning 19 patients. However, the regimen did not result in durable remissions following venetoclax, with an ORR of 32% and a median PFS of only two months [55].

Novel drugs

While there is reassuring information on venetoclax treatment after BCR inhibitors therapy failure, data regarding the efficacy of BCR inhibitors in the treatment of patients who relapsed after receiving venetoclax is scarce [15, 19, 52, 56, 57]. Several reports have pointed to a response to ibrutinib following venetoclax discontinuation in previously ibrutinib-naïve patients, although the data is limited in terms of patient numbers and follow-up [52]. These were five studies with six, 11, five, 27 and 23 patients [43, 52, 57–59].

One of the first studies of venetoclax-treated patients from early clinical trials reported that 6 of 8 patients with progressive CLL received ibrutinib after venetoclax, and five had a partial remission (PR) [41]. Another retrospective report showed 10 of 11 patients achieved PR under ibrutinib therapy after venetoclax [58]. In the previously mentioned study by Mato et al. [43], 23 patients required therapy after progression following venetoclax treatment. Of them, 20.8% received ibrutinib; however, responses were not satisfying (one patient achieved PR, whereas two had stable disease [SD] and one progressive disease [PD]) [43]. In addition, an analysis of 27 ibrutinib-naïve patients [one patient received another Bruton's tyrosine kinase inhibitors (BTKi)] with progression after venetoclax reported 56.0% ORR to ibrutinib (of the 25 response-evaluable patients, 13 had PR and one achieved CR). Time to progression on ibrutinib ranged from 3 to 53 months, and the median duration of ibrutinib therapy was 18.3 months [60]. In the analysis by Lin et al. [59], BTKi therapy was shown to achieve durable disease control after progression on venetoclax and clinical efficacy for patients with acquired resistance to venetoclax. Among the analyzed group, 23 patients received BTKi and 20 patients had a response (90% ORR), with 16 PR or PR with lymphocytosis (PR-L) and four achieved CR. Median PFS after BTKi initiation was 34 months. Moreover, ≥24 months remission during venetoclax or deep responses (CR or undetectable MRD) during venetoclax therapy were associated with longer PFS after initiation of a BTKi. It is worth mentioning that 8 of 19 tested patients had a BCL2 Gly101Val mutation. At a median follow-up of 33 months, the median PFS while receiving a BTKi had not been reached for these eight patients, suggesting that BTKi is a possible therapeutic modality in such patients [59].

The analysis of the MURANO trial reported follow-up data on 18 patients who received ibrutinib when relapsed after a venetoclax-rituximab combination. The ORR was 100% (7.1% achieved CR, 92.9% PR) [53, 54].

Subsequently, a multicenter retrospective cohort study identified 326 patients who discontinued venetoclax and required treatment. Of the 74 patients treated with BTKi, 44 were BTKi naïve and 30 were previously BTKi-exposed. They received ibrutinib or acalabrutinib, or a noncovalently binding BTKi monotherapy within a clinical trial. The ORR was 84% (9% CR) in the BTKi-naïve patients with a median PFS of 32 months. This was significantly higher compared to outcomes of previously BTKi-exposed pre-venetoclax patients (53.4% ORR, 10% CR, median PFS 12 months) [55]. In the same study, 17 patients received PI3Ki (idelalisib or duvelisib). All of the patients were previously exposed to PI3Ki and BTKi before venetoclax. The ORR was 46.9% (5.9% CR), but the responses were not durable, with a median PFS of only five months [55].

As venetoclax treatment after BCR inhibitors therapy failure is proven to be effective, it is necessary not to forget about the small group of patients who progress on venetoclax, but are ibrutinib- (and other covalent BTKis) resistant [15, 19, 52, 61]. PI3Kis would be the most available next treatment for that group, but the responses are typically short-lived [19, 55]. Resistance to ibrutinib is mostly the result of acquired cysteine-to-serine mutation in BTK [62, 63]. Reversible, noncovalent BTKis, with activity against Cys481-mutated BTK, may overcome BTKi resistance [22]. Although trials of noncovalent BTKis are ongoing and in early phases, preliminary data suggests that these agents have clinical activity in heavily pretreated patients [64–66]. A promising new agent is LOXO-305 (pirtobrutinib). In

Table I. Summary of selected studies assessing subsequent therapies following venetoclax failure

Author	Study	Number of patients	ORR (with CR)	Median PFS (months)	Median OS (months)	Comments
Mato et al. [43]	Retrospective study	Anthracycline-based immunochemotherapy — 3	ORR 0.0% (CR 0.0%)	NA	NA	Short observation time with a median follow-up of 7 months
		Rituximab monotherapy — 3	ORR 66.7% (CR 0.0%)			
		Ibrutinib — 5	ORR 20.0% (CR 0.0%)			
		Idelalisib — 2	ORR 50.0% (CR 50.0%)			
		CAR-T — 2	No assessment			
		allo-HCT — 3	ORR 66.7% (CR 66.7%)			
Anderson et al. [41]	Retrospective study	Immunochemotherapy — 1	Unknown response	NA	NA	
		Ibrutinib — 6	ORR 83.3% (CR 0.0%)			
Harrup et al. [54]	Retrospective study	Immunochemotherapy — 15	Unknown response	NA	NA	Patients treated earlier within phase III MURANO trial
		BTKi — 18	ORR 100.0% (CR 7.1%)			
		Retreatment with venetoclax — 32	ORR 72.2% (CR 5.6%)			
Mato et al. [55]	Retrospective study	BTKI: ibrutinib, acalabrutinib (BTKi-naïve) — 44	ORR 83.9% (CR 9.0%)	32	NA	With a median follow-up of 7.7 months (1–48 months) for patients treated with BTKi post-venetoclax, estimated median PFS to post-venetoclax BTKi was 32 months in BTKi--naive patients, not reached in BTKi-intolerant patients, but was only 4 months in patients who were known to be BTKi resistant
		BTKi: ibrutinib, acalabrutinib, noncovalent BTKi (BTKi-exposed) — 30	ORR 53.4% CR 10.0%)	12	NA	
		PI3Ki — 17	ORR 46.9% (CR 5.9%)	5 9	NA NA	
		CAR-T — 18	ORR 66.6% (CR 33.3%)	2	NA	
		Anti-CD20 — 19	ORR 32.0% (CR 16.0%)			
Brown et al. [58]	Retrospective study	Ibrutinib — 11	ORR 90.9% (CR 0.0%)	NA	NA	Time on ibrutinib therapy ranged from 0.5 to 30 months, with only three patients having discontinued

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Table I (cont.). Summary of selected studies assessing subsequent therapies following venetoclax failure

Author	Study	Number of patients	ORR (with CR)	Median PFS (months)	Median OS (months)	Comments
Brown et al. [60]	Retrospective study	Ibrutinib — 27	ORR 56.0% (CR 4.0%)	NA	NA	Ibrutinib-naïve patients progressing after venetoclax ORRs were 1/25 CR, 13/25 PR. Time to progression on ibrutinib ranged from 3.0 to 53.0 months (n = 10). Median duration of ibrutinib therapy was 18.3 (3.7–53.2) months, and 20.0 (4.9–44.3) months for those remaining on ibrutinib (8/27)
Lin et al. [59]	Retrospective study	BTKi: ibrutinib — 21, zanubrutinib — 2	ORR 90.0% (CR 13.0%)	34	42	
Mato et al. [67]	Phase 1/2 study	LOXO-305 — 121	ORR 62.0% (CR 0.0%)	NA	NA	

allo-HCT — allogeneic hematopoietic cell transplantation; BTKi — Bruton's tyrosine kinase inhibitor; CAR-T — chimeric antigen receptor t-cell; CR — complete remission; NA — not reached; ORR — overall response rate; PFS — progression-free survival; PI3Ki — phosphoinositide 3-kinase inhibitor; PR — partial remission

a I/II study, the ORR in patients with relapsed and refractory CLL was 63% and the response rates were consistent in subgroups previously receiving BTKis, venetoclax, or both drugs [67]. Other noncovalent BTKis, including GDC-0853, ARQ-531, and vecabrutinib, also have activity independent of Cys481-mutated *BTK*, but only limited clinical data is currently available [22, 66, 68, 69].

Allogeneic stem cell transplantation and CAR T-cell therapy

Little is known about the outcomes of allogeneic stem cell transplantation (allo-HCT) in CLL at the time of novel drugs. The number of allo-HCTs performed for CLL has steadily declined, with a 58% decrease in the number of allo-HCTs performed from 2010 to 2018 in the USA [70]. Roeker et al. published an analysis of 65 patients with CLL undergoing allo-HCT after being treated with one or more of the new agents. The PFS and OS were 60% and 82% at 24 months, respectively. Before allo-HCT, patients had received a median of three lines of therapy and one of the selective agents. The three most common new drugs used in any line of therapy prior to allo-HCT were ibrutinib (82%), venetoclax (40%), and idelalisib (20%), while 26% had received both ibrutinib and venetoclax. Only 18 patients were 'chemotherapy-free', receiving exclusively novel drugs before allo-HCT. No significant differences in PFS and OS were shown between patients receiving only/exclusively novel agents. Notably, the groups that received ibrutinib (as opposed to venetoclax) as their line of therapy directly preceding allo-HCT were examined in order to explore the optimal bridging strategy to transplantation. No significant differences in PFS or OS were observed between these groups; however, the 12-month relapse incidence was 20% for ibrutinib-bridged patients vs. 9% for venetoclax-bridged patients [71].

CAR T-cells are also a promising therapeutic approach in CLL in the setting of venetoclax failure. In the largest multicenter study to assess the efficacy of different post-venetoclax therapies, 18 patients received CD19 directed CAR-T therapy resulting in a 66.6% ORR (33.3% CR) with a median PFS of nine months [19]. A phase I/II study in relapsed and refractory CLL patients treated with the anti-CD19–directed CAR T-cell product (TRANSCEND-CLL-004) included 15 patients refractory to BTKi and venetoclax. Eight of these patients had ongoing responses (6 CR and 2 PR) [72]. Additionally, Gauthier et al. [73] presented a study of 19 CLL patients treated with CD19-targeted CAR T-cells with concurrent ibrutinib after ibrutinib failure. The data included 11 patients with previous venetoclax treatment (six had progression during treatment). The outcomes of patients treated with venetoclax were not reported separately. However, the 1-year PFS of 59% suggests that ibrutinib in combination with anti-CD19–directed CAR T-cell therapy could be a promising strategy in the future [57, 73].

Re-treatment with venetoclax

In CLL patients treated with immunochemotherapy, re-treatment with the same regimen should be considered in cases of durable remission and absence of del17p and *TP53* mutations [33]. Similarly, there is still a key unanswered clinical question as to whether re-treatment with venetoclax should be considered. In the original phase Ib study evaluating venetoclax and rituximab, 18 patients

stopped venetoclax in deep response and four patients had progressive disease. They were re-treated with venetoclax and all responded, with second remissions ranging from 19 to over 40 months [18, 74].

In the MURANO update, there were 32 response-evaluable patients treated with venetoclax and rituximab. They were subsequently treated with venetoclax or venetoclax-based regimens. The ORR to retreatment was 72%, with 50% of patients remaining on therapy after a median observation time of 11 months. Compared to the patients who received BTKi for progression after venetoclax-rituximab combination, the ORR was 100%, with 71% of patients continuing therapy at a median observation time of 22 months [53, 54, 75].

Richter transformation during venetoclax therapy

The true Richter transformation (RT) is a recognized manifestation of CLL clonal evolution and typically occurs early in venetoclax therapy (median 7.9 months), particularly among heavily pretreated patients with refractoriness to fludarabine or with complex karyotype [41]. In the study by Anderson et al., in a group of 25 patients with progression on venetoclax, 14 patients developed Richter transformation to diffuse large B-cell lymphoma (DLBCL) and three patients to Hodgkin lymphoma. RT treatments were varied and included high-dose chemotherapy in six cases followed by autologous stem cell transplantation (auto-HCT), allo-HCT, or radiotherapy as a part of a proven treatment procedure [76]. The responses to salvage therapies were 31% CR, and 19% PR; 50% had no response [41]. Patients with Hodgkin lymphoma RT represented a prognostically favorable subgroup (CR 100%) as similarly observed when RT does not emerge on venetoclax [41, 77]. In contrast, DLBCL RT is often associated with dismal outcomes [78]. However, some patients with DLBCL RT emerging on venetoclax can achieve durable responses to salvage therapy. In the described group, three patients who responded to chemotherapy subsequently progressed with CLL and then received BTKi therapy, leading to prolonged survival (with PFS up to 45 months) [41].

BTKi or immune-checkpoint inhibitor monotherapy have achieved modest ORRs in small cohorts of RT patients, but CRs are infrequent and survival is poor [75, 78]. In a phase I/II study of acalabrutinib monotherapy in RT, ORR was 40%, including CR in two (8%) and PR in eight (32%) patients with a median PFS of 3.2 months [79]. In a phase II trial of 23 patients with RT, the combination of nivolumab and ibrutinib achieved an ORR of 43%, although the median remission duration was short (9.3 months) [80]. However, in neither study was the group of RT after venetoclax separately assessed.

Finally, the preliminary results for CAR T-cells therapy for patients with RT after targeted agents are promising [75]. In the study by Benjamini et al. [81], out of eight patients, five received venetoclax as the last CLL treatment before the transformation. After CD19-targeted CAR T-cells therapy, 71% of patients achieved CR [81].

Treatment standard and future perspectives

To date, little data has been published regarding the optimal therapy following venetoclax failure. This clinical issue should be addressed promptly to help find the proper treatment. In the setting of disease progression following venetoclax exposure, several factors should be considered before planning the next therapy i.e. time-limited or continous venetoclax therapy, duration of remission after venetoclax therapy, prior exposure to BTKi, and mechanism of resistance to BTKi or BCL-2 antagonist therapy (Figure 1).

Taking into account the current scarce data, it seems the most plausible to qualify patients to BTK-based next line therapy, especially BTKi-naïve patients. In cases of long-lasting remissions following venetoclax-based therapy, retreatment with the agent is also a suitable option, although there is no strict definition of a long-lasting remission in this treatment scenario. The open question remains whether in the case of repeated venetoclax therapy additional *BCL2* mutation testing before treatment initiation should be performed.

It seems that patients with venetoclax failure and prior resistance to BTKi treatment pose the most difficult clinical pchallenge. In this group, the initiation of another BTKi or a PI3Ki will result in only time-limited responses, while the effects of immunochemotherapy will probably be unsatisfactory. The combination of novel agents with CD20 antibodies is an interesting option in such patients however, and cellular-based therapies (CAR T-cells and allo-HCT) should be strongly considered.

In the case of RT under venetoclax therapy, there have been no specific guidelines published, and such cases should be treated depending on the type of histological transformation and the patient's comorbid status.

Conclusions

The increasing use of venetoclax in CLL treatment and possible therapy-related failures may pose a significant clinical problem in the future. So far, no specific guidelines for this clinical setting have been published. However, an individually tailored treatment approach, based on previous types of therapies and patient comorbidities, seems the most reasonable method of choosing the next line of treatment.

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Authors' contributions

Both authors wrote and revised the manuscript.

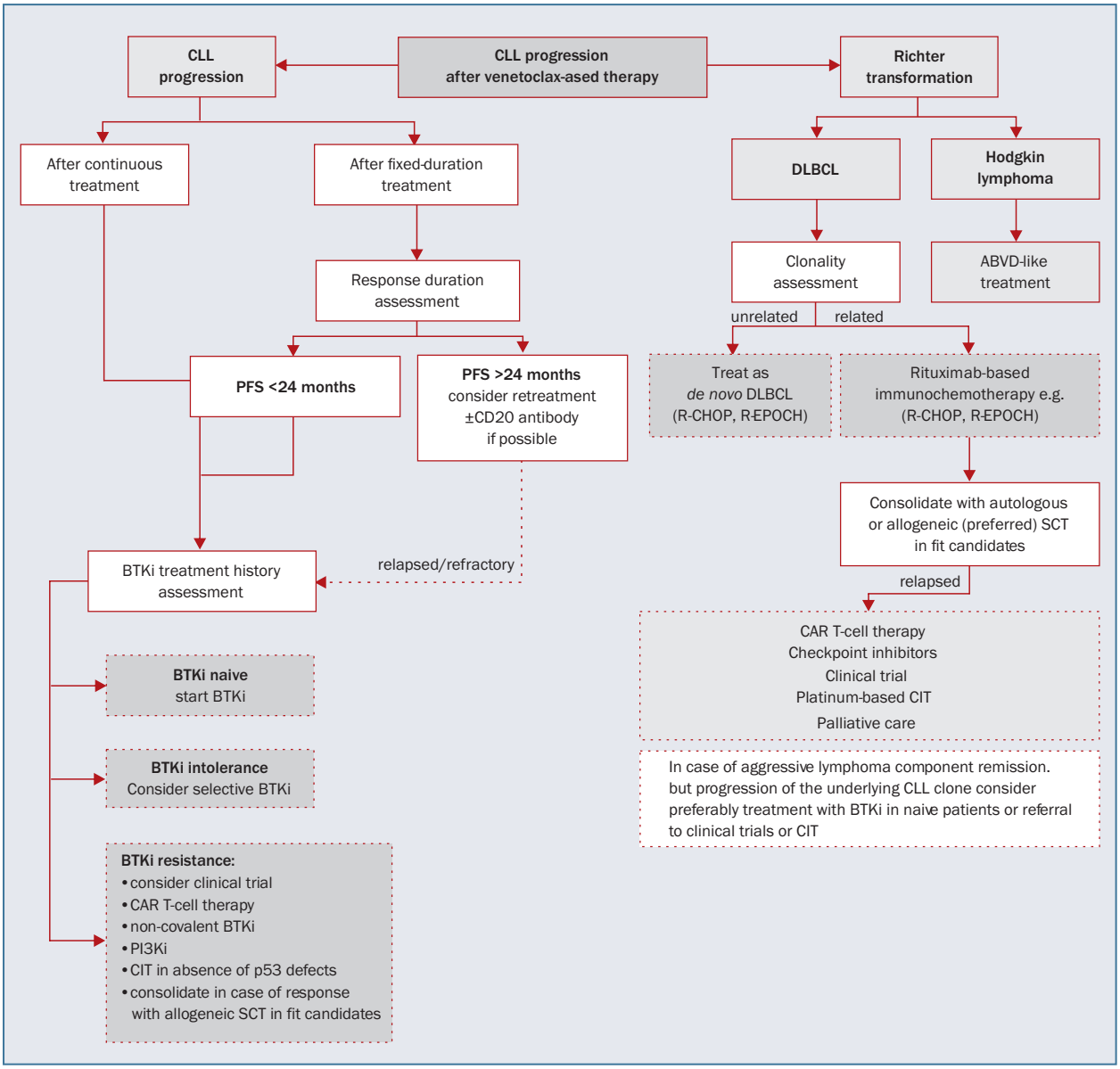

Figure 1. Proposed treatment algorithm in patients with chronic lymphocytic leukemia (CLL) following venetoclax treatment failure; ABVD — adriamycin, bleomycin, vinblastine, dacarbazine; BTKi — Bruton's tyrosine kinase inhibitors; CAR — chimeric antigen receptor; CIT — chemoimmunotherapy; DLBCL — diffuse large B-cell lymphoma; PFS — progression-free survival; PI3Ki — phosphatidylinositol-3-kinase inhibitor; R-EPOCH — rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; SCT — stem cell transplantation

Conflict of interest

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Ethics

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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REVIEW ARTICLE

VIA MEDICA

Diagnostic pitfalls and challenges associated with basic hematological tests

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Abstract

Several generations of automated hematology analyzers are currently being used to determine a wide range of hematological parameters. As their results form the basis of many medical interventions, it is required that they undergo analytical validation. Samples flagged as being pathological or non-diagnostic require re-testing in a different mode, revision, or additional diagnostic workup (e.g. microscopic smear). In order to avoid mistakes, close cooperation and continuous communication are needed between laboratory and medical staff. To address this, in this review we discuss the most frequent errors and pitfalls associated with the preanalytical and analytical phases of basic hematological tests. While not all diagnostic pitfalls are avoidable, this guidance regarding potentially problematic diagnostic situations will allow for their quick verification at the laboratory stage. An awareness of the causes of errors and of the existence of pitfalls can lower the costs of analytical procedures by minimizing the need to repeat analyses of potentially pathological samples, and have a positive impact on patient safety. In addition, reducing the potential for laboratory errors can improve the accuracy of medical diagnoses and avoid unnecessary treatment.

Key words: complete blood count, diagnostic pitfalls, hematological parameters, laboratory errors

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Introduction

Although the most important diagnostic component of hematological disorders is medical examination, according to the rules generally applicable in internal medicine a significant role in establishing the diagnosis and implementation of treatment is nevertheless played by laboratory tests.

Analytical results are therefore the basis of many medical interventions, and it is of paramount importance that they are free from laboratory errors which can be a defect occurring at any stage of the laboratory cycle [1]. Laboratory errors can take place in the preanalytical, analytical, or postanalytical phase, i.e. from the moment of ordering the tests to reporting their results and interpreting them. The preanalytical phase includes ordering the test, collecting the material, identifying the patient and the sample, and transporting, storing, fractionating and/or pre-processing the sample. The analytical phase comprises the sample processing procedure directly associated with the assessment of the analyzed parameter, while the postanalytical phase consists of the reporting of results and their analysis by the physician. The evidence indicates that the pre- and postanalytical phases are more likely sources of error than the analytical steps [2].

Results discordant with the true clinical condition of a patient can be caused by incorrect collection of laboratory material, such as insufficient blood volume or blood sampling from cannulas, as well as by the use of the wrong anticoagulant or excessive storage of material from collection to processing. As a consequence of laboratory errors, blood resampling may be necessary in order to avoid incorrect diagnoses [1]. Therefore, to avoid unexpected

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laboratory pitfalls, it is important for laboratory staff to pay attention to such data as patient age and sex, to check the results of each sample, and to compare them to results obtained for the same patient in previous analyses; the diagnostician should also be aware of the properties of the reagents used and the principles of their measurement. In addition, close cooperation is needed between laboratory and medical staff.

The most basic test performed in a hematological laboratory is the complete blood count (CBC) with differential white cells count. Recent technological progress in hematological analyzers has greatly increased the range of parameters that can be estimated [2]. However, despite the high degree of automation in modern hematological laboratories, and the consequent decrease in analytical errors, some factors related to blood sampling procedures or principles of measurement for example can still distort the results of tests. Such problems are typically referred to as 'hematology pitfalls'. Therefore, it is very important to know which of these may be encountered by laboratory staff, and how they can be avoided.

This review presents the most common pitfalls encountered primarily in the pre-analytical and analytical phases of the determination of basic hematological parameters.

Laboratory pitfalls in preanalytical phase

Although each laboratory method must be standardized to yield results that are both reproducible and comparable between laboratories, errors related to the preanalytical phase account for up to 70% of all laboratory errors [3]. The preanalytical phase of a laboratory diagnostic test is influenced by many factors, including any activities performed by the patient before blood sampling. Blood samples should always be collected at the same time of day to avoid diurnal variations of the parameter tested. As a general rule, samples should be collected between 7am and 9am, and at least eight hours after the last meal, and, if possible, before taking medications [4]. The exact time of blood collection should be marked on the test order. It should be remembered that CBC results can also be influenced by other factors including age, gender, pregnancy, inflammatory diseases, time of day, alcohol intake and medications. Correct labeling of the tube is very important as well.

Factors that can lead to preanalytical errors include:

- errors in preparing the patient for the test;
- missing or incorrect patient data, including incorrect tube labeling;
- use of the wrong anticoagulant;
- use of the wrong type or size of tube;
- incorrect collection or excessive storage of material from collection to testing, or insufficient mixing of the sample with the anticoagulant;
- improper sample transportation and storage;
- the presence of factors interfering with diagnostic reagents such as hemolysis, jaundice, lipemia or presence of lupus anticoagulant;
- lack of communication between laboratory and medical staff.

Anticoagulants and collecting material

There is no universal anticoagulant for all blood tests, but the most commonly used anticoagulant in hematological tests is ethylenediaminetetraacetic acid (EDTA). Biochemical tests are mostly performed on serum, and molecular tests with EDTA. Citrate is used especially for coagulation tests, while heparin is commonly used in cytogenetic analyses. Some anticoagulants cover the inner wall of the test tube, while others may be added to the tube as a solution [5–8].

To avoid diagnostic errors, it is important to select an appropriate anticoagulant and to ensure that the correct blood volume is drawn. It is also important to check the expiry date of the tube before blood collection. In expired anticoagulant tubes, there is the risk of disrupting the proportion between anticoagulant and blood sample, which can lead to a false result.

EDTA

Three different sub-types of EDTA are in common use: Na_2EDTA, K_2EDTA and K_3EDTA [5]. Of these, K_2EDTA (edetate dipotassium dihydrate) is recommended by the International Committee for Standardization in Hematology (ICSH) [5–8] as the anticoagulant of choice for hematological tests. It is also routinely used in blood banks for blood group testing and Rh typing, or for antibody screening. Being a calcium chelating compound, the presence of K_2EDTA can interfere with some ion tests, e.g. zinc or magnesium binding. Therefore, it is very important to achieve an optimal ratio between the volumes of blood and EDTA in the test tube. Fresh human whole blood samples, anticoagulated with K_2EDTA (or K_3EDTA), should be used and processed within 4–8 h after blood sampling if stored at room temperature. If samples are refrigerated, hematological parameters are stable for longer [9]. An inadequate EDTA volume may lead to false results of red blood cell (RBC) parameters and potential clotting, while excessive EDTA volume may result in changes in erythrocyte morphology and the formation of echinocytes in the peripheral blood smear due to hypertonic constriction [5].

However, EDTA is not an ideal anticoagulant for platelet (PLT) evaluation. In the presence of EDTA, the PLTs change shape from discoid to spherical within about 60 minutes of blood collection and stabilize within about three hours, leading in turn to disturbances in mean platelet volume (MPV) and overestimation of MPV. Another diagnostic problem related to PLTs is EDTA-induced pseudothrombocytopenia caused by the presence of EDTA-dependent anti-platelet

antibodies in the serum of some individuals, which bring about platelet aggregation and thus a false low count value. It should be remembered that PLTs aggregation does not occur immediately after blood collection; only a slight reduction may be noted by the analyzer within the first few minutes. A more significant decrease in PLTs count is observed within three hours of blood collection. Therefore, if pseudothrombocytopenia is suspected, blood should be collected to the tube using another anticoagulant, usually citrate. However, in some cases, the PLTs count determined immediately after blood collection can be slightly lower in citrate than in an EDTA sample [5]. This can be caused by the blood being diluted by the citrate, which is a liquid anticoagulant (see below) or by accidental centrifugation of the sample for PLTs evaluation [6]. It is important to underscore that a simultaneous determination of the PLTs count from blood drawn on EDTA and citrate should be performed in order to exclude, or confirm, the existence of pseudo EDTA-dependent thrombocytopenia.

Heparin

Heparin acts mainly by creating a bond with antithrombin III, which can interfere with some antibody-antigen reactions. In order to obtain high-quality heparinized plasma samples and to avoid fibrin formation, it is recommended to use lithium heparin at a final concentration of 10–30 USP units per 1 mL of blood. This concentration leads to effective anticoagulation. Higher concentrations of heparin are no more efficacious, and have no effect on a range of the most commonly-requested blood parameters [7]. Tubes containing sodium or lithium heparin are commonly used for blood gasometry, ionized calcium tests, cytogenetics and plasma analysis in clinical chemistry. Heparin is, however, unsuitable for some tests such as coagulation or Wright's stained blood smears, as it can cause staining artifacts (i.e. the smear may become too blue), which affect blood smear examination [8].

Sodium citrate

Sodium citrate is a standard anticoagulant for blood coagulation tests, such as activated partial thromboplastin time (APTT) and prothrombin time (PT), as well as for the classic Westergren erythrocyte sedimentation rate (ESR). Trisodium citrate forms complexes with calcium ions, and stabilizes the labile coagulation factors V and VIII. Sodium citrate solutions are typically used in two concentrations, 3.2% and 3.8%, which are available in buffered or not-buffered liquid forms. The tubes containing the citrate are calibrated to maintain a blood-to-citrate ratio of 9:1 for both the abovementioned concentrations of citrate. These are recommended for coagulation tests [10]. The stability of the citrate samples is satisfactory only up to three hours after blood collection. During analysis, a correction factor of 1.17 must be applied to account for citrate dilution of the blood sample [5, 11]. In addition, as sodium citrate dilutes the blood sample, it is generally unsuitable for most other hematological tests.

In addition to the choice of anticoagulant, it is also important to choose the right type of test tube for the type of blood test. To avoid contamination by anticoagulants during material collection, peripheral blood for different types of tests should be drawn in the correct order. The recommended order of blood collection for various tests is [12]:

- tube for bacteriology;
- tube for coagulation tests with sodium citrate — always as a second tube (when no tube for bacteriology was collected, a non-additive tube should be used first);
- tube with clot activator, or tubes without anticoagulant for chemistry, immunology and serology tests;
- tube with lithium heparin for cytogenetics or gasometry;
- tube with EDTA for CBC;
- tube with acid-citrate-dextrose (ACD, ACDA or ACDB) for human leukocyte antigen (HLA) tissue typing, paternity testing and DNA studies;
- tube with sodium fluoride for glucose test;
- tube for Westergren erytrocyte sedimentation rate (ESR).

The main consequences of incorrect blood collection are hemolysis, bacterial contamination, and platelet aggregation. Of these, hemolysis seems to be the most common problem, usually occurring at the preanalytical stage. Hemolysis *in vitro* may be induced by several factors, and may be aggravated by forced aspiration of blood into vacuum tubes. The aspiration method is believed to be a safer sampling method, especially for patients during chemotherapy, or when venipuncture is difficult, when a vacuum approach could increase the chance of false hemolysis. Lippi et al. [13] reported a significant increase of serum potassium concentration and lactate dehydrogenase (LDH) activity after the collection of blood into vacuum tubes compared to aspiration ones. In addition, excessive time from blood collection to test performance can also lead to hemolysis and the artificial elevation of serum potassium concentration. However, both the aspiration and the vacuum method can result in significant microhemolysis in samples [13].

The probability of hemolysis is further increased by using an under-gauge needle (23G or smaller), or taking a blood sample from an intravenous cannula or central line. Additionally, excessive pressure in the syringe when drawing blood into the tube results in the destruction of a number of RBCs and an underestimation of their count. Other common errors include the collection of a blood sample before complete drying of the disinfectant agent used on the skin, or too intensive mixing of the tubes with collected blood. In blood from pediatric patients, hemolysis can also be caused by the use of an oversized tube or syringe (10–20 mL) [12].

In vitro hemolysis, occurring as a result of incorrect blood collection, is characterized by reduced RBCs count and lowered hematocrit (HCT) value with normal

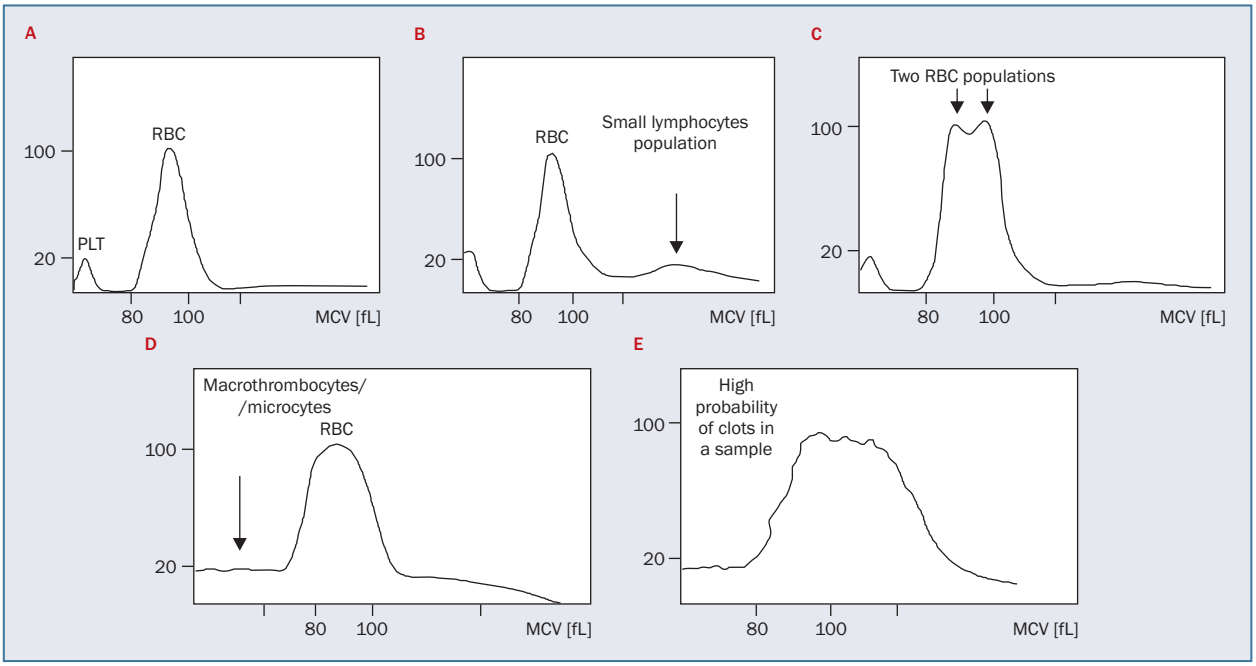

Figure 1. Examples of red blood cells (RBC) histograms: **A.** Normal histogram, normocytosis; **B.** Histogram in micro- and macocytosis; **C.** Histogram distorted by macrothrombocytes, clots, microclots, hemolysis; **D.** Histogram distorted by cold agglutinins; **E.** Lack of separation of cells into individual populations; PLT — platelets ; MCV — mean platelet volume

hemoglobin (HGB) concentration. Such changes can result in incorrect estimation of certain parameters, such as mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC). It should be also remembered that *in vivo* hemolysis is indicated by the presence of reticulocytosis and true fragments of RBCs (FRBCs). In contrast, in *in vitro* hemolysis, damaged RBCs are counted by the analyzer as FRBCs ('pseudo' FRBCs) [14, 15].

Transport and storage

Transport and storage of the collected materials also play important roles in the analytical process. The ICSH recommends that samples should be stored at 4 °C [16]. The stability of hematological parameters depends on the type of test, method, and the technology of hematological analyzers and reagents used for analysis. Therefore, it is recommended to follow the instructions provided by the manufacturer. Blood samples should be transported in special containers which ensure the right temperature. The recommended time between blood collection and test performance must not be exceeded, as excessive transport time, especially when the ambient temperature is higher than 22 °C, can lead to false test results [17].

Diagnostic pitfalls in analytical phase (CBC parameters and microscopic smear)

Modern automatic hematological analyzers employ a range of technologies to determine CBCs parameters, including impedance, spectrophotometry, optical methods and flow cytometry [18, 19].

In addition, laboratory pitfalls observed during the analytical phase may concern many aspects of cell morphology. Impedance-based analysis can simultaneously assess RBCs and PLTs count in one detector.

Figure 1A demonstrates the normal RBCs histogram. However, high leukocytosis with the presence of a small lymphocyte population can falsify RBCs count (Figure 1B). The presence of two RBCs peaks at the histogram indicates two populations of erythrocytes, which may occur after blood transfusion (Figure 1C). The presence of cryoglobulins, macrothrombocytes (giant PLTs), high leukocytosis and low plasma volume (hypovolemia) can result in an overestimation of RBCs count. In the case of the presence of a population of macrothrombocytes, a clear separation of the RBCs from the PLTs population is not seen on the histogram, and the curve corresponding to macrothrombocytes is shifted above the baseline. Additionally, the presence of microcytes is classified by the analyzer as PLTs (Figure 1D). The RBCs count can be lowered by the presence of blood clots or microclots in the tube which may be induced by the cold agglutinins or *in vitro* hemolysis due to the presence of artifacts, e.g. fragments of damaged cell. The histogram shows a lack of separation of the cells into individual populations (Figure 1E). Current automatic hematological analyzers are equipped with the option of heating the sample to 37°C, which allows the influence of cold agglutinins to be excluded. Additionally,

Table I. Most common causes of false increases or decreases in selected parameters associated with complete blood count (based on [20–22])

Parameter	↑ false increase	↓ false decrease
Red blood cells (RBC)	Cryoglobulins	Clots or microclots, hemolysis, cold agglutinins, blood dilution
Hematocrit (HCT)	Cryoglobulins, hyperglycemia	Clots or microclots, hemolysis, autoagglutination of erythrocytes, excess of EDTA in tube
Hemoglobin (HGB)	Carboxyhemoglobin, high leukocytosis, cryoglobulinemia, hyperbilirubinemia, hyperlipidemia	Clots and microclots
Platelets (PLT)	Hemolysis in presence of very small erythrocytes (microcytes), samples contaminated by physical or biological factors (artifacts), too intensive mixing of samples	EDTA-related pseudothromocytopenia, platelet aggregation, platelet degranulation or even their complete degradation, presence of large macrothrombocytes, too long time from blood collection to analysis (MPV ↑), blood dilution, clots and microclots
White blood cells (WBC)	Cryoglobulins, hyperlipidemia, or presence of erythroblasts, very large PLTs and platelet aggregates	Clots or microclots, blood dilution, excessive degradation of some WBCs, agglutination of WBCs in presence of EDTA

EDTA — ethylenediaminetetraacetic acid; MPV — mean platelet volume

underestimations of RBCs count can also result from blood dilution caused by the drawing of blood from the drip infusion site or an increase of patient intravascular liquid volume (hypervolemia) [20].

In automated analyzers, HCT is calculated as the sum of each RBCs volume passing through the detector of the analyzer in a given time [20]. A falsely elevated HCT value may be caused by similar factors to those responsible for the increase of RBCs counts, as well as hyperglycemia above 600 mg/dL [18]. In contrast, a false lowering in HCT value can be caused by excess EDTA in the tube, autoagglutination of erythrocytes, or the presence of a clot or hemolysis in the tube [20] (Table I).

The cyanmethemoglobin method is recommended by the ICSH for the measurement of HGB concentration, a basic diagnostic parameter in any CBC [19, 20]. However, falsely-elevated HGB concentrations can result from the presence of more than 10% carboxyhemoglobin, high leukocytosis, cryoglobulinemia, hyperbilirubinemia and hyperlipidemia, while underestimated HGB values can be associated with the presence of clots and microclots in the tube [20]. In cases of major intravascular hemolysis, mechanical hemolysis associated with artificial heart valves or hemolytic anemias associated with blood transfusions, the presence of free HGB concentration in plasma may be elevated enough to affect HGB measurement by the analyzer. If free plasma HGB concentration is above 200 mg/L, the only reliable parameter is RBCs count [21] (Table I).

Nucleated red blood cells (NRBCs) are not only found in the blood under pathological conditions, they can also be observed under physiological conditions, such as after major hemorrhage or in newborns. They are counted in the appropriate channel of the analyzer under the influence of the lysing fluid, which disintegrates the erythroblast membrane without disturbing the cell nucleus. Specific fluorescent markers labeling nucleic acids can be used to avoid counting NRBCs as PLTs or, if they are large enough, as WBCs [21–23].

Reticulocytes can be separated from mature RBCs, WBCs, and NRBCs by means of frontal scattering light and a fluorescent signal. However, in nearly 9% of cases, the number of reticulocytes can be falsely overestimated in automatic analyzers [24]. Reticulocyte count has been found to be associated with the presence of parasites such as malaria and drug-induced autofluorescence. Reticulocyte count can also be falsely lowered due to the presence of FRBCs in the sample, among other causes, although such disturbances can be detected by modern automatic analyzers which employ alarm alerts and flagging algorithms.

Overestimated PLT values are observed in cases of hemolysis (FRBCs presence) and in the presence of very small erythrocytes (microcytes), which are counted as PLTs instead of RBCs by automatic analyzers. In addition, some physical factors, or bacteria and fungi in the blood as biological contaminants, can also be counted by the analyzers as PLTs, resulting in a falsely elevated count. In contrast, PLTs counts can be underestimated due to EDTA-related pseudothromocytopenia, spontaneous platelet aggregation, platelet satellitism, the occurrence of platelet degranulation or degradation, and the presence of large macrothrombocytes counted as RBCs instead of PLTs (Table I).

A false decrease in platelet count due to PLTs aggregation is a common phenomenon, and is often caused by excessive time from blood collection to analysis; this may result in an overestimation of MPV. In contrast, excessive mixing of the sample can lead to PLTs degradation and thus a decrease in MPV [18]. Additionally, as mentioned above, the influence of anticoagulant on MPV values depends on the method used; for example, MPV may be slightly overestimated when an impedance method is used. Therefore, a light scattering-based method is recommended to check the accuracy of determination of all PLTs parameters [5, 25].

As in the case of EDTA-related thrombocytopenia discussed above, the presence of EDTA can lead to agglutination of WBCs and so to a falsely-lowered WBCs number [20]. WBCs values may be increased by the presence of cryoglobulins, hyperlipidemia, erythroblasts and very large PLTs and platelet aggregates, which can be counted by the analyzer as WBCs [21]. In contrast, falsely lowered WBCs values are mainly caused by the presence of blood clots, blood dilution, or excessive degradation of some WBCs, but also by the occurrence of pseudo-neutropenia deriving from the abnormal distribution of granulocytes in the circulation, when a significant number of granulocytes shift from the bloodstream onto the wall of the blood vessels. The use of hydrocortisone causes a shift of granulocytes back from the vessel wall to the circulation, resulting in the WBCs count returning to normal values (Table I).

The number of WBCs needed to influence HGB concentration remains poorly understood. Some authors have suggested that leukocytosis of 250 G/L can interfere with HGB concentration, while others suggest that values of 100 G/L or even 50 G/L can falsely increase the true HGB value [20, 21]. In patients with hematological disorders, especially in the case of leukopenia or leukocytosis, a flagged CBC is reported. In such cases, a differential WBCs count should be performed on a peripheral blood smear assessed under a microscope.

It is essential to prepare and stain the smear properly: inadequate dye proportions and incorrect staining times can result in the granules in the cells being too dark or even completely obscured. Such improper staining of the blood smear can result in interpretation errors e.g. blast cells may be taken for lymphocytes or *vice versa*.

Several factors can influence smear quality. For example, if the blood drop is too small or if the smearing is too slow, or if the smearing slide is applied to the blood drop at the wrong angle, the procedure can result in a thin smear, distorted erythrocytes or white blood cells being displaced onto the side edges and feathered edge (tail) of the slide. A similar effect can be observed when the HCT value is low, e.g. in anemia. In contrast, blood with high HCT values (e.g. in patients with polycythemia) may result in thick smears, making it difficult to evaluate erythrocyte morphology.

The presence of FRBCs in a peripheral blood smear indicates pathology, and usually requires urgent medical attention. In newborns however, both schistocytes and erythroblasts can be present in the peripheral blood in physiological conditions [26–30]. State-of-the-art analyzers are able to estimate the number of FRBCs by giving both their percentage and absolute value. The presence of schistocytes may result in anisopoikilocytosis [29, 31, 32]. Studies have noted examples where automatically-counted FRCs have been overestimated after PLTs transfusion [26, 27–32].

The distribution of WBCs may be presented as an absolute value or as a percentage. However, it should be underscored that the percentage of the CBC values has no clinical significance, and should not be taken into account at all as long as we have the absolute values, which are the parameters directly counted by the analyzers. An increase of the percentage of the population of WBCs does not necessarily lead to an increase in total WBCs number. Changes in WBCs percentage distribution, e.g. high lymphocyte counts in adults with normal or only slightly increased total WBCs counts, may indicate a viral infection but also some hematological disorders [e.g. monoclonal B-cell lymphocytosis (MBCL) or small lymphocytic lymphoma (SLL)]; this can also be noted in children [33, 34]. In such cases, it is recommended to use absolute values instead of percentages because they provide more accurate diagnostic information.

If the blood sample is mixed too vigorously, this can result in a significant increase in PLTs count due to the disruption of RBCs; these fragments are counted as PLTs by the analyzer. In contrast, insufficient mixing results in clot formation and thus false underestimation of WBCs, PLTs, RBCs count, HCT and HGB concentration [35].

Quality evaluation of hematological tests

In hematology, normal peripheral blood can be used as a control to calibrate hematological analyzers.

Quality evaluation of hematological tests requires the use of 3-level quality controls which enable the laboratory to minimize the risk of analytical errors and assess the linearity of the determinations. While day-to-day intra-laboratory control is the responsibility of laboratory staff, further calibration is usually performed by an external technical service responsible for the device. The results of the daily intra-laboratory control can be presented graphically using Levey-Jennings charts. The Westgard rules should be used to interpret the results of control material [36, 37].

Conclusions

Thanks to recent technical progress, modern analyzers are capable of fully-automated digital assessment of blood cell counts and blood smear staining. However, despite this

high degree of automation in medical laboratories, the results of laboratory tests can be influenced by a number of factors which may be sources of error. A thorough knowledge of preanalytical phase variables and their impact on the results of hematological tests and/or analytical phase pitfalls is necessary to obtain accurate results which reflect the patient's true condition and to minimize the need to repeat analyses of potentially pathological samples to avoid unnecessary treatment and ensure proper medical care.

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Authors' contributions

AK — writing the article, literature analysis and interpretationfinal, approval of article; EZ — literature analysis and interpretation, writing the article; AKW — writing the article, critical revision of the article, final approval of article.

Conflict of interest

The authors have no conflict of interest to declare.

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Ethics

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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ORIGINAL RESEARCH ARTICLE

Incidence and prevalence of lymphatic neoplasms in Poland 2009–2015 determined on analysis of National Health Fund data used in the 'Maps of healthcare needs — database of systemic and implementation analyses' project

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Abstract

Introduction: The need for epidemiological data on blood neoplasms is driven by both systemic and scientific requirements. Due to the fact that all services provided to patients with these cancers in Poland are reported to the National Health Fund (NHF), the aim of this study was to try to use this data to estimate the incidence and prevalence of lymphatic neoplasms in Poland, as well as to determine overall survival (OS) in this group of patients.

Materials and methods: The analysis was carried out as part of the 'Maps of health needs — database of system and implementation analyses' project, co-financed by the European Union through the European Social Fund under the Operational Program Knowledge Education Development.

Results: The registered incidence of follicular lymphoma (FL) in 2014 was 1.74/100,000, whilst the registered prevalence was 15.56/100,000. The median OS of patients registered in the NHF system in 2009–2015 with an FL diagnosis was over 60 months, and the estimated 3- and 5-year OS rates were 76.6% and 68.8% respectively. In 2014, the incidence and prevalence of diffuse large B-cell lymphomas (DLBCL) was 3.76/100,000 and 27.48/100,000, respectively. The median OS was over 60 months, and the estimated 3- and 5-year OS rates were 68.7% and 61.1%, respectively. On the other hand, the incidence and prevalence of chronic lymphocytic leukemia (CLL) were 8.65/100,000/year and 38.28/100,000/year, respectively. The median OS was over 60 months, and the estimated 3- and 5-year OS rates were 77.8% and 64.8%, respectively. In the case of plasma cell myeloma (PCM), the registered incidence and prevalence were 4.92/100,000/year and 23.28/100,000/year, respectively. The median OS was 60 months, and the 3- and 5-year OS rates were 62.8% and 49.7%, respectively.

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Conclusions: The data reported to the National Health Fund in order to obtain reimbursement of medical services seems to be the most reliable data covering such a large population of patients. The results are similar to data from European and American registries for DLBCL and PCM. However, the FL and CLL data requires further verification.

Key words: registered incidence, registered morbidity, overall survival probability, follicular lymphoma, diffuse large B-cell lymphoma, chronic lymphocytic leukemia, plasma cell myeloma

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Introduction

Epidemiological data on lymphatic neoplasms are well characterized in many registries. However, most national registries and epidemiological studies do not cover the specific subtypes of lymphoma defined according to the World Health Organization (WHO) classification, except for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and plasma cell myeloma (PCM). Much less precise epidemiological data is available for the most common lymphoma subtypes, i.e. diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma (FL).

It must be emphasized, however, that in recent years there has been a clear tendency towards more detailed reporting of data regarding the incidence of individual lymphoma subtypes. This is, among other things, related to the high heterogeneity of the clinical course of these neoplasms, and thus the different amounts of funding allocated to medical care [1–4].

In Poland, cases of newly diagnosed cancers are reported to the National Cancer Registry (NCR). Currently, the 10th Revision of the International Statistical Classification of Diseases and Health-Related Problems (ICD-10) is in force in Poland, and all entities contributing to the public statistics research program are obliged to apply this version. However, the cancer incidence data collected in the NCR seems to be underestimated, for various reasons [5]. For example, in the case of solid tumors, in the NCR there was an average 26% underestimation, and depending on the type of cancer this figure ranges from 14% (breast cancer) to 50% (salivary gland cancer) [6].

New cases of hematological malignancies are also reported to the NCR, and under the common name 'lymphoid and hematopoietic tissue tumors' (ICD-10 C81–C96) are grouped as follows: Hodgkin lymphoma (ICD-10 C81), non-Hodgkin lymphomas (ICD-10 C82–C85), multiple myeloma and malignant plasma cell neoplasms (ICD-10 C90), leukemias (ICD-10 C91–95), lymphocytic leukemia (ICD-10 C91), and myeloid leukemia (ICD-10 C92). The current ICD-10 makes it difficult to obtain epidemiological data on hematological malignancies in accordance with the current WHO classification. The published epidemiological data, which is generally available on the NCR website, is limited to two-digit ICD-10 codes, which, inter alia, make it impossible to distinguish between acute lymphoblastic leukemia (C91.0) and CLL (C91.1) and between acute myeloid leukemias (AML) and chronic myelogenous leukemia (CML) (C92.1) [5].

On the other hand, all healthcare entities financed from public funds, when reporting the provision of medical services to the National Health Fund (NHF), report cancer diagnoses according to the ICD-10 classification in a 5-character format, which allows for a more precise determination of cancer type, including the differentiation of acute from chronic leukemias. Moreover, due to reporting to the PESEL level, it is also possible to determine morbidity by analyzing the patient care pathway [5].

The aim of this study was to analyze the data of the National Health Fund in order to determine the incidence and prevalence of the four most common lymphatic neoplasms in Poland, as well as to estimate overall survival (OS) in this group of patients irrespective of the cause of death.

Materials and methods

The analysis was carried out as part of the project entitled 'Maps of Healthcare Needs—Database of Systemic and Implementation Analyses' co-financed by the European Union through the European Social Fund under the Operational Program Knowledge Education Development. As part of this project, on 31 December, 2016, the 'Health Needs Maps — database of system and implementation analyses' was published on the website of the Ministry of Health [7]. The project was implemented by the Department of Analyses and Strategies of the Ministry of Health, and its aim was to improve the quality of management in the healthcare system by supporting data-based management decisions. Regular preparation and publication of analyses leads to a substantive discussion on the healthcare system and substantive explanation of management decisions at the national (macro) level, the regional (meso) level, and the individual service provider (micro) level [5, 7].

In 'Maps of health needs — database of system and implementation analyses', hematological malignancies were grouped based on the WHO classification, using the ICD-10 classification codes used in reporting to the National

Health Fund. The analyses used pseudonymized data reported to the National Health Fund in the SWIAD message for the period 1 January, 2014, to 31 December, 2014, as well as on data on deaths recorded in the Social Insurance Central Registry. The analyses included those patients reported to the National Health Fund with diagnoses of FL (codes ICD-10: C82, C82.0, C82.1, C82.2, C82.3, C82.7 i C82.9), DLBCL (codes ICD-10: C83, C83.0, C83.1, C83.2, C83.3, C83.4, C83.5, C83.6, C83.7, C83.8, C83.9), CLL (codes ICD-10: C91.1), and PCM (codes ICD-10: C90, C90.0, C90.1, C90.2).

Bearing in mind that from an epidemiological point of view lymphatic neoplasms are considered to be non-transient, i.e. chronic, diseases, the registered incidence and the registered prevalence of particular groups of malignancies were calculated. The term 'registered' was introduced to indicate that this is not an incidence or prevalence determined on the basis of epidemiological studies, but rather based on events registered by the public payer [5, 7].

The 'registered incidence' rate was defined as the number of newly diagnosed patients reported under the healthcare system financed from public funds per 100,000 inhabitants during the year. In the case of chronic diseases, the incidence was calculated for 2014, based on the National Health Fund data from 2009–2015 (giving the possibility of analyzing the patient's history at least five years backwards and one year forwards). A patient reported to the NHF in this period was considered a new one (a first-time patient) if he or she was diagnosed for the first time in 2014. The number of new cases in the public healthcare system (registered incidence) should take into account each first appearance of a patient in the system. However, due to the fact that the analysis was carried out based on the National Health Fund data, wherever it was possible to report a diagnosis which could not be confirmed until later after referral to a specialist center, the rule was adopted that only those patients who appeared in the public healthcare system at least twice could be regarded as patients with a given diagnosis, which therefore means having a given disease [5, 7]. In the case of FL and DLBCL incidence, due to the potential difficulty of making a precise diagnosis outside a hematooncological center, an additional criterion for identifying a new diagnosis was adopted: i.e. the first contact of the patient with a diagnosis appropriate for the analyzed group of lymphomas (codes C82 with extensions for FL, codes C83 with extensions for DLBCL) or with a diagnosis of C85 (other and unspecified types of non-Hodgkin lymphoma), and the second contact of the patient reported with the diagnosis of C82 with extensions for FL or C83 with extensions for DLBCL. Three ways of 'entering' the patient into the system were considered: hospital, specialist outpatient care, and hospital emergency department [7]. The incidence rates recorded for 2014 were stratified by age and by gender [5].

The 'prevalence' rate was defined by registering all patients reported in a given year, totalling the number of patients who were first reported to the system in a given year and the patients who had been reported as newly diagnosed in previous years but who were still alive in the year for which the analysis was performed, regardless of whether or not they were provided with medical services for hematological malignancy in the course of that particular year. Registered morbidity was estimated as of 31 December, 2014. This means that all patients classified as new cases in the public healthcare system since 2009 and who had not died by 31 December, 2014, were considered to be registered cases on that date. We must underscore that the analysis at the voivodeship level took into account the patient's place of residence declared to the public payer, not the place where the service was provided [5, 7].

The probability of OS was estimated based on the Kaplan-Meier method, and the patient's survival was calculated in the period from diagnosis to death, regardless of its cause. The analyses and visualizations were made with the use of R software, version 3.3.1, and IDE RStudio, version 1.0.136 [8–13].

Results

Follicular lymphoma

There were 700 newly diagnosed cases of FL in adults in 2014, with a registered incidence of 1.74/100,000 population. The number of patients with FL in Poland was estimated at 6,000, and the registered prevalence was 15.56/100,000. The registered incidence and prevalence rates for individual voivodeships are set out in Table I. Figure 1 shows FL incidence, with the size of the district reflecting the absolute number of new cases in a given voivodeship [the highest (100) being in Silesia voivodeship and the lowest (12) in Podlaskie voivodeship], taking into account the three means of patient 'entry' into the system described above. The color intensity of the voivodeship shows the incidence level per 100,000 population (the highest value, 2.21, in Subcarpathia voivodeship, and the lowest value, 0.97, in Warmia–Masuria voivodeship).

In 2014, among FL patients, male and female patients accounted for 46% and 54%, respectively. The FL registered incidence by sex in individual provinces is set out in Figure 2.

The median age of patients reported using FL codes was 62 years (range 18–96): women 63 (18–93 years) and men 61 (21–96 years). Figure 3 shows the structure of the registered incidence by age group, and Figure 4 shows the registered incidence by age group in individual voivodeships.

Based on the dates of death, the probability of OS was estimated in all patients registered in the National Health

Table I. Registered incidence and prevalence rates for follicular lymphoma according to defined region of Poland

Province/country	Incidence per 100,000	Prevalence per 100,000
POLAND	**1.74**	**15.56**
Lower Silesia	1.99	16.06
Kuyavia–Pomerania	1.63	12.25
Lublin	1.35	8.80
Lubusz	1.27	16.76
Lodz	1.28	11.15
Lesser Poland	2.11	13.39
Masovia	1.78	14.66
Opole	2.00	25.89
Subcarpathia	2.21	16.21
Podlaskie	1.01	12.17
Pomerania	1.74	17.42
Silesia	2.18	23.56
Holy Cross Province	1.03	11.48
Warmia–Masuria	0.97	11.15
Greater Poland	1.87	18.26
West Pomerania	1.46	12.77

Fund in 2009–2014 with the diagnoses of FL, i.e. C82, C82.0, C82.1, C82.2, C82.3, C82.7 and C82.9 (Figure 5). Median OS was over 60 months. The estimated 3-year and the 5-year OS rates were 76.6% and 68.8%, respectively. The probability of OS in patients reported using the above-mentioned ICD-10 codes was also calculated by age groups with respective 3-year and 5-year OS rates (Figure 6, Table II).

Diffuse large B-cell lymphomas

There were 1,400 newly diagnosed cases of DLBCL in adults in 2014 with the registered incidence of 3.76/100,000 population. The number of patients with DLBCL in Poland was estimated at 10,600, and the registered prevalence was 27.48/100,000. The registered incidence and prevalence rates for individual voivodeships are set out in Table III. Figure 7 shows DLBCL incidence, with the size of the district reflecting the absolute number of new cases in a given voivodeship [the highest (200) in Masovia voivodeship and the lowest (30) in Lubusz voivodeship], taking into account the three ways of patient entry to the system. The color intensity of the voivodeship shows the incidence level per 100,000 population (the highest value of 5.21 in Subcarpathia voivodeship, and the lowest value of 2.60 in Podlaskie voivodeship).

In 2014, among DLBCL patients, male and female patients accounted for 49% and 51%, respectively. The DLBCL registered incidence by sex in individual provinces is set out in Figure 8.

The median age of patients reported using DLBCL codes was 65 years (range 18–96): women 66 (18–96) and men 63 (18–96). Figure 9 shows the structure of the registered incidence by age group, and Figure 10 shows the registered incidence by age group in individual voivodeships.

Based on the dates of death, the probability of OS was estimated in all patients registered in the National Health Fund in 2009–2014 with the diagnoses of DLBCL, i.e. C83, C83.0, C83.1, C83.2, C83.3, C83.4, C83.5, C83.6, C83.7, C83.8, C83.9 (Figure 11). Median OS was over 60 months. The estimated 3-year and 5-year OS rates were 68.7% and 61.1%, respectively. The probability of OS in patients reported using the above-mentioned ICD-10 codes was also calculated by age groups with respective 3-year and 5-year OS rates (Figure 12, Table IV).

Chronic lymphocytic leukemia

There were 3,300 newly diagnosed cases of CLL in adults in 2014 with the registered incidence of 8.65/100,000 population. The number of patients with CLL in Poland was estimated at 14,700, and the registered prevalence was 38.28/100,000. The registered incidence and prevalence rates for individual voivodeships are set out in Table V. Figure 13 shows CLL incidence, with the size of the district reflecting the absolute number of new cases in a given voivodeship [the highest (700) in Lodz voivodeship and the lowest (43) in Lubusz voivodeship], taking into account the three ways of patient entry to the system. The color intensity of the voivodeship shows the incidence level per 100,000

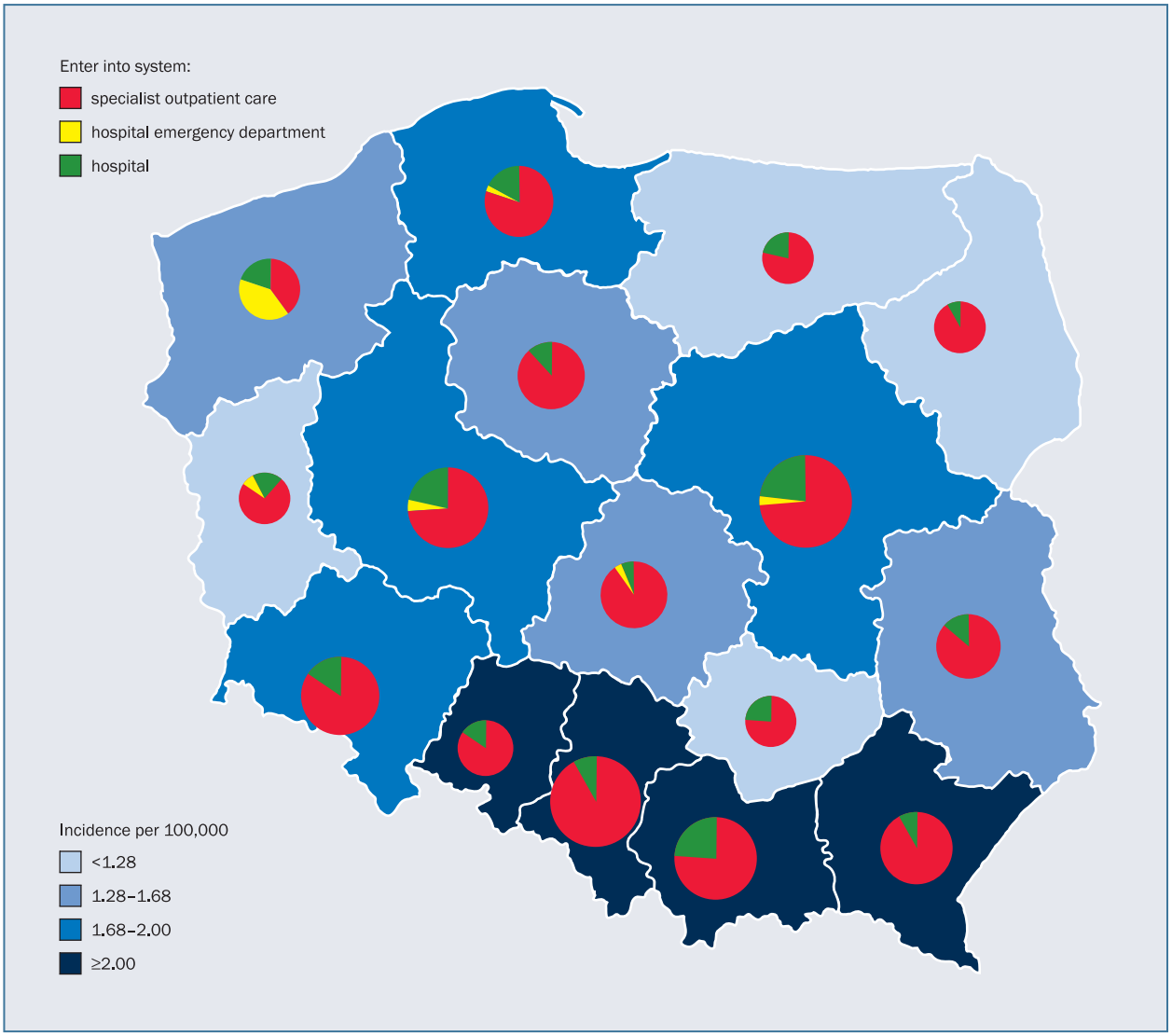

Figure 1. Registered incidence rate for follicular lymphoma according to defined region of Poland

population (the highest value of 29.20 in Lodz voivodeship, and the lowest value of 4.22 in Lubusz voivodeship).

In 2014, among CLL patients, male and female patients accounted for 55% and 45%, respectively. The CLL registered incidence by sex in individual provinces is presented in Figure 14.

The median age of patients reported using CLL codes was 69 years (range 20–101 years): women 71 (20–101) and men 68 (21–97). Figure 15 shows the structure of the registered incidence by age group, and Figure 16 shows the registered incidence by age group in individual voivodeships.

Based on the dates of death, the probability of OS was estimated in all patients registered in the National Health Fund in 2009–2014 with the diagnoses of CLL, i.e. C91.1 (Figure 17). Median OS was over 60 months. The estimated 3-year and 5-year OS rates were 77.8% and 64.8%, respectively. The probability of OS in patients reported using the above-mentioned ICD-10 codes was also calculated by age groups with respective 3-year and 5-year OS rates (Figure 18, Table VI).

Plasma cell myeloma

There were 1,900 newly diagnosed cases of PCM in adults in 2014 with the registered incidence of 4.92/100,000 population. The number of patients with DLBCL in Poland was estimated at 9,000, and the registered prevalence was 23.28/100,000. The registered incidence and prevalence rates for individual voivodeships are set out in Table VII. Figure 19 shows PCM incidence, with the size of the district reflecting the absolute number of new cases in a given voivodeship [the highest (400) in Masovia voivodeship and the lowest (44) in Lubusz voivodeship], taking into account the three ways of patient entry to the system. The color

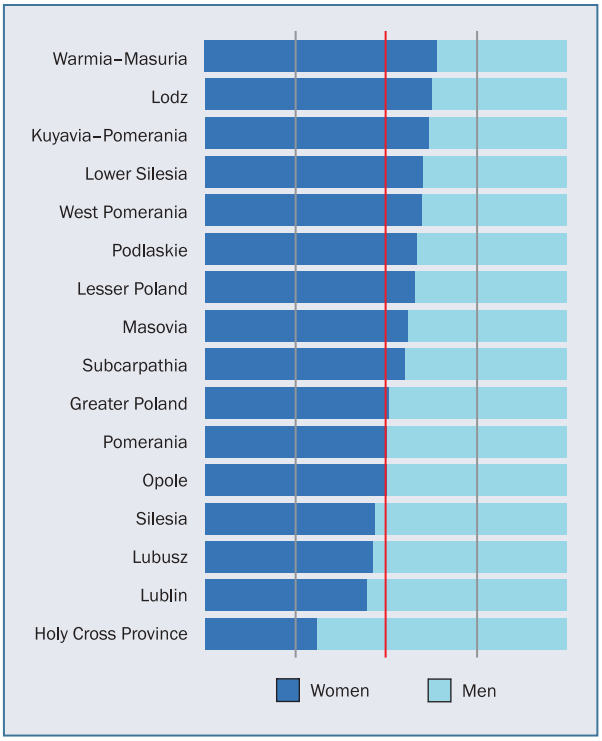

Figure 2. Pattern of registered incidence of follicular lymphoma according to gender and region of Poland

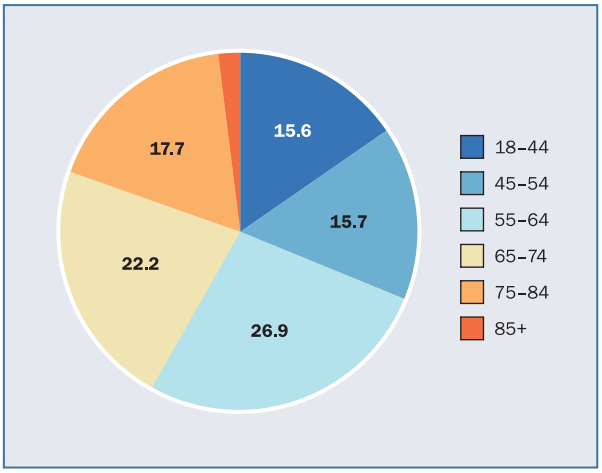

Figure 3. Pattern of registered incidence of follicular lymphoma according to age group

intensity of the voivodeship shows the incidence level per 100,000 population (the highest value of 6.84 in Masovia voivodeship, and the lowest value of 3.19 in Warmia–Masuria voivodeship).

In 2014, among PCM patients, male and female patients accounted for 48% and 52%, respectively. The DLBCL

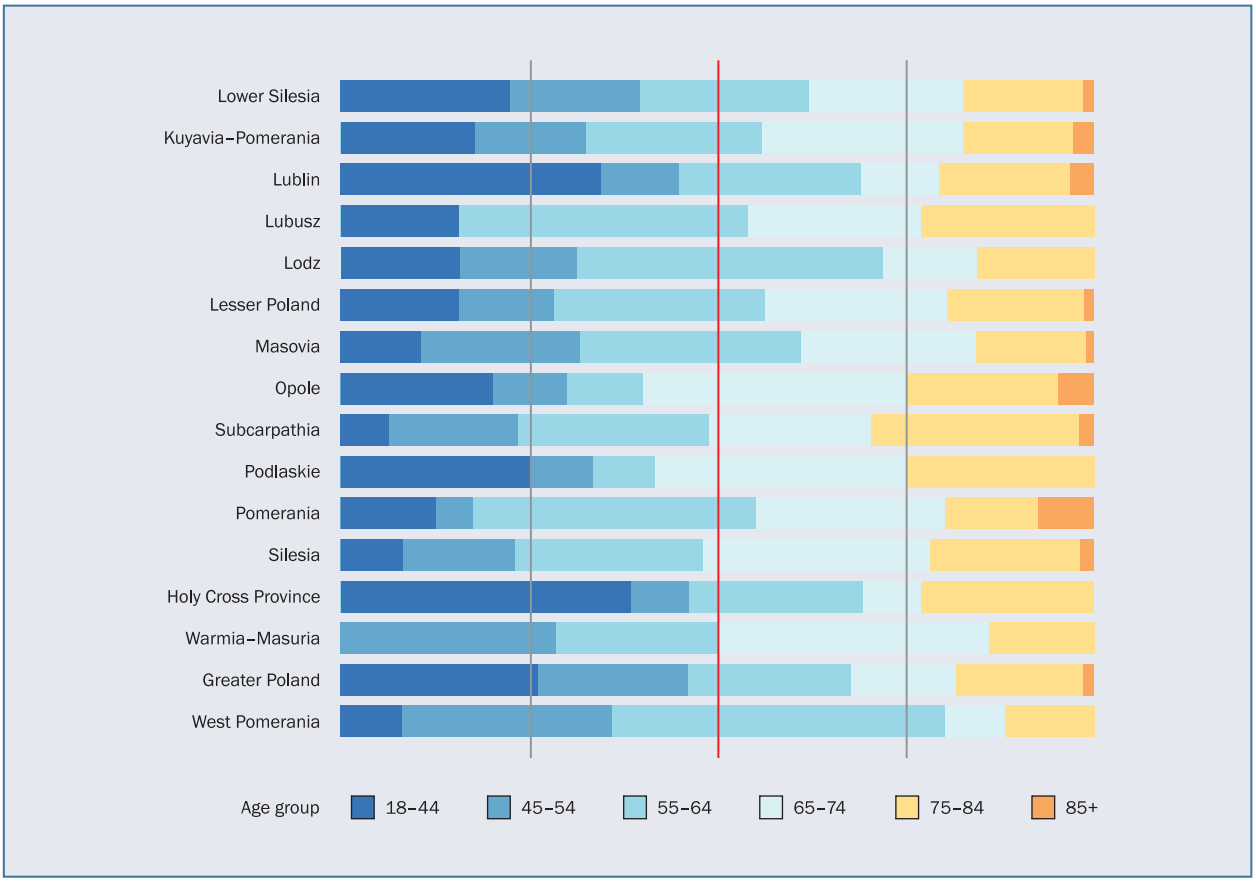

Figure 4. Pattern of registered incidence of follicular lymphoma according to age group and region of Poland

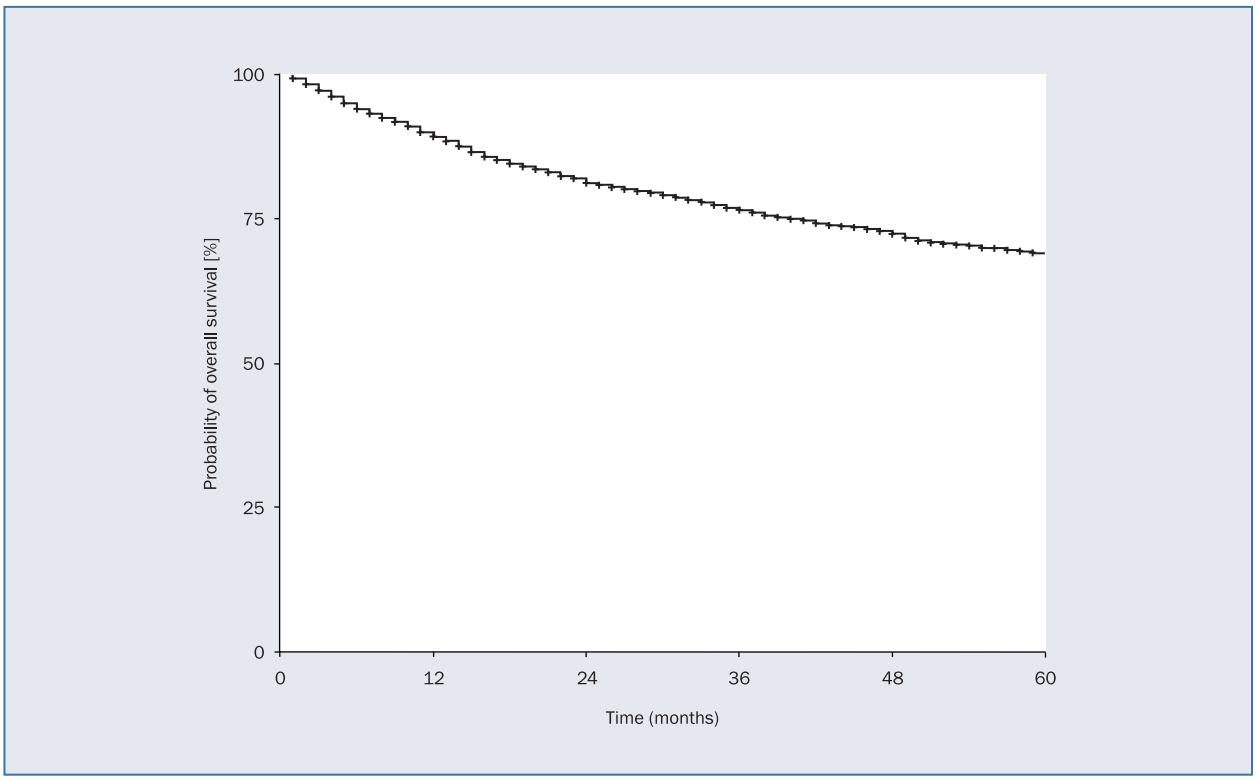

Figure 5. Probability of overall survival in patients registered with follicular lymphoma

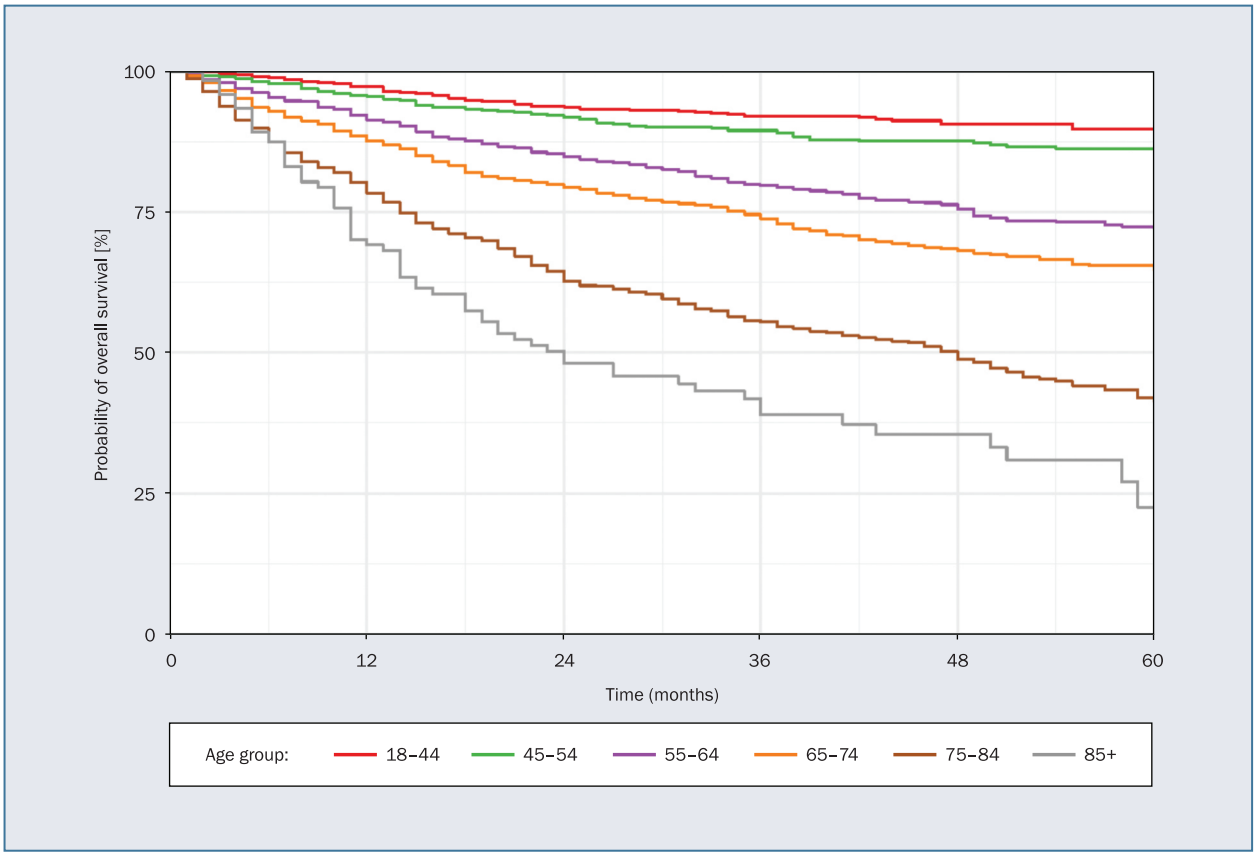

Figure 6. Probability of overall survival in patients registered with follicular lymphoma according to age group

Table II. Estimated 3- and 5-year overall survival (OS) in patients registered with follicular lymphoma according to age group

Age group (years)	Median (months)	3-year OS (range)	5- year OS (range)
18–44	>60	92% (90–94%)	90% (87–92%)
45–54	>60	89% (87–92%)	86% (83–89%)
55–64	>60	80% (77–82%)	72% (69–75%)
65–74	>60	74% (71–77%)	65% (61–68%)
75–84	48	55% (52–59%)	41% (37–46%)
85+	24	39% (30–50%)	23% (13–39%)

Table III. Registered incidence and prevalence rates for diffuse large B-cell lymphomas according to defined region of Poland

Province/country	Incidence per 100,000	Prevalence per 100,000
POLAND	**3.76**	**27.48**
Lower Silesia	3.99	25.59
Kuyavia–Pomerania	3.25	18.90
Lublin	5.17	31.34
Lubusz	2.94	25.39
Lodz	4.15	28.68
Lesser Poland	4.10	38.84
Masovia	3.54	31.57
Opole	3.10	24.79
Subcarpathia	5.21	31.52
Podlaskie	2.60	18.12
Pomerania	4.61	27.16
Silesia	3.18	23.95
Holy Cross Province	3.17	21.78
Warmia–Masuria	3.53	29.92
Greater Poland	3.37	22.73
West Pomerania	3.32	25.48

registered incidence by sex in individual provinces is set out in Figure 20.

The median age of patients reported using PCM codes was 67 years (range 18–95 years): women 69 (18–95) and men 66 (18–94). Figure 21 shows the structure of the registered incidence by age group, and Figure 22 shows the registered incidence by age group in individual voivodeships.

Based on the dates of death, the probability of OS was estimated in all patients registered in the National Health Fund in 2009–2014 with the diagnoses of PCM, i.e. C90, C90.0, C90.1, C90.2 (Figure 23). Median OS was over 60 months. The estimated 3-year and 5-year OS rates were 62.8% and 49.7%, respectively. The probability of OS in patients reported using the above-mentioned ICD-10 codes was also calculated by age groups with respective 3-year and 5-year OS rates (Figure 24, Table VIII).

Discussion

Follicular lymphoma

According to the European HAEMACARE study, which reported the incidence data of hematological malignancies from 44 European registries between 2000 and 2002, the raw incidence rate of FL in Europe was 2.18/100,000/year (4,881 new cases) [14]. In the British Hematological Malignancy Research Network (HMRN) registry, in which the reported data concerned several subtypes of lymphomas, the raw incidence rate of FL in 2004–2014 was 3.23/100,000/year [15]. In turn, according to the SEER (Surveillance, Epidemiology, and End Results Program) of the NCI (US National Cancer Institute), the total standardized incidence rate of malignant lymphoma, regardless of subtype, in 2010–2014 was 19.5/100,000/year [1].

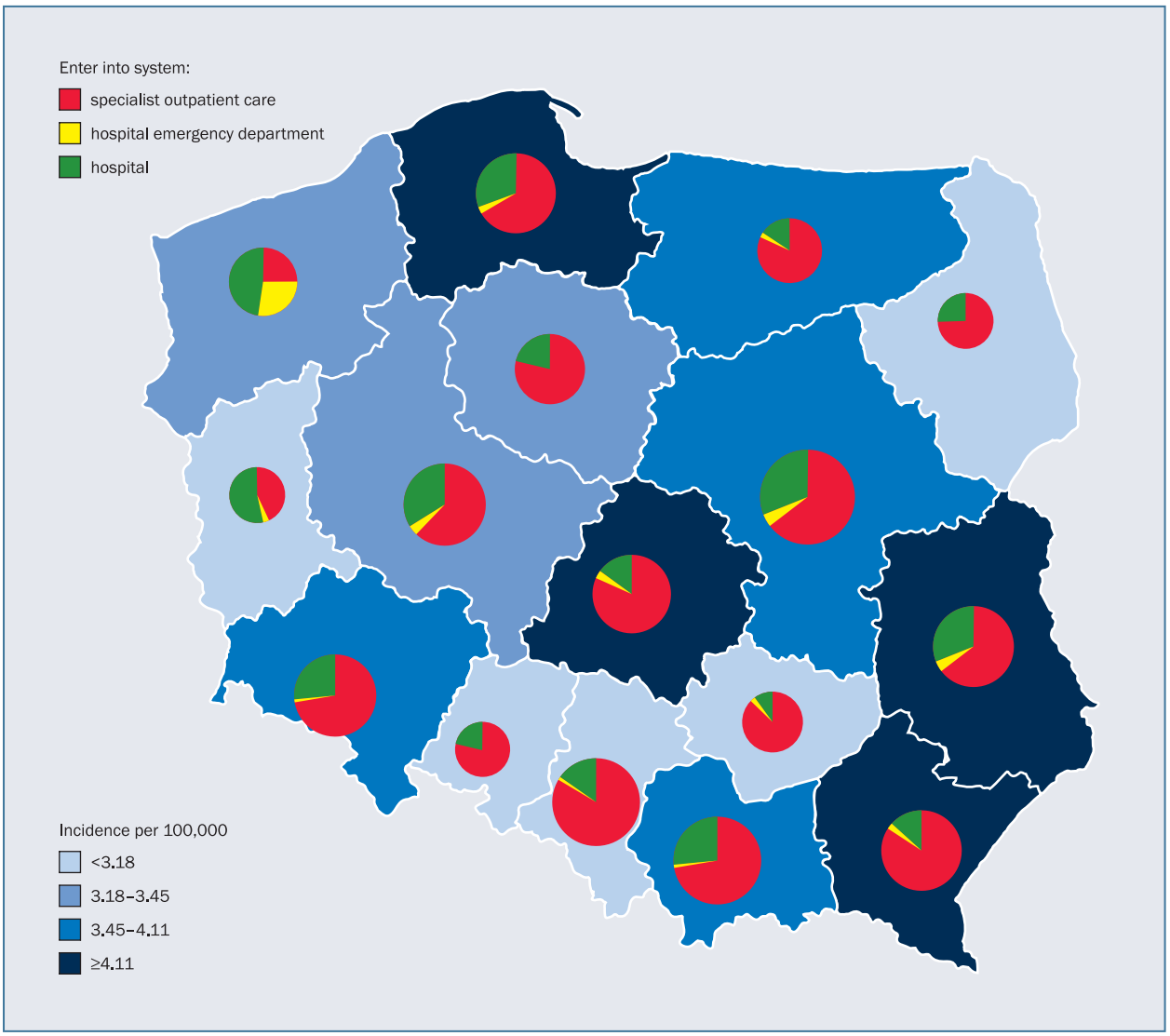

Figure 7. Registered incidence rate of diffuse large B-cell lymphomas according to defined regions of Poland

Difficulties in the analysis of epidemiological data on individual subtypes of non-Hodgkin lymphomas (NHL) result from the fact that the clinical and pathomorphological classifications of these neoplasms have changed many times over the last 50 years [16]. In order to facilitate the analysis of NHL epidemiological data, the Pathology Working Group of the International Lymphoma Epidemiology Consortium (PWG–InterLymph) proposed a classification of lymphatic neoplasms based on the current WHO classifications and the International Classification of Diseases–Oncology Third Edition (ICD-O-3) [16, 17]. Morton et al. used the PWG–InterLymph classification to analyze the epidemiological data of the SEER database for 2001–2003 and determined the incidence of FL to be 3.51/100,000/year (7,543 new cases) [16].

According to unpublished NCR data (data obtained courtesy of Prof. J. Didkowska as part of the cooperation in the above-mentioned project), the incidence of FL in Poland in 2010–2014 was 1.12 (430 new cases), and this was lower than the registered incidence rate (1.74/100,000/year) calculated on the basis of data reported to the National Health Fund. The differences also concerned the prevalence rate, which according to the NCR data was 4.36/100,000, and the number of patients with FL in Poland was estimated at 1,677. The prevalence obtained based on analysis of data reported to the National Health Fund was 15.56/100,000, which translates to some 6,000 patients with FL and is comparable with the data from the British HMRN registry [15]. A comparative analysis of data obtained from the National Health Fund and the NCR indicates the need to improve the reporting of FL cases to the NCR.

Nevertheless, both the recorded incidence and the incidence rates of FL according to the NCR data are lower than the values observed in the HAEMACARE study, the

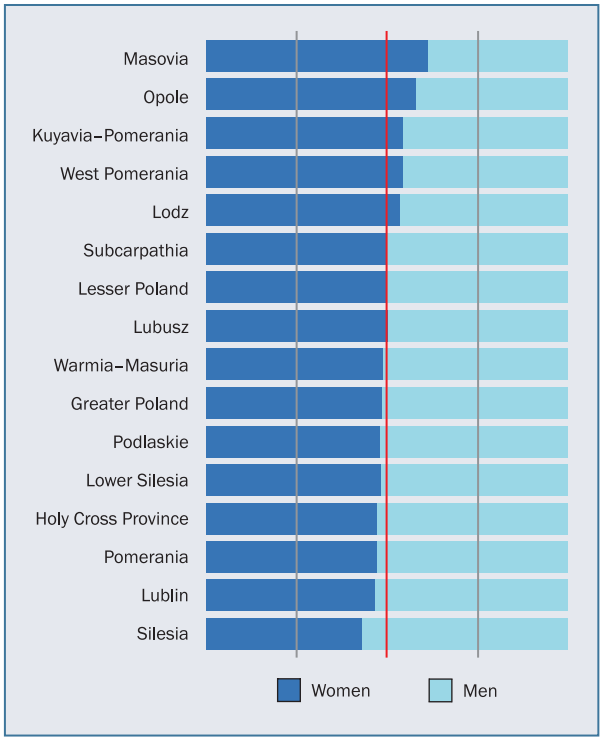

Figure 8. Pattern of registered incidence of diffuse large B-cell lymphomas according to gender and region of Poland

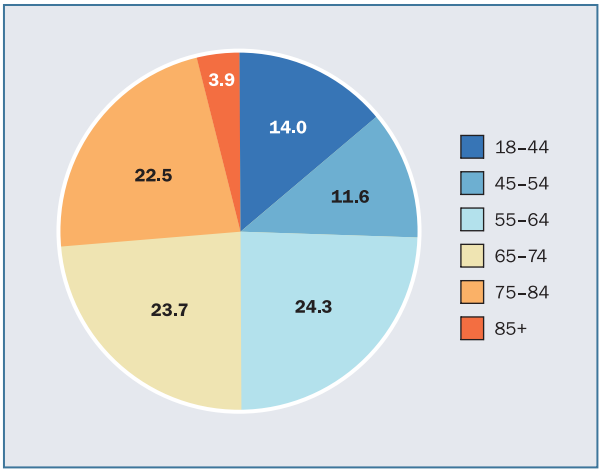

Figure 9. Pattern of registered incidence of diffuse large B-cell lymphomas according to age group

HMRN registry, and the PWG–InterLymph study [14–16]. This may be caused by insufficient quality of data reported by healthcare providers and the use of the ICD-10 C85 code for patients diagnosed with FL.

The median age of patients with FL calculated in the study was 62 years and this was similar to those reported

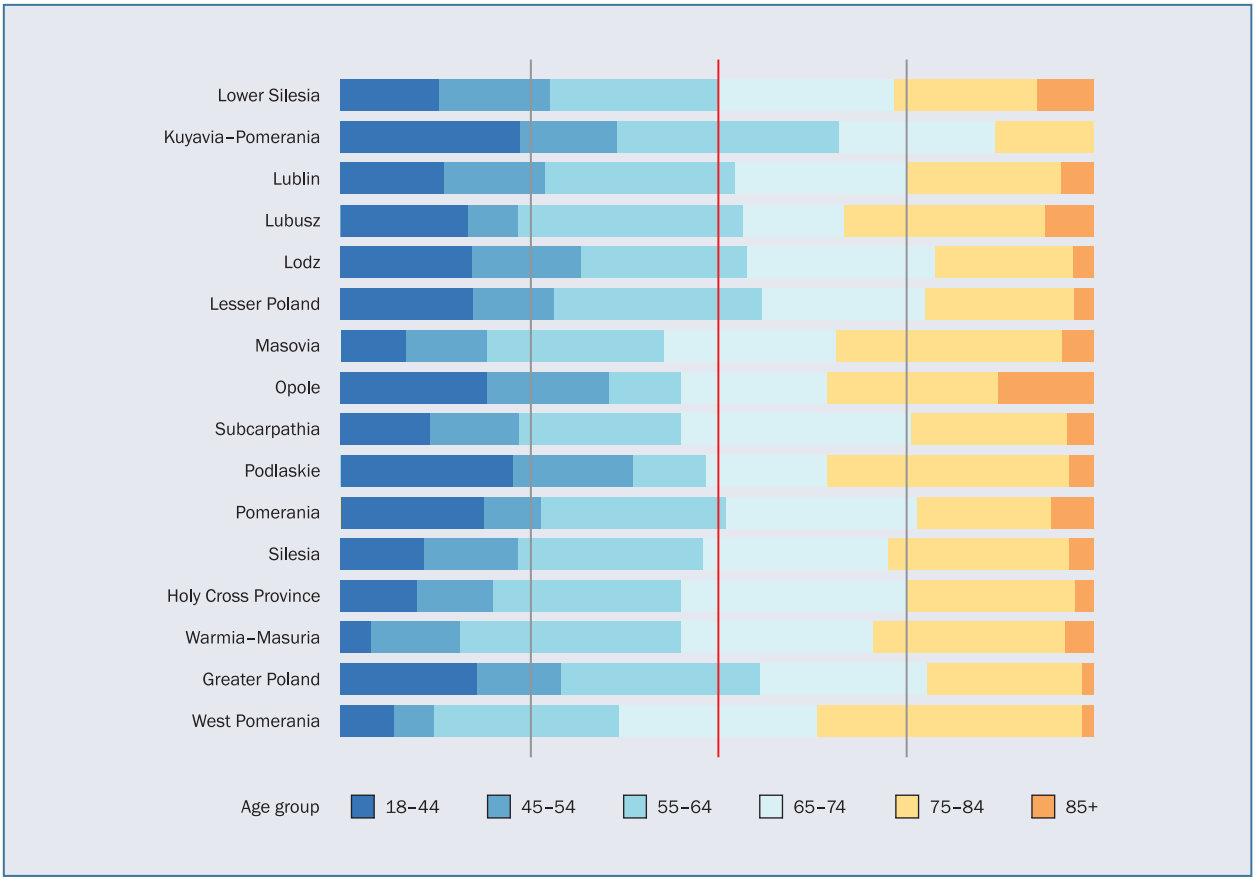

Figure 10. Pattern of registered incidence of diffuse large B-cell lymphomas according to age group and region of Poland

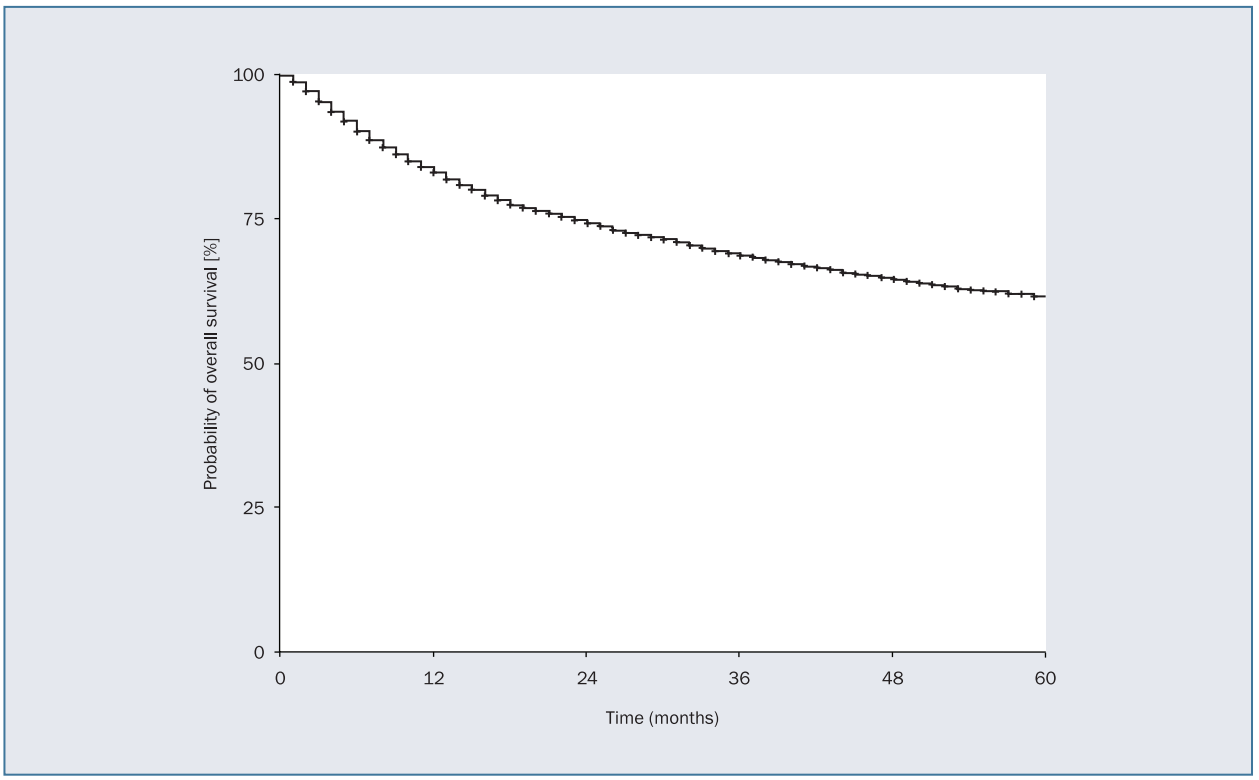

Figure 11. Probability of overall survival in patients registered with diffuse large B-cell lymphomas

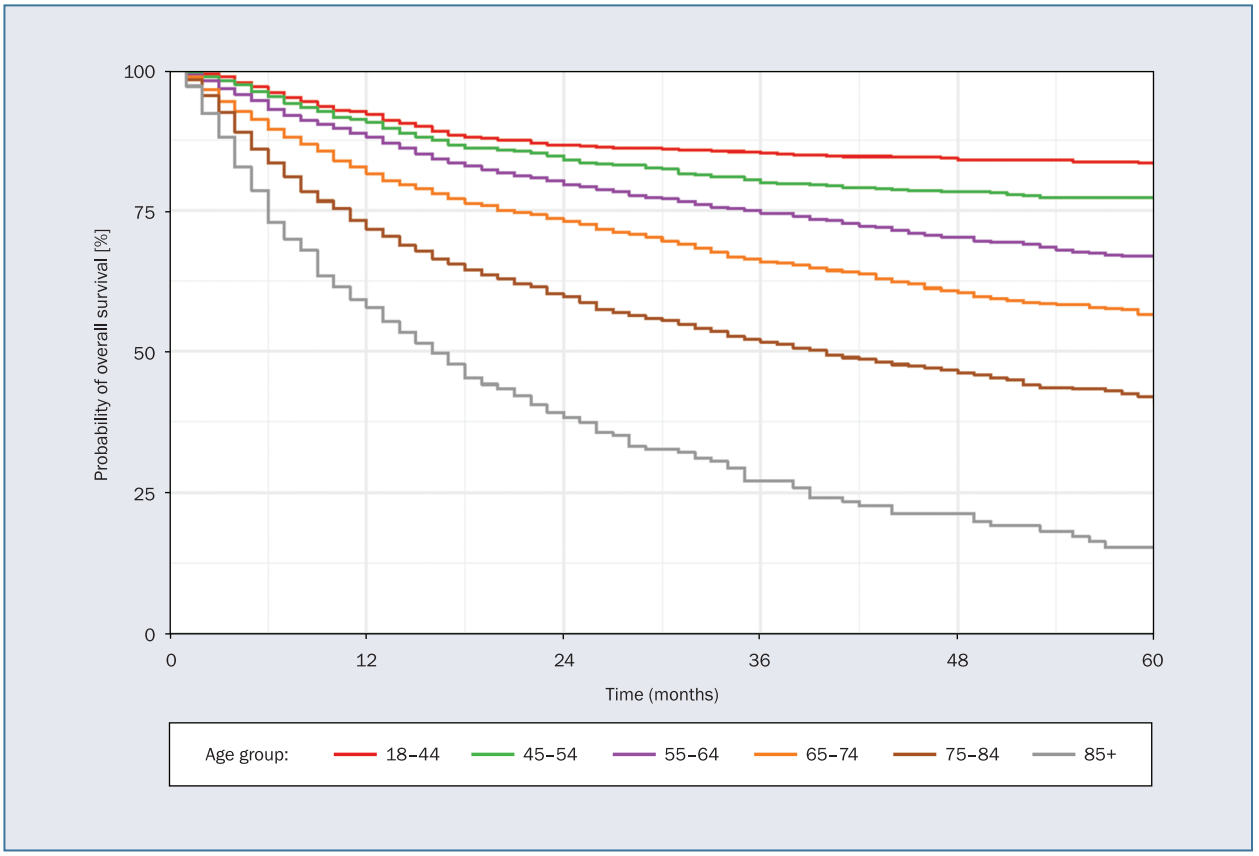

Figure 12. Probability of overall survival in patients registered with diffuse large B-cell lymphomas according to age group

Table IV. Estimated 3- and 5-year overall survival (OS) in patients registered with diffuse large B-cell lymphomas according to age group

Age group (years)	Median (months)	3-year OS (range)	5- year OS (range)
18–44	>60	85% (83–87%)	83% (80–85%)
45–54	>60	80% (77–82%)	77% (74–80%)
55–64	>60	75% (73–76%)	66% (64–69%)
65–74	>60	66% (64–68%)	56% (54–59%)
75–84	40	52% (49–54%)	41% (38–44%)
85+	16	27% (22–33%)	15% (11–22%)

Table V. Registered incidence and prevalence rates for chronic lymphocytic leukemia according to defined region of Poland

Province/country	Incidence per 100,000	Prevalence per 100,000
POLAND	**8.65**	**38.28**
Lower Silesia	6.84	45.23
Kuyavia–Pomerania	6.70	43.79
Lublin	6.75	43.96
Lubusz	4.22	23.53
Lodz	29.20	39.63
Lesser Poland	7.66	39.05
Masovia	6.90	37.44
Opole	8.00	45.99
Subcarpathia	5.78	35.56
Podlaskie	7.13	46.73
Pomerania	4.95	25.90
Silesia	12.48	35.23
Holy Cross Province	7.44	41.02
Warmia–Masuria	6.30	38.93
Greater Poland	5.30	36.87
West Pomerania	5.89	38.66

in other studies [15]. Unlike the majority of hematological neoplasms, in the group of patients diagnosed with FL there was a slight predominance of women (54%), similar to other registries [14, 15].

The probability of 5-year OS in patients registered in the NHF system using FL codes was 68.8%, slightly lower than the 5-year OS observed in the largest European study EUROCARE-5 covering data from 2006–2008, i.e. 74% [18], in the HMRN study 76% [15], or in the HAEMACARE study 72% [19]. According to unpublished NCR data, the probability of a 5-year OS in 2010–2014 was 85% and this was higher than the values observed in European studies [15, 18, 19]. These differences may result from the underestimated number of FL patients reported to the NCR by service providers.

Diffuse large B-cell lymphomas

The registered incidence of DLBCL estimated based on the analysis of services reported to the National Health Fund was 3.76/100,000/year, very close to the raw incidence rate in the HAEMACARE study of 3.81/100,000/year [14]. DLBCL incidence rates in the British HMRN registry and in the PWG–InterLymph study were higher: 8.31/100,000/year and 6.8/100,000/year, respectively [15, 16].

According to unpublished data of the NCR (data obtained courtesy of Prof. J. Didkowska as part of the cooperation in the above-mentioned project), the DLBCL incidence in Poland in 2010–2014 was 4.49/100,000/year, and this was similar to the registered incidence. As in the case of FL, the differences concerned the prevalence, which according to the NCR data was 15.58/100,000. The number of DLBCL patients in Poland was estimated at 5,992. The prevalence obtained based on analysis of services reported to the National Health Fund was 27.48/100,000 and this was comparable with the HMRN report, in which it was 25.9/100,000 [15].

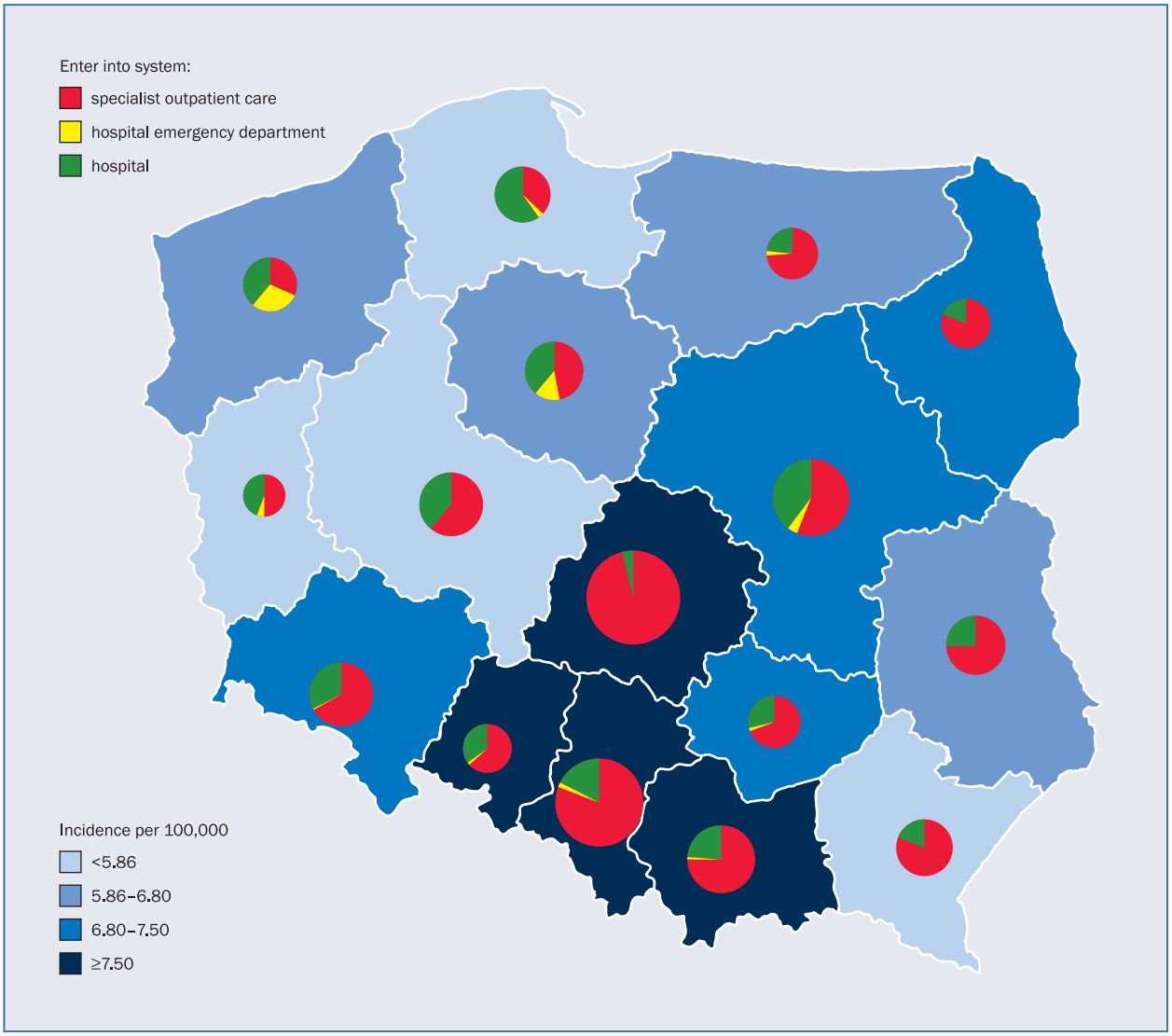

Figure 13. Registered incidence rate for chronic lymphocytic leukemia according to defined region of Poland

The median age of DLBCL patients in the present study was 65 years, compared to 70 years in the HMRN study [15]. In the group of patients diagnosed with DLBCL, women accounted for 51% and the gender distribution of DLBCL patients was similar to that observed in the HMRN and HAEMACARE registries [14, 15].

The probability of a 5-year OS in patients registered in the NHF system using DLBCL codes was 61.1% and this was higher than reported in the EUROCARE-5 study in 2006–2008, i.e. 55%, in the HMRN study 46%, and in the HAEMACARE study 49.3% [15, 18, 19]. According to unpublished NCR data, the probability of a 5-year OS in DLBCL patients in 2010–2014 was 70% and this was even higher than that reported in the present study and in European studies [14, 15]. The observed differences may result from the underestimated prevalence of DLBCL in the NCR.

Chronic lymphocytic leukemia

According to SEER NCI data, the incidence of CLL/SLL in the American population in 2010–2014 was 4.7/100,000/year, and the number of new cases in 2017 was estimated at 20,110 [1]. On the other hand, an analysis of epidemiological data in the HAEMACARE study showed that the raw incidence rate of CLL/SLL in Europe was 4.92/100,000/year (11,019 new cases) [14]. According to unpublished NCR data (data obtained courtesy of Prof. J. Didkowska as part of the cooperation in the above-mentioned project), the incidence of CLL/SLL in 2010–2014 was 3.93 (1,512 new cases), the number of patients with CLL/SLL in Poland was estimated at 5,850, and the prevalence was estimated at 15.21/100,000. For comparison, in the United Kingdom, 3,709 new cases of CLL were registered in 2015, and the prevalence at the end of 2010 was 20,200 patients [20].

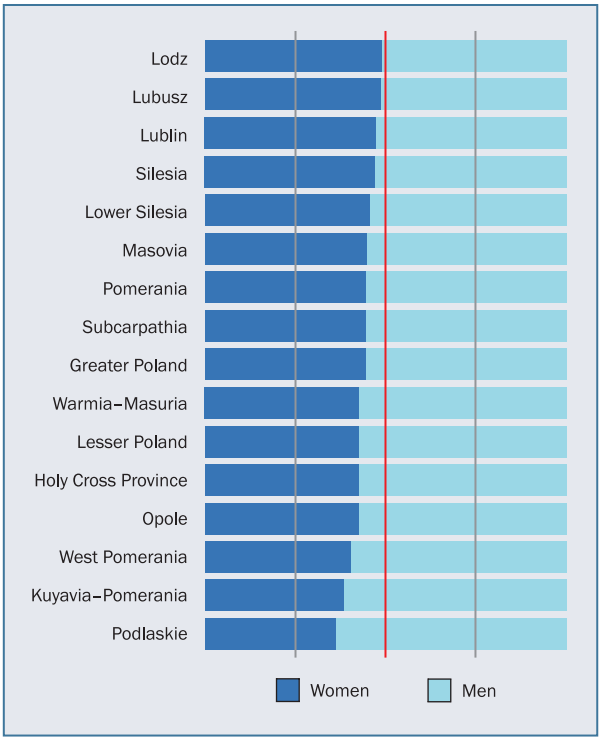

Figure 14. Pattern of registered incidence of chronic lymphocytic leukemia according to gender and region of Poland

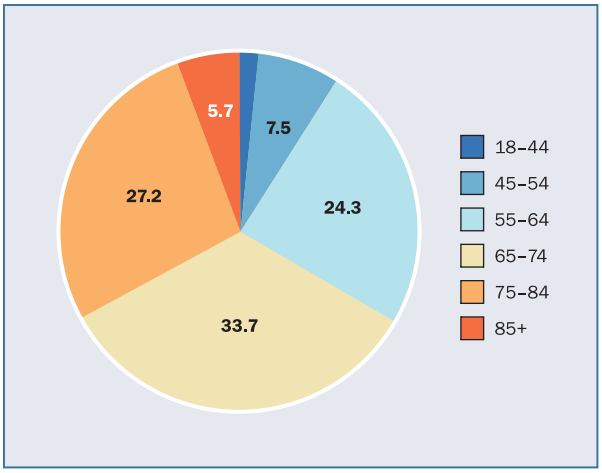

Figure 15. Pattern of registered incidence of chronic lymphocytic leukemia according to age group

The incidence (8.65/100,000/year) and prevalence (38.28/100,000) rates of CLL/SLL obtained in the presented study based on analysis of services reported to the National Health Fund could be considered to be overestimated compared to the above-cited epidemiological studies. This may be associated with a much higher incidence rate observed

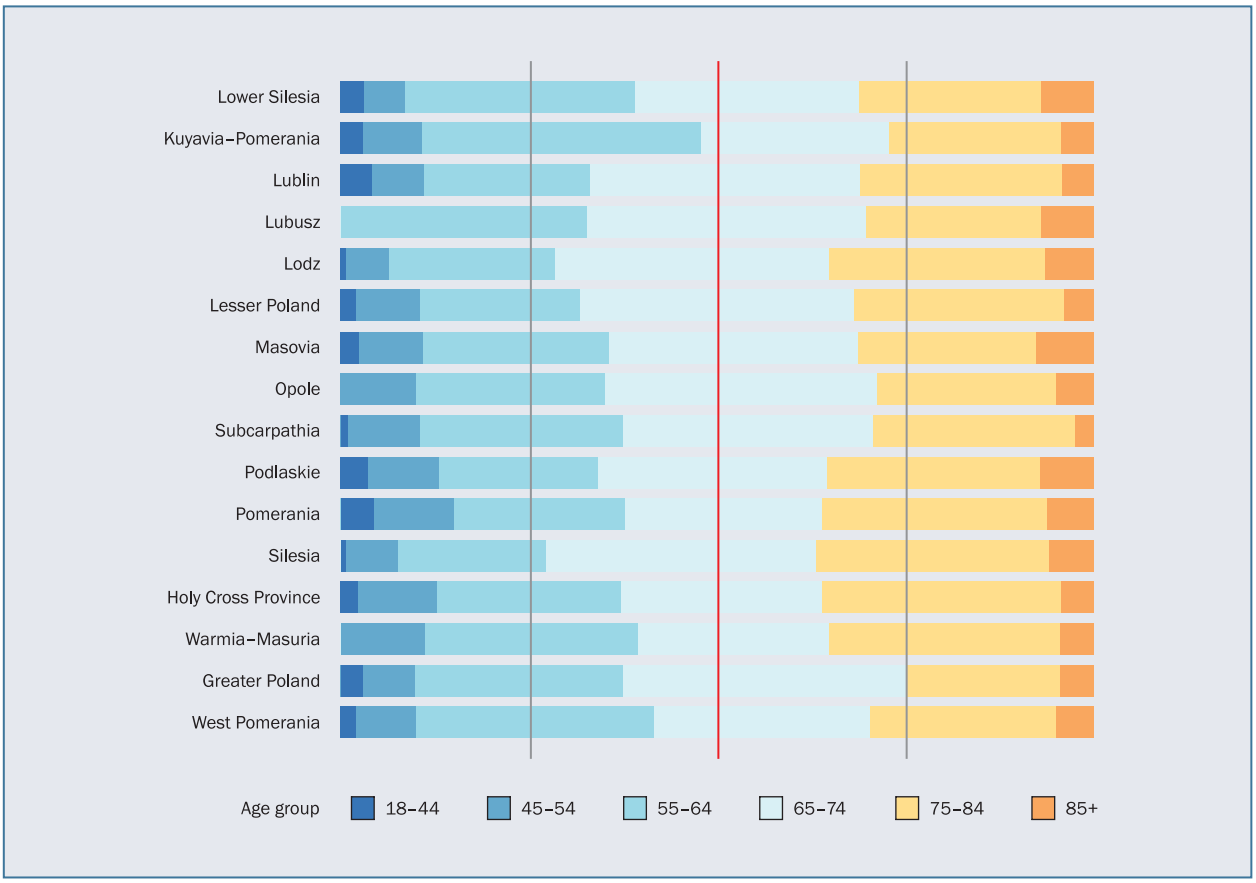

Figure 16. Pattern of registered incidence of chronic lymphocytic leukemia according to age group and region of Poland

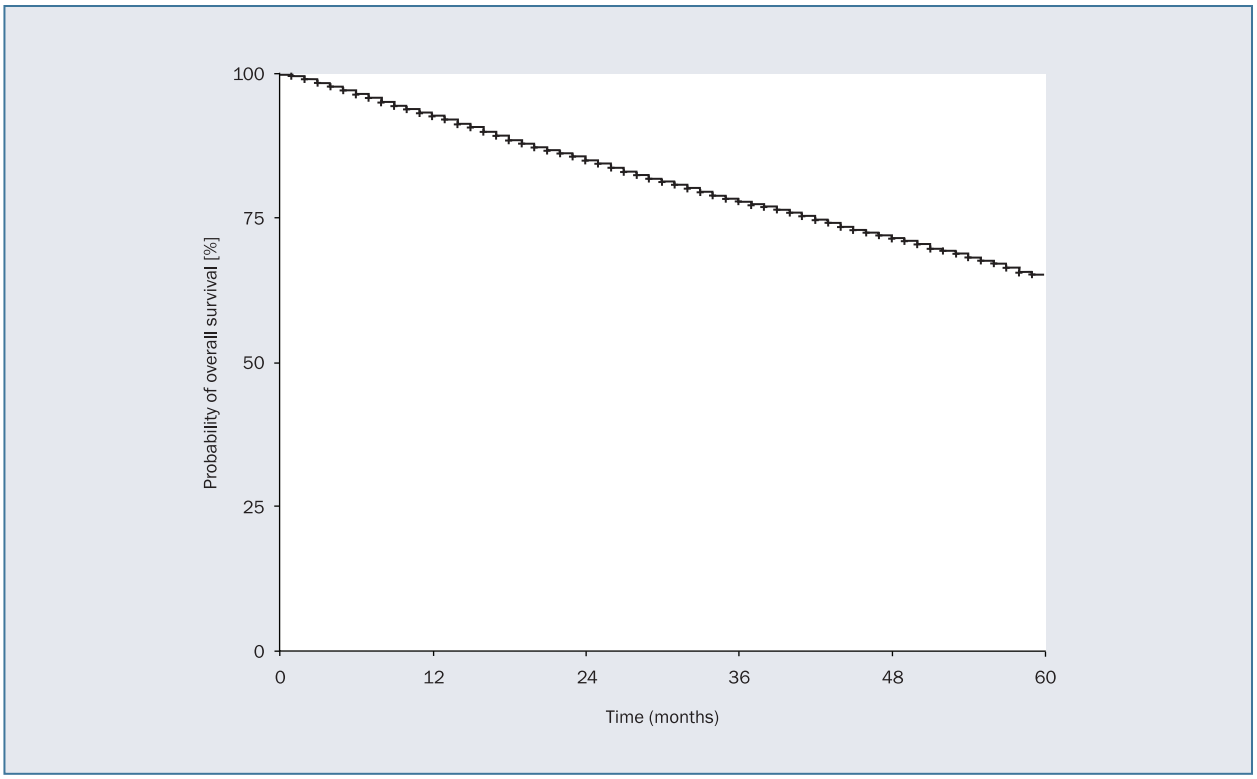

Figure 17. Probability of overall survival in patients registered with chronic lymphocytic leukemia

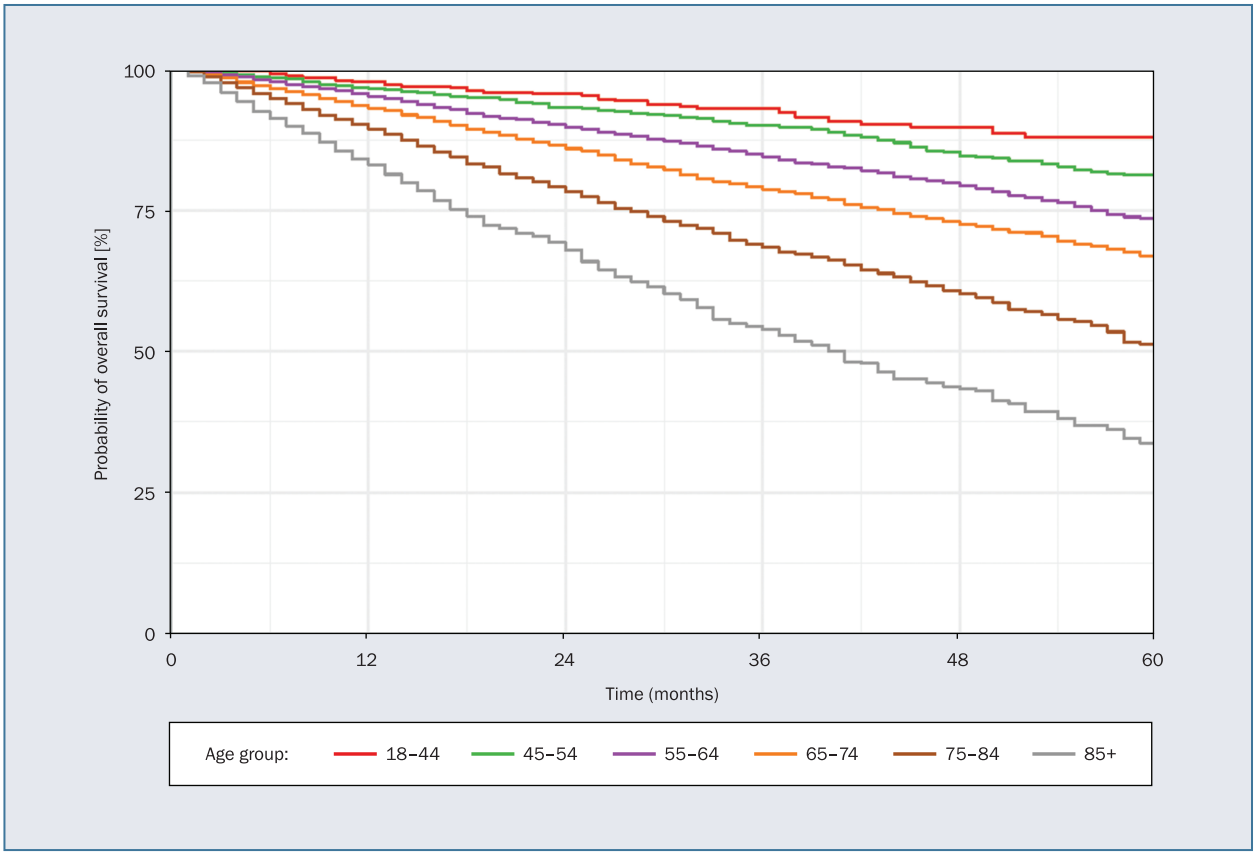

Figure 18. Probability of overall survival in patients registered with chronic lymphocytic leukemia according to age group

Table VI. Estimated 3- and 5-year overall survival (OS) in patients registered with chronic lymphocytic leukemia according to age group

Age group (years)	Median (months)	3-year OS (range)	5- year OS (range)
18–44	>60	93% (91–96%)	88% (84–92%)
45–54	>60	90% (88–92%)	81% (78–84%)
55–64	>60	85% (83–86%)	73% (71–75%)
65–74	>60	79% (77–80%)	67% (65–69%)
75–84	>60	68% (67–70%)	50% (48–53%)
85+	40	54% (50–58%)	33% (28–39%)

Table VII. Registered incidence and prevalence rates for plasma cell myeloma according to defined region of Poland

Province/country	Incidence per 100,000	Prevalence per 100,000
POLAND	**4.92**	**23.28**
Lower Silesia	5.74	26.66
Kuyavia–Pomerania	4.50	22.06
Lublin	4.75	21.05
Lubusz	4.31	21.47
Lodz	4.47	18.58
Lesser Poland	4.81	22.81
Masovia	6.84	32.10
Opole	4.50	23.99
Subcarpathia	4.56	21.75
Podlaskie	4.70	26.35
Pomerania	5.43	26.20
Silesia	4.71	23.23
Holy Cross Province	4.36	19.40
Warmia–Masuria	3.19	16.76
Greater Poland	4.03	18.49
West Pomerania	3.85	16.79

in the Lodz voivodeship (29.20/100,000/year) compared to other voivodeships (the range of differences between the values ranges from 2.3 to 6.9 times). The analysis of median age of CLL/SLL patients at diagnosis, the distribution of age groups, and death rates due to CLL/SLL in the Lodz voivodeship were comparable to values observed in other provinces. This would suggest that this difference may have resulted from the method of reporting data to the NHF.

The median age of CLL/SLL patients in Poland was 69 years, similar to that reported in other studies [1, 14, 20] with a slight predominance of men (55%), again similar to other registries [1, 14, 20].

The probability of a 5-year OS in patients registered in the NHF system with CLL/SLL code was 64.8% and this was comparable to those reported in other European countries. In the EUROCARE-5 study, the relative 5-year OS of CLL/SLL patients in 2006–2008 was 69%, similar to the HAEMACARE study [18, 19]. In turn, according to SEER data, the relative 5-year OS rate in 2007–2013 in CLL/SLL patients was 83% [1]. According to unpublished NCR data, the probability of a 5-year OS in CLL/SLL patients in Poland in 2010–2014 was 61%. It should be noted, however, that population indices define 'relative survival' as the ratio of the observed survival to the expected survival for all persons of a given age and gender in the studied population, which can differ from survival calculated with the use of the Kaplan-Meier method. The lower survival rates observed in the European population compared to the American population may be associated with limited or later access to new drugs, and/or differences in the frequency of diagnostic tests, especially in the elderly [18].

Plasma cell myeloma

Based on epidemiological data from 2010–2014 in the SEER NCI database, the incidence rate of PCM in the American population was 6.6/100,000/year. Based on

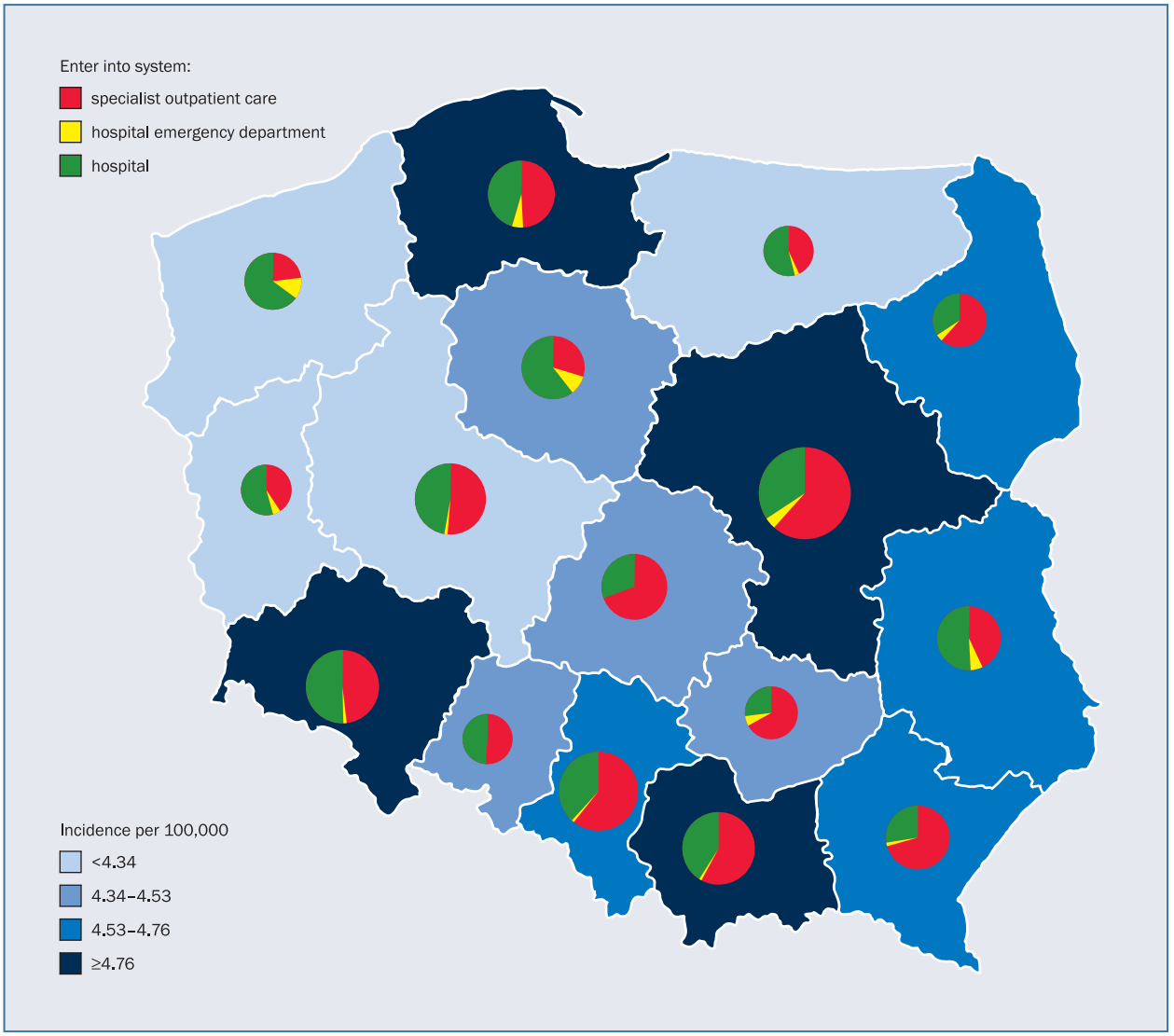

Figure 19. Registered incidence rate of plasma cell myeloma according to defined region of Poland

this, the estimated number of new cases in 2017 was 30,280 [1]. On the other hand, an analysis of the HAEMACARE study showed that the raw incidence rate of PCM in Europe was 5.44/100,000/year (12,192 new cases) [14].

According to unpublished NCR data (data obtained courtesy of Prof. J. Didkowska as part of the cooperation in the above-mentioned project), the incidence of PCM in Poland in 2010–2014 was 3.45 (1,327 new cases) and this was lower than the recorded incidence, i.e. 4.92/100,000/year. Similarly, the prevalence rate according to the NCR data (11.19/100,000) was half that of the registered prevalence rate (23.28/100,000). The incidence and the registered prevalence of PCM obtained in the presented study based on the analysis of services reported to the National Health Fund are similar to the epidemiological indices in British, German and American registers [4, 14, 16].

The median age of PCM patients was 67 years and this was similar to those reported in other studies [1, 14]. On the other hand, in the presented study, in patients reported with a diagnosis of PCM, there was a slight predominance of women (52%), in contrast to the HAEMACARE study, the SEER NCI registry, and the German registry, where more frequent PCM cases were in men [1, 4, 14].

The probability of 5-year OS in patients reporting to the National Health Fund using the PCM code was 49.7% and this was identical to the survival in 2007–2013 in the NCI SEER registry [1]. In the largest European study, EUROCARE-5, the relative 5-year OS of PCM patients in 2006–2008 was 64%, and in the HAEMACARE study in 2000–2002 it was 33% [14, 18]. The above differences between 5-year OS rates are most likely due to the much greater availability of new drugs used in the treatment of PCM patients over the last 10 years. In turn, according

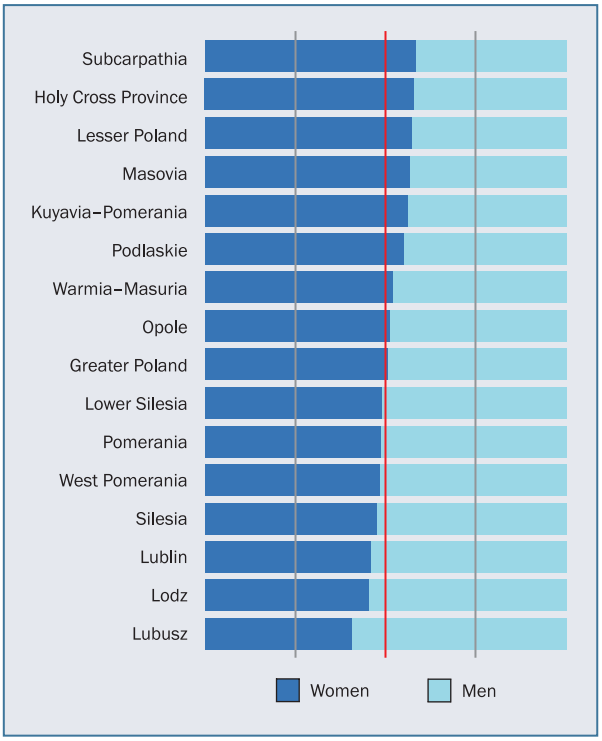

Figure 20. Pattern of registered incidence of plasma cell myeloma according to gender and region of Poland

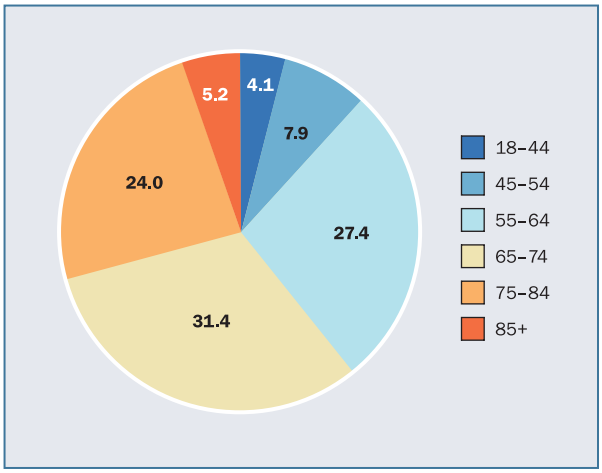

Figure 21. Pattern of registered incidence of plasma cell myeloma according to age group

to unpublished NCR data, the probability of 5-year OS of PCM patients in Poland in 2010–2014 was as high as 77%. The observed differences may result from a significant underestimation of the incidence and prevalence in the NCR data due to insufficient reporting by patient service providers.

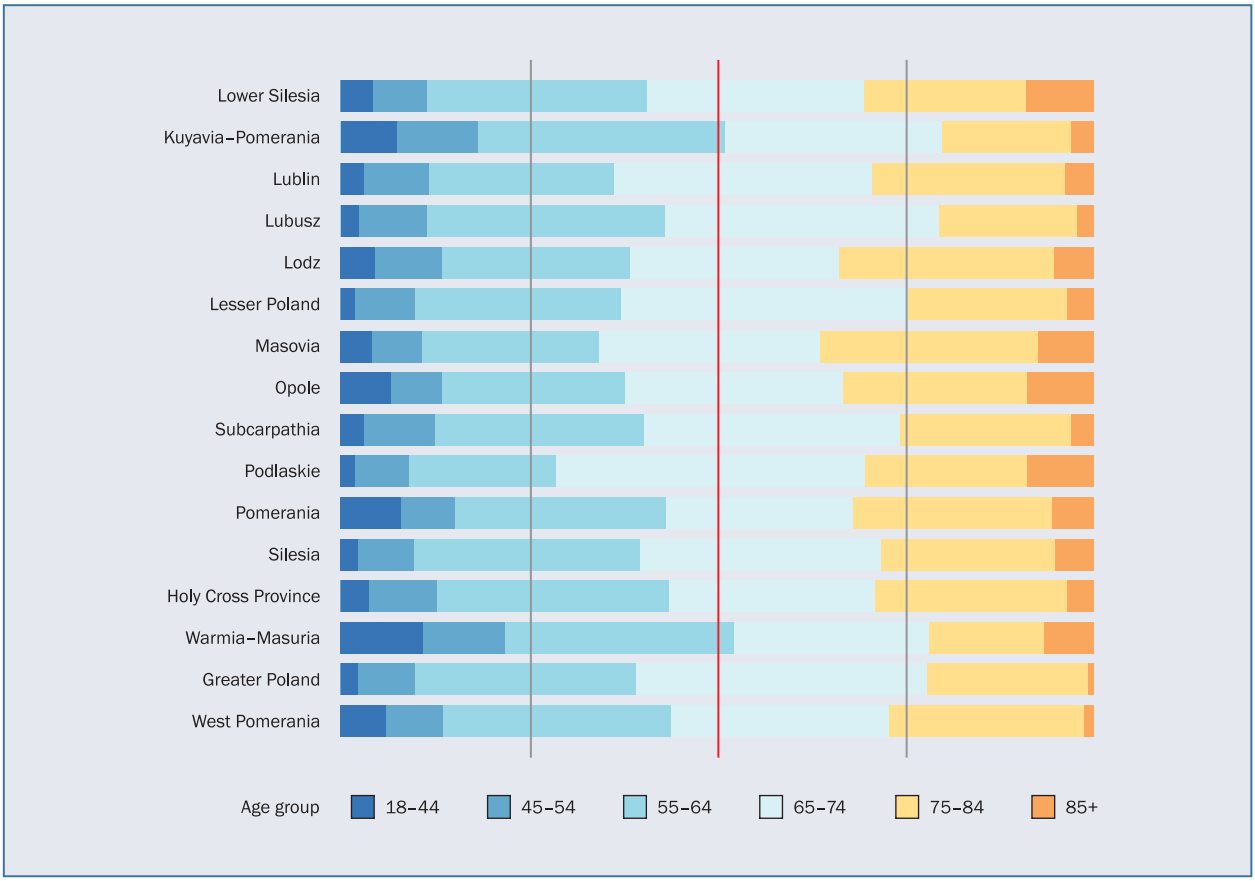

Figure 22. Pattern of registered incidence of plasma cell myeloma according to age group and region of Poland

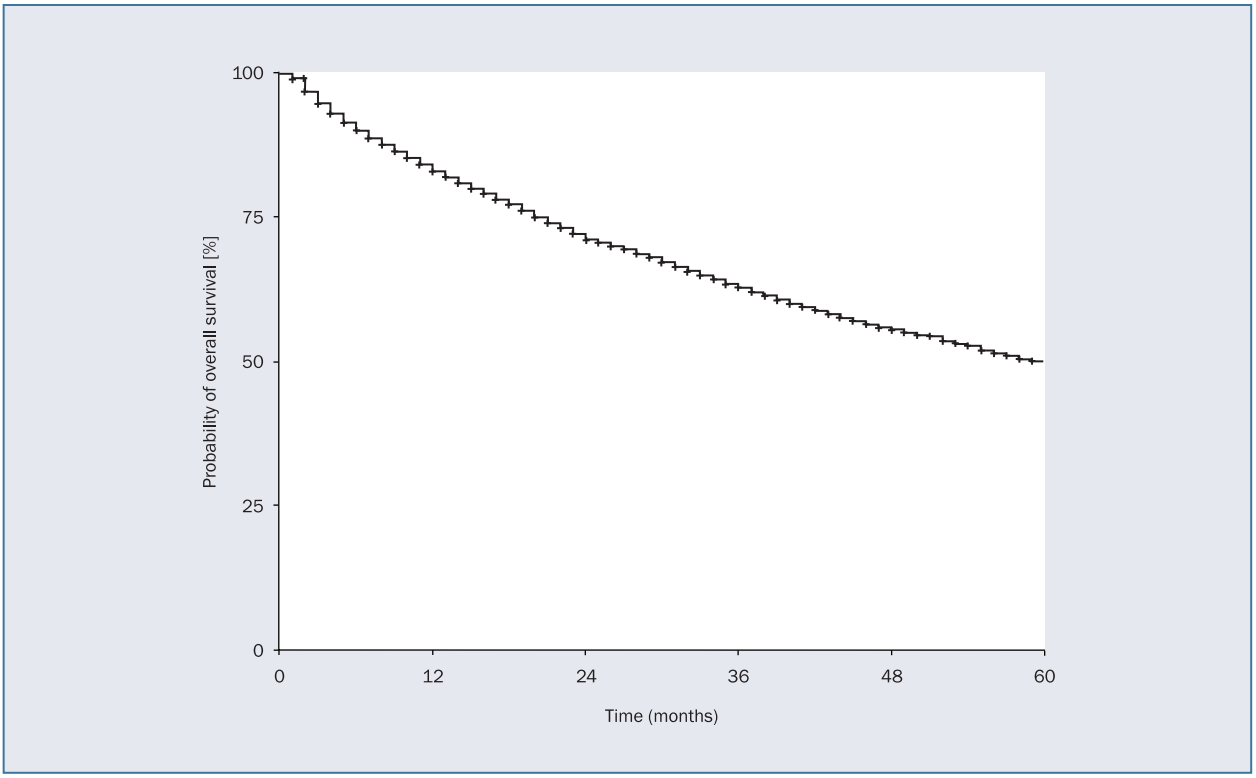

Figure 23. Probability of overall survival in patients registered with plasma cell myeloma

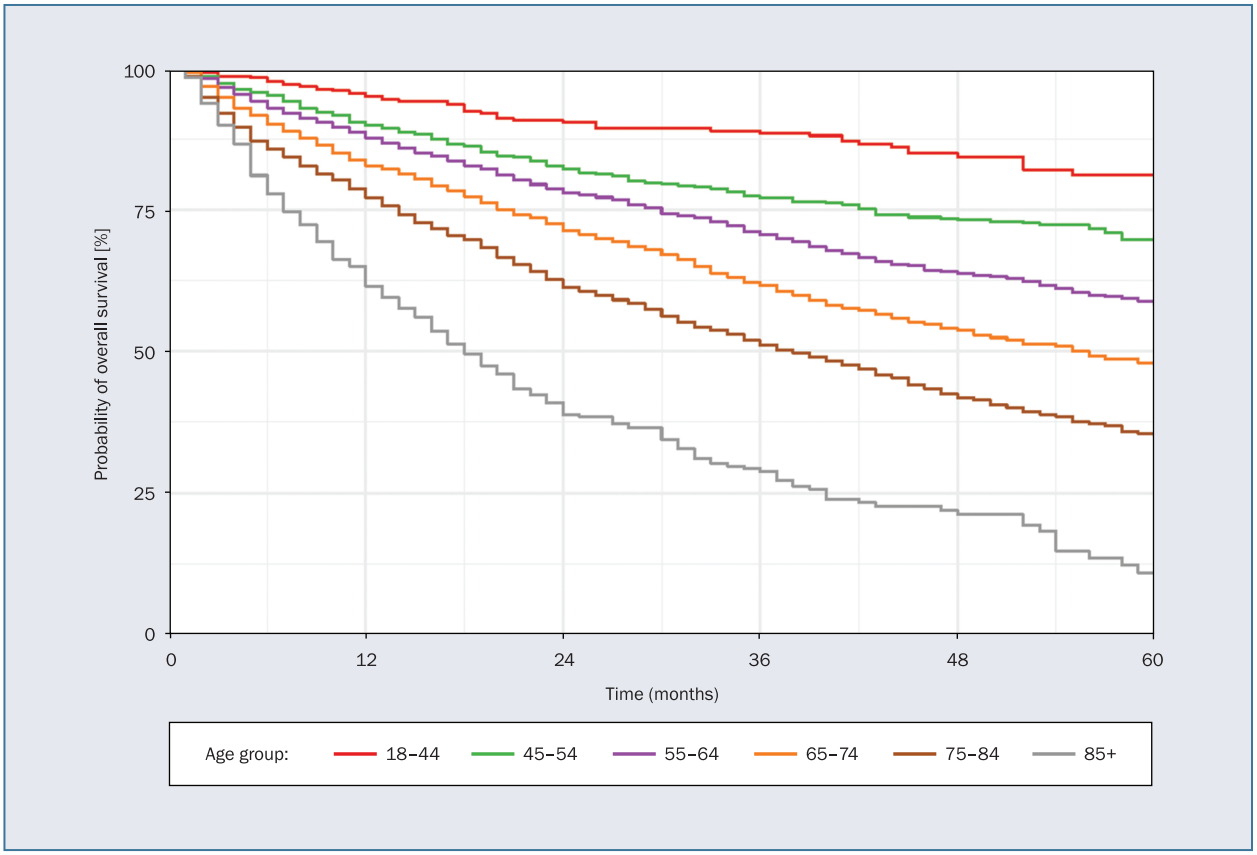

Figure 24. Probability of overall survival in patients registered with plasma cell myeloma according to age group

Table VIII. Estimated 3- and 5-year overall survival (OS) in patients registered with plasma cell myeloma according to age group

Age group (years)	Median (months)	3-year OS (range)	5- year OS (range)
18–44	>60	89% (85–92%)	81% (76–86%)
45–54	>60	77% (74–80%)	70% (66–74%)
55–64	>60	71% (69–72%)	58% (56–61%)
65–74	56	62% (60–64%)	48% (45–50%)
75–84	38	51% (49–53%)	35% (32–38%)
85+	18	29% (24–34%)	11% (7–18%)

Conclusions

The incidence and prevalence rates presented in this study for the four most common lymphatic neoplasms are based on data reported to the National Health Fund in order to obtain reimbursement of services, and therefore seem to be the most reliable data covering such a large population of patients. It should also be emphasized that this is some of the first data on the prevalence of FL, DLBCL, CLL and PCM in Poland. Despite the fact that the data reported to the National Health Fund may be affected by errors (resulting from the insufficient quality of the cancer coding system and the failure to adapt the 10th Revision of the ICD-10 to the obligatory WHO classifications), it is similar to the data from European and American registries in relation to DLBCL and PCM, whilst the FL-related data seems to be underestimated. However, with regard to the incidence of CLL, the presented data requires further verification, in particular in Lodz voivodeship, where the incidence rate differs by several magnitudes from the value for the entire country.

Nevertheless, the presented results reflect the actual burden of lymphatic neoplastic diseases on the Polish healthcare system, and this is their most important value. Better understanding of the incidence, prevalence and overall survival of patients with hematological malignancies is important not only for clinical and scientific purposes, but could also be an important element influencing the organization of hematooncology care in Poland.

Authors' contributions

ELM, BKB — were responsible for the conception and design of the study, analysis and interpretation of data, writing the manuscript, critical manuscript revision, and proofreading; TM, BW, JD — were responsible for big data techniques, economic, financial, and statistical analysis, and critical manuscript revision; WWJ — was responsible for the conception of the study, analysis and interpretation of data, and critical manuscript revision.

Conflict of interest

The authors have no conflict of interest to declare.

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Ethics

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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Assessment of colonization and infection epidemiology in patients undergoing autologous hematopoietic stem cell transplantation: a single-center study

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Abstract

Introduction: Infections are one of the main causes of early death after autologous hematopoietic stem cell transplantation (auto-HSCT).

Material and methods: We present a single-center retrospective analysis of colonization and infection epidemiology in 115 patients with median age 63 years (range 21–72), who underwent auto-HSCT in 2017 or 2018 in the course of multiple myeloma [79.1% (n = 91)], Hodgkin lymphoma [18.3% (n = 21)] and non-Hodgkin lymphoma [2.6% (n = 3)].

Results: Colonization was observed in 40.9% of patients before auto-HSCT, the most common location being the urinary tract — 54.3%. Multi-drug resistant bacteria (MDR) accounted for 20.9% of positive colonization cultures before auto-HSCT.

In the post-transplantation period, infections occurred in 77.4% of patients after auto-HSCT. Bacteremia was observed in 43.5% of patients and it was mostly caused by methicillin-resistant coagulase-negative *Staphylococcus epidermidis* (MRCNSE) — 27.6%. Infection of the skin near the central vascular catheter was found in 18.3% of patients, urinary tract infections in 11.3%, and gastrointestinal infections in 20.9%. MDR pathogens accounted for 65.2%. The most common of these was methicillin-resistant coagulase-negative *Staphylococcus* (MRCNS) — 73.9%. Fungal and viral infections were reported in 21.7% and 7%, respectively. The median duration of empirical and targeted antibiotic therapy was 5 (range 1–20) and 7 (range 4–31) days, respectively. Death due to septic shock occurred in 2/115 (1.7%) patients during the neutropenia period.

Conclusions: Evaluation of the epidemiology of colonization and infection in patients undergoing auto-HSCT can be an effective tool in providing control and therapy for infections in HSCT recipients. Such knowledge is also essential in monitoring potential pathogen transmission and helping to improve local infection management standards.

Key words: colonization, infections, auto-HSCT

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Introduction

In 2017, the European Society for Blood and Marrow Transplantation (EBMT) reported c.45,500 hematopoietic stem cell transplantations (HSCTs). The number of patients who received autologous hematopoietic stem cell transplantation (auto-HSCT), most commonly used in the treatment of multiple myeloma and lymphoma, was approximately 24,000 (58%), whereas allogeneic hematopoietic stem cell transplantations (allo-HSCT),

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used primarily for the treatment of acute leukemia and non-Hodgkin lymphoma, were performed in approximately 17,000 patients (42%) [1].

The number of transplantations is constantly increasing, and is currently over 1.4 million. However, this procedure is still associated with a high risk of treatment-related mortality (TRM). The main causes of TRM are infections, organ toxicity, and graft-versus-host disease (GvHD) [2].

The Center for International Blood and Marrow Transplant Research (CIBMTR) estimates that for auto-HSCT, infections are responsible for 29% of deaths up to 100 days after HSCT, and for 5% in the late post-transplantation period [3].

More than half of the infections causing death after HSCT are associated with unspecified etiology. Of the known factors, bacteria make up about 15%, fungi 11%, viruses 9%, parasites 1%, and infections of mixed origin account for 5% [2]. The EBMT analysis for the period 1980–2001 revealed a significant increase in the median time of 5-year survival after HSCT, which is mainly related to a decreased number of lethal infectious complications [2, 4].

Infections after auto-HSCT are connected with a specific cascade of immunological dysfunction associated with a decrease in the number of circulating mature B cells followed by a reduction in immunoglobulin levels. Restoration of the individual components of the immune system occurs with different dynamics in which innate immunity (neutrophils, monocytes, and natural killer cells) typically precedes adaptive immunity (T- and B-lymphocytes). Complete immune reconstitution can take from several months up to two years after HSCT [5]. Although infections and immune dysfunction in the auto-HSCT setting are not as severe as in allo-HSCT, a related etiology and chronological order of infections typical of HSCT may also be observed.

In the first phase (phase I), lasting from the beginning of conditioning to the engraftment, neutropenia and mucosal damage occur leading to predominant bacterial, fungal (*Candida spp.* and *Aspergillus spp.*) and herpes virus infections [herpes simplex virus (HSV), human herpesvirus 6 (HHV-6)]. During this period, the infections are usually located in the blood and airways. Phase II, which starts upon the engraftment and lasts for a period of 100 days after HSCT, is related to lymphopenia. Gram (–) bacteria infections and often severe, invasive fungal infections with *Aspergillus spp.* and *Pneumocystis jiroveci* (PJ) are dominant in this phase. Besides, reactivation or new infections with cytomegalovirus (CMV), Epstein-Bárr virus (EBV), and polyoma- and adenovirus may be observed. In late phase III, which starts more than 100 days after HSCT, infections with encapsulated bacteria prevail, and they include *Streptococcus pneumoniae, Haemophilus influenzae,* or *Neisseria meningitidis*. Fungal infections (*Aspergillus spp., Candida spp.,* PJ) may also occur. Phase II/III may also be characterized by infection of varicella zoster virus (VZV). There is always a correlation between the amount of helper CD4+ T lymphocytes and the etiology of the infection [6].

A variety of risk factors for infections after auto-HSCT have been defined, including duration and severity of neutropenia induced by treatment [<7 vs. >7 days; absolute neutrophil count (ANC) <0.5 G/L], virological status, and type of cancer [2, 7–9]. Apart from the above, local epidemiology of microorganisms in the transplantation center, as well as colonization of the patient and applied anti-infection prophylaxis have a significant impact on transplant-related infections.

This study aimed to assess the colonization with pathogenic microorganisms and the incidence of infections during the peritransplantation period, as well as the effectiveness of applied prophylaxis in patients who underwent auto-HSCT in the Department of Hematology at the Medical University of Łódź, Poland.

Material and methods

A retrospective analysis of medical records was used in our study. Colonization with pathogens was assessed in each patient during the pre-transplantation period based on an analysis of microbiological cultures of material collected from the throat, nasal cavity, and anal area, as well as urine culture. The tests were taken by a trained nursing team. Each patient gave their informed consent for access to clinical data.

All 115 patients [men 54.8% (n = 63); women 45.2% (n = 52)] with median age 63 years (range 21–72) underwent auto-HSCT transplantation between 1 January 2017 and 31 December 2018 in the Department of Hematology of the Medical University of Łódź. The patients treated with auto-HSCT were diagnosed with multiple myeloma [79.1% (n = 91)], Hodgkin lymphoma [18.3% (n = 21)] or non-Hodgkin lymphoma [2.6% (n = 3)]. The types of conditioning treatment regimens are presented in Table I.

The median duration of hospitalization was 29 days (range 17–50). Prophylactic antimicrobial, antiviral and antifungal treatment was applied in all patients from the beginning of chemotherapy to reaching ANC >0.5 G/L and immune reconstitution. The prophylaxis for all patients consisted of ciprofloxacin 500 mg twice daily (bid) and fluconazole 400 mg once daily during the peritransplantation period; cotrimoxazole 960 mg three times a week since neutrophil recovery until six months after HSCT; acyclovir 800 mg bid during the peritransplantation period and after engraftment 200 mg three times a day for six months after HSCT.

In addition, all patients underwent environmental prophylaxis, manifesting with increased restriction of aseptic and antiseptic regimens in the Bone Marrow Transplantation Ward, including air-conditioned isolation rooms with high-efficiency particulate arrestance (HEPA) air, limited

Table I. Types of conditioning regimen

Diagnosis	Type of conditioning regimen	Number of patients N [%]
Multiple myeloma	Melphalan 200 mg/m^2	50 (43.5)
	Melphalan 140 mg/m^2	26 (22.6)
	Melphalan 100 mg/m^2	15 (13.0)
Hodgkin lymphoma	BEAM	19 (16.5)
	BeEAM	2 (1.7)
Non-Hodgkin lymphoma	BEAM	1 (0.9)
	BeEAM	1 (0.9)
	TEAM	1 (0.9)

BEAM — carmustine (BCNU), etoposide, cytarabine, melphalan; BeEAM — bendamustine, etoposide, cytarabine, melphalan; TEAM — thiotepa, etoposide, cytarabine, melphalan

contact with visitors, an adequate diet, and strict personal hygiene.

In all patients, a central vascular catheter was implanted before the transplantation procedure. In the case of fever in patients with no clinically apparent signs of infection, lack of colonization with pathogens, and/or previous infection with a resistant pathogen, one of two empirical treatment options were used: cephalosporine with activity against *Pseudomonas* (cefepime or ceftazidime) or piperacillin with tazobactam. Patients with a complicated clinical course were administered carbapenem combined with glycopeptide/oxazolidine or beta-lactam antibiotic acting against *Pseudomonas* together with aminoglycoside combined with glycopeptide/oxazolidine. In the case of a severe non-colonized condition, the patient was administered carbapenem together with aminoglycoside and glycopeptide/oxazolidine [10].

The presence of colonization and/or a history of infection with a resistant pathogen were the reasons for implementing an adequate antibiotic therapy.

The recommendations were modified according to the results of microbiological cultures and imaging examinations, and the treatment was continued for at least 72 hours after the fever and other symptoms of infection had subsided, and the granulocyte system (ANC >0.5 G/L)had regenerated for two days. Patients with fever lasting more than 72–96 hours despite the introduction of broad-spectrum antibiotic therapy, were applied an empirical antifungal treatment with the amphotericin B lipid complex or caspofungin [10].

Bacteremia was defined as a positive result of microbiological culture from a single sample, or in the case of Gram (+) bacteria infections from a double blood sample, taken from a febrile patient.

The analysis evaluated the frequency and type of colonization and its influence on post-transplantation infections, as well as the incidence of infections and the pathogens responsible for them.

Results

Evaluation of colonization

Colonization with a pathogen was revealed in 47/115 (40.9%) patients, and in 16 (13.9%) patients the analyzed area was colonized by more than one pathogen.

The total number of pathogens responsible for colonization was 70 (67 positive bacterial cultures, three positive fungal cultures). Bacteria were responsible for 67 positive cultures of all colonizing pathogens, of which 14/67 (20.9%) were multidrug-resistant (MDR) bacteria. Extended-spectrum beta-lactamases (ESBL) was the most common type of resistance; it accounted for 13/14 (92.9%) of all resistance types.

The most commonly colonized area was the urinary tract 38/70 (54.3%), followed by the anal area 15/70 (21.4%), then the nose 11/70 (15.7%), and then the throat 6/70 (8.6%).

The analyzed group demonstrated 38 positive cultures in the urinary tract, with *Enterococcus spp.* (12/38; 31.6%) being the most frequent pathogen. In 15 positive cultures from the anal area, Escherichia coli strain producing ESBL was most frequently found (8/15; 53.3%). Positive throat and nasal cultures were observed in six and 11 cases, respectively, and the most common bacteria was methicillin-sensitive *Staphylococcus aureus* (MSSA), of which the frequency of occurrence was 2/6 (33.3%) in the throat and 11/11 (100%) in the nasal cavity (Table II).

Infection evaluation

Post-transplantation infections occurred in 89/115 (77.4%) of patients. Among patients with fever, of which the median duration was three days, microbiologically documented infections were found in 58/89 (65.1%) patients, fever of unknown origin in 28/89 (31.5%), and clinically documented infections in 3/89 (3.4%).

The total number of pathogens responsible for infection was 174 (141 positive bacterial cultures, 25 positive fungal cultures, and eight viral infections). So, on average, there were 1.5 (174/115) infection factors per patient after auto-HSCT.

Bacterial infections

There were 141 microbiologically confirmed positive bacterial cultures in patients after auto-HSCT. Gram-positive bacteria predominated, accounting for 117/141 (82.9%). MDR pathogens accounted for 92/141 (65.2%). The most common type of bacterial resistance was MRCNS, making up 68/92 (73.9%).

Bacteremia occurred in 50/115 (43.5%) and catheter-induced infections were found in 30/115 (26.1%) patients. In 27/115 (23.5%) patients, bacteremia was caused by more than one pathogen. In total, 87 positive blood cultures were noted. Methicillin-resistant coagulase-negative

Table II. Etiology of colonizing pathogens before autologous hematopoietic stem cell transplantation (auto-HSCT) depending on location*

Location of colonization	Etiology of colonization	Positive cultures N [%]
Urinary tract	*Enterococcus spp.*	12 (31.5)
	Lactobacillus spp.	7 (18.4)
	Coagulase-negative *staphylococcus*	5 (13.2)
	Enterobacteriaceae	5 (13.2)
	Escherichia coli ESBL (–)	4 (10.5)
	Klebsiella pneumoniae ESBL (+)	2 (5.3)
	Streptococcus agalactiae	2 (5.3)
	Proteus mirabilis ESBL (–)	1 (2.6)
	Total	38 (100)
Anal area	*Escherichia coli* ESBL (+)	8 (53.3)
	Klebsiella pneumoniae ESBL (+)	2 (13.3)
	Bacteroides vulgates	1 (6.7)
	Enterobacter cloacae ESBL (+)	1 (6.7)
	Enterococcus raffinosus	1 (6.7)
	Enterococcus faecium	1 (6.7)
	Aspergillus fumigates	1 (6.7)
	Total	15 (100)
Nasal cavity	*Staphylococcus aureus* MSSA	11 (100)
	Total	11 (100)
Pharynx	*Staphylococcus aureus* MSSA	2 (33.3)
	Staphylococcus aureus MRSA	1 (16.7)
	Candida albicans	1 (16.7)
	Candida krusei	1 (16.7)
	Streptococcus viridians	1 (16.7)
	Total	6 (100)

*In 16 (13.9%) patients before auto-HSCT, location was colonized by >1 pathogen; ESBL — extended-spectrum beta-lactamases; MSSA — methicillin-sensitive *Staphylococcus aureus*; MRSA — methicillin-resistant *Staphylococcus aureus*

Staphylococcus epidermidis (MRCNSE) was the most common pathogen, accounting for 24/87 (27.6%) of the etiological factors responsible for blood infections.

The skin in the central vascular catheter was infected in 21/115 (18.3%) patients. There were 30 positive cultures and the main etiological agent was MRCNSE, which accounted for 16/30 (53.3%) of pathogens infecting this area.

Urinary tract infections occurred in 13/115 (11.3%) patients and the most common etiological agent was *Escherichia coli* ESBL (–). It accounted for 6/15 (40%) of positive cultures.

Positive stool cultures were observed in 24/115 (20.9%) patients. Bacteria accounted for nine positive stool cultures, and fungi accounted for 25. *Clostridium difficile* (8/9; 88.9%) was the predominant bacterial pathogen in this group (Table III).

Only 3/47 (6.4%) colonized patients developed in total three infections with the pathogen responsible for their previous colonization. These infections affected the urinary tract and they were connected with earlier colonization of the anus. *Klebsiella pneumoniae* ESBL (+) was responsible for 2/3 (66.7%) of all infections with the colonizing pathogen, and *Escherichia coli* ESBL (+) for 1/3 (33.3%).

Fungal infections

Fungal infections occurred in 25/115 (21.7%) patients. 25 positive cultures of fungal pathogens were reported in the gastrointestinal tract. *Candida albicans* was observed most often — 11/25 (44%) (Table III).

Viral infections

Viral infections occurred in 8/115 (7%) patients after auto-HSCT. HSV was found in 5/115 (4.3%) and viral respiratory tract infection was reported in 2.6% (3/115) of patients.

The median duration of empirical and targeted antibiotic therapy was 5 (range 1–20) and 7 (range 4–31) days, respectively.

After auto-HSCT, death occurred in 2/115 (1.7%) patients (aged 21 and 54) during the neutropenia period. Deaths were caused by septic shock caused by *Enterobacter cloacae* MDR and *Escherichia coli* ESBL (+) bacteremia, and affected patients with lymphomas in partial response to previous chemotherapy. These bacteria were not responsible for the colonization of these patients before auto-HSCT.

Discussion

Despite the development of modern preventive strategies, and a better understanding of mechanisms of immunosuppression, post-transplantation infections remain a problem. Infections connected with HSCT are the most common cause of early death in the post-transplantation period after auto-HSCT [3].

In our study, we conducted a comprehensive analysis of the colonization of patients undergoing auto-HSCT and its influence on post-transplantation infections. Moreover, we determined the frequency and type of infections involved in the post-transplantation period.

In the literature review, no study has analyzed the etiology and frequency of colonization of all sites which are subject to standardized microbiological evaluation before HSCT. In our study, we observed colonization with at least one pathogen in 40.9% of patients before auto-HSCT. The urinary tract appeared to be the most colonized region — 54.3%.

In our study, MDR bacteria accounted for 20.9% of positive colonization cultures before auto-HSCT. MDR bacteria most frequently colonized the anal region and this occurred in 11/115 (9.6%) patients before auto-HSCT. The analysis by Girmenia et al. which assessed the presence of Gram (–) colonization of the gastrointestinal tract at 54 Italian centers in 1,625 patients before auto-HSCT MDR reached 9% [11].

Table III. Etiology of infection after autologous hematopoietic stem cell transplantation in relation to number of positive cultures

Location of infection	Type of infection	Etiology of infection	Positive cultures N (%)
Bacteremia			
	Gram-positive bacteria	*Staphylococcus epidermidis* MRCNSE	24 (27.6)
		Staphylococcus hominis MRCNS	14 (16.1)
		Staphylococcus haemolyticus MRCNS	13 (14.9)
		Staphylococcus spp. MLS_B (+)	11 (12.6)
		Staphylococcus epidermidis MSCNS	8 (9.2)
		Streptococcus parasanguinis	1 (1.1)
		Enterococcus faecium GRE, HLGR	1 (1.1)
		Enterococcus faecium	1 (1.1)
		Corynebacterium afermentans	1 (1.1)
		Bacillus spp.	1 (1.1)
		Bacillus cereus	1 (1.1)
		Clostridium difficile	1 (1.1)
	Gram-negative bacteria	*Escherichia coli* ESBL (–)	6 (6.5)
		Escherichia coli ESBL (+)	1 (1.1)
		Enterobacter cloacale ESBL (+)	1 (1.1)
		Enterobacter cloacae MDR	1 (1.1)
		Acinetobacter ursingii	1 (1.1)
	Total		87 (100)
Skin of central line area			
	Gram-positive bacteria	*Staphylococcus epidermidis* MRCNSE	16 (53.3)
		Staphylococcus epidermidis MSCNS	6 (20)
		Staphylococcus spp. MLS_B (+)	3 (10)
		Staphylococcus hominis MRCNS	1 (3.3)
		Staphylococcus warneri MSCNS	1 (3.3)
		Enterococcus spp.	1 (3.3)
	Gram-negative bacteria	*Escherichia coli* ESBL (–)	2 (6.7)
	Total		30 (100)
Urinary tract			
	Gram-positive bacteria	*Enterococcus faecium*	2 (13.3)
		Enterococcus spp.	1 (6.7)
		Enterococcus faecalis	1 (6.7)
	Gram-negative bacteria	*Escherichia coli* ESBL (–)	6 (40)
		Escherichia coli ESBL (+)	3 (20)
		Klebsiella pneumoniae ESBL (+)	2 (13.3)
	Total		15 (100)
Gastrointestinal tract			
	Gram-positive bacteria	*Clostridium difficile*	8 (23.5)
	Gram-negative bacteria	*Klebsiella pneumoniae* ESBL (+)	1 (2.9)
	Fungi	*Candida albicans*	11 (32.4)
		Candida glabrata	7 (20.6)
		Saccharomyces cerevisiae	3 (8.8)
		Candida pararugosa	1 (2.9)
		Candida dubliniensis	1 (2.9)
		Candida parapsilosis	1 (2.9)
		Candida tropicalis	1 (2.9)
	Total		34 (100)

MRCNSE — methicillin-resistant coagulase-negative *Staphylococcus epidermidis*; MRCNS — methicillin-resistant coagulase-negative *Staphylococcus*; MLS_B — resistance to macrolides, lincosamides and streptogramin B; MSCNS — methicillin-susceptible coagulase-negative *Staphylococcus*; GRE — glycopeptide-resistant *Enterococci*; HLGR — high-level gentamicin-resistant; ESBL — extended-spectrum beta-lactamases; MDR — multidrug-resistance

Post-transplantation infections occurred in 77.4% of analyzed patients after auto-HSCT. In the study conducted by Gil et al. in the years 1994–2005, 92% of 314 patients after auto-HSCT demonstrated infectious complications [12]. In an analysis of 112 patients undergoing auto-HSCT between 2004 and 2009, Santos et al. recorded 57% of infections [13]. In the studies conducted on groups of patients after auto-HSCT by Salazar et al. (126 patients; 1992–1996) and Celebi et al. (45 patients; 1997–1999), much lower percentages of infections were obtained: 40% and 42%, respectively. This low percentage of infectious complications could have been related to the fact that these studies also considered infections in patients treated for solid tumors. In addition, the included patients were <60 years old, presenting a very good general condition and a lack of accompanying diseases [14, 15]. The number of infections after HSCT observed in our study is similar to results received in other transplantation centers in Poland and worldwide, where, despite applied anti-infection prevention, infections still occur in 80–100% of patients [12, 16].

In our study, bacteremia was found in 43.5% (50/115) of patients. In other studies, such as the one conducted by Salazar et al., bacteremia was described in 31% of patients after auto-HSCT, while in a study conducted by Wang et al. in the period 2005–2014, the prevalence of bacteremia reached 20% [14, 17].

It is estimated that up to 90% of blood infections with hospital pathogens are caused by the presence of a central venous catheter (CVC), 90% of which is associated with an untunnelled catheter [18]. Criteria of the US Center for Disease Control and Prevention (CDC) regarding the diagnosis of CVC-related blood infections [central line-associated bloodstream infection (CLABSI)] include a catheter which is inserted for at least two days, at least one positive catheter blood culture with the pathogen or at least two positive catheter blood cultures with a commensal pathogen, together with concurrent symptoms of systemic infection (fever >38°C, chills, hypotension). Furthermore, the symptoms must not be related to any other source of infection [19, 20].

We observed CLABSI in 26.1% (30/115) of patients after auto-HSCT. Analysis conducted by other centers, such as the study by Santos et al., revealed that CLABSI occurred in 26% of patients after auto-HSCT [13], while in a study conducted by Satlin et al., CLABSI was found in 15–40% of auto-HSCT receivers depending on the prophylaxis that was used [21]. Results obtained in our center are thus comparable to those presented by other researchers [13, 21, 22].

As far as neutropenic fever after auto-HSCT is concerned, the results vary significantly depending on the underlying disease and the treatment used, usually ranging from 50–90% [23–25]. In our analysis, febrile neutropenia complicated the post-transplantation period in 77.4% (89/115) of patients after auto-HSCT.

Exogenous hospital microorganisms, mainly Gram-positive bacteria, and endogenous bacterial flora of the gastrointestinal tract which contributes to Gram-negative infections, are an important source of bacterial infections after HSCT. In our center, in the group after auto-HSCT, Gram-positive bacteria were responsible for 82.9% of all bacterial infections, with a predominance of coagulase-negative *Staphylococci*. In the study by Gil et al. [13] in patients after auto-HSCT, Gram-positive bacteria accounted for 60% of pathogens infecting blood. Besides, coagulase-negative *Staphylococci* were also most frequently observed [12]. The higher percentage of Gram-positive bacteria (+) observed in our study is probably because in addition to blood, other infection sites, such as the gastrointestinal tract, urinary tract, and skin, were included in the assessment of bacterial count.

Over recent years, the number of MDR infections has significantly increased, thus creating numerous problems for effective antibiotic therapy. The prevalence of MDR pathogens varies depending on the location of transplant centers and their local infection epidemiology, and is strongly dependent on the type of infection prophylaxis and the treatment provided. In our study, MDR pathogens accounted for 65.2% of etiological factors of detected infections. The literature review does not contain a multi-drug resistance analysis covering multiple locations of infection and different types of resistance like those shown in our study [methicillin-resistant coagulase-negative *Staphylococcus* (MRCNS), resistance to macrolides, lincosamides and streptogramin B (MLS_B), ESBL, MDR, glycopeptide-resistant *Enterococci* (GRE), high-level gentamicin-resistant (HLGR)] simultaneously. In a multicenter analysis, Averbuch et al. evaluated the Gram-negative bacteria resistance of 241 recipients of auto-HSCT in 2014–2015. The percentage of Gram-negative MDR rods was 20% for the auto-HSCT group [26].

Invasive fungal infections are an important type of complication associated with the transplantation procedure. In our analysis, infection with at least one fungal pathogen occurred in 21.7% and it was mostly caused by *Candida spp.* — being responsible for 88% (22/25) of all fungal pathogens, headed by *C. albicans* — 44% (11/25). According to scientific reports, the incidence of infections caused by *Candida spp.*, and in particular by *C. albicans*, has decreased in recent years, due to widespread prophylactic and therapeutic activities, including the use of second-generation azoles [27]. On the other hand, intensive prophylaxis has contributed to an increase in the incidence of resistant strains, such as *C. glabrata* [28–30]. In the presented study, *C. glabrata* constituted 28% (7/25) of all detected fungal pathogens. A similar trend is observable in the study by Kontoyiannis et al. [31] conducted on 16,200 patients after auto- and allo-HSCT between 2001 and 2006: *C. glabrata* (33%) and *C. albicans* (20%) cultures predominated in the group of invasive candidiasis.

Viral infection was reported in 7% (8/115) of auto-HSCT receivers. Neither CMV nor EBV reactivation was detected. The most common viral infection was caused by HSV and this occurred in 4.3%. This percentage of cases attributed to reactivation is undoubtedly a result of a high baseline population seroprevalence of HSV which can be found in 50–96% of people [32].

In our study, 6.4% of patients who appeared to be colonized before auto-HSCT could not avoid infection with pathogens that were associated with colonization. The literature review has no analysis which would simultaneously evaluate different locations of colonization with etiology and influence on post-transplantation infections. Colonization with a pathogen may increase the risk of infection and furthermore affect the effectiveness of subsequent antibiotic therapy, thus posing a threat to the effective regeneration of the hematopoietic system. The assessment of colonization can be a useful tool to identify patients with a high risk of developing infections caused by the colonizing pathogen. The analysis of both colonization and infection should be carried out systematically in the transplantation center, providing an opportunity for proper prevention and empirical treatment.

Conclusions

Neutropenic patients are susceptible to many types of infection, including bloodstream infections and gastrointestinal infections, as well as those connected with the urinary tract and skin.

The etiology and frequency of infection depend largely on the local infection epidemiology of each center, including principles of prophylaxis and patterns of empirical and targeted antibiotic treatment.

Searching for risk factors such as those associated with colonization, helps to identify neutropenic patients at the highest risk of infection and death.

Evaluation of colonization and infection in patients undergoing auto-HSCT can be effective in monitoring potential pathogen transmission, and provides a useful tool for improving local standards for managing infections. Such knowledge is also essential to guide infection control measures and effective infection therapy in HSCT recipients.

Authors' contributions

KMK and AP were responsible for creating the study protocol; KMK, MCz and PS were responsible for patient enrolment and data acquisition; KMK and AP were responsible for writing the manuscript; AW and AP were responsible for manuscript revision and proofreading.

Conflict of interest

None.

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None.

Ethics

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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Chemotherapy delays in children with acute lymphoblastic leukemia might influence the outcome of treatment

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Abstract

Introduction: Acute lymphoblastic leukemia (ALL) is one of the most commonly occurring cancers among children with one of the highest survival rates, thanks to its very strict treatment protocol. In this paper, the impact of delays in treatment during the induction phase was assessed.

Material and methods: Retrospective single center analysis of 127 patients treated between years 2003 and 2015 was performed. Patients were categorized by their respective gender, age, leukemia variant, risk group and chemotherapy protocol used. The delays were measured using protocol milestones as reference points. The associations between treatment delay intervals and event-free survival (PFS) or overall survival (OS) were evaluated using Kaplan-Meier curves and univariate Cox proportional hazards regression models.

Results: Delays in treatment which occurred before the 8th day were associated with a 30% increase in the risk of death ($p < 0.01$) and a 33% increase in the risk of relapse or death ($p < 0.01$). The influence of delays after the 8th day was statistically insignificant. Delays were proven to have the most influence on outcome in the high-risk group, especially before the 8th day.

Conclusions: The ALL treatment protocols should be strictly followed as any delay may lead to worse patients' survival.

Key words: acute lymphoblastic leukemia, delays, oncology, hematology

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Introduction

Leukemias are one of the most commonly occurring types of neoplasms among children that account for about 30% of oncological diagnoses among pediatric patients. Out of all bone marrow derived neoplasms, acute lymphoblastic leukemia (ALL) is the most widespread type, occurring in 80% of patients suffering from leukemias. It also belongs to one of the most efficiently combated cancers, with 5-year survival rates nearing 90% [1]. Such efficiency can be contributed to rapid development of chemotherapy protocols, which have been constantly improved since their introduction in 1960s. Although different hospitals use different protocols, they share common core characteristics. A broad spectrum of chemotherapeutic agents is utilized, their administration is governed by a very strict time schedule and their dosage is adjusted depending on each patient's individual variables.

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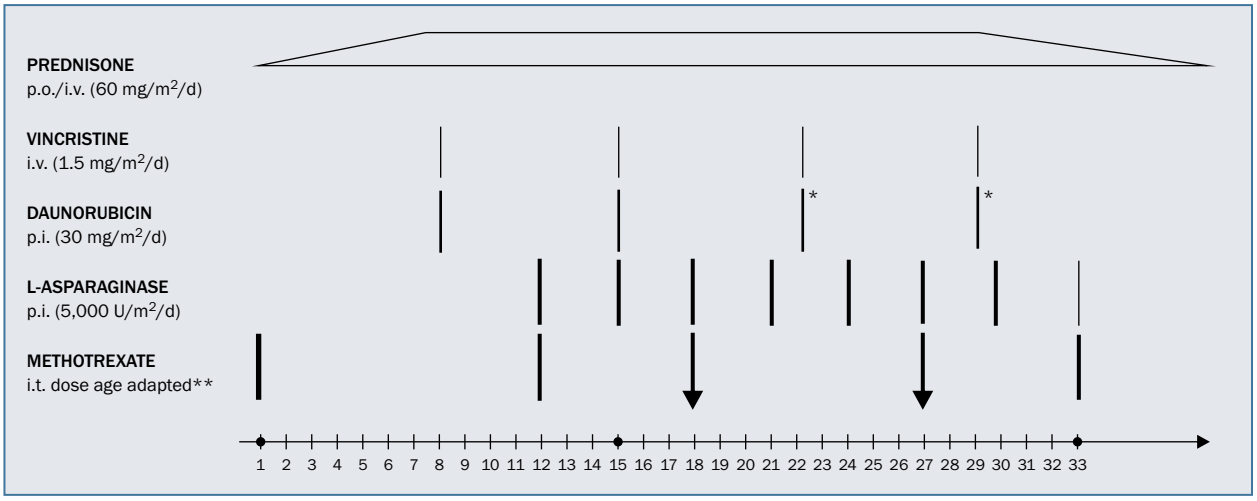

Figure 1. ALLIC BFM 2009 induction protocol, as taken from the official Berlin–Frankfurt–Munster Group Final Version of Therapy Protocol from August 14, 2009. The lines indicate the days of drug administration; *in case of standard risk (SR) T-cell acute lymphoblastic leukemia (T-ALL) and intermediate risk (IR) or high risk (HR) ALL additional doses of daunorubicin are administered on days 22 and 29. The days of bone marrow biopsies were marked with a dot on days 1, 15 and 33. Prednisone is given in 3 single doses per day, began with a total or 25% of the calculated dose, depending on clinical condition of the child, and increased rapidly considering laboratory findings, clinical response and diuresis. The withdrawal of prednisone should be started on the 29th day and last 9 days; **methotrexate (MTX) dose is age-adapted and given as follows: 6 mg for children <1 yo, 8 mg ≥1 and <2 yo, 10 mg ≥2 and <3 yo and 12 mg when the child is 3 years old or older. In case of central nervous system involvement or presence of blasts in the cerebrospinal fluid or traumatic lumbar puncture additional MTX is administered on days 18 and 27; p.o. — per os; i.v. — intravenous; p.i. — per infusionem; i.t. — intrathecal

ALLIC BFM (Berlin–Frankfurt–Munster) chemotherapeutic protocol from year 2002 and its improved version from year 2009 both consist of three main blocks of treatment: remission induction, consolidation and maintenance with the first phase, responsible for forcing the disease into remission, being the most intensive one [2]. The first 33 days of treatment protocol, shown in Figure 1, are decisive in the process of risk group stratification and play a crucial role in further prognosis. It has long been known that early treatment response, in particular the response to the prednisone prophase (absolute blast count on day 8, after 7 days of prednisone and one dose of intrathecal methotrexate) is one of the strongest independent prognostic factors of treatment outcome and has been extensively analyzed [3–5]. However, the effect of treatment delay in the early phases of the protocol on survival has not received enough attention [6]. It has been reported that the abandonment of therapy and treatment-related mortality is especially high in resource-poor settings [7, 8]. While, the rates of abandonment of therapy or toxic deaths are low in high-income countries [9]. Thus, treatment delay is believed to be one of the major contributors to inferior outcomes in low-income countries. In the light of these reports, the aim of this research was to assess the influence of treatment delay during the beginning of the induction phase of ALLIC BFM 2002 and 2009 protocols on the outcome of treatment. Finally, we compared ALLIC BFM 2002 and 2009 protocols.

Material and methods

This retrospective analysis included children suffering from ALL treated at the single pediatric oncology center between 2003 and 2015. All patients diagnosed with both T-cell ALL (ALL-T) and B-cell ALL (ALL-B) treated with ALLIC BFM 2002 and ALLIC BFM 2009 protocols were included in the study. Clinical data were obtained from hospital records and assessed retrospectively. Treatment protocol, age of onset, sex, leukemia variant, prognostic risk group [standard risk (SR), intermediate risk (IR) and high risk (HR)], date of diagnosis, date of progression or relapse and date of last follow-up were identified.

In order to assess delay in treatment we used established protocol milestones, which represent the crucial days of protocol treatment. The 1st day of treatment, the measurement of steroid resistance from peripheral blood on the 8th day and the bone marrow biopsies on the 15th and the 33rd day were regarded to be the pivotal points in treatment regimens and are crucial in the process of risk group stratification. The expected dates of treatment corresponding to the 8th, 15th and 33rd days of the protocol were determined on the grounds of the 1st day of treatment and compared with the actual dates taken from hospital records. The intervals between the expected dates of the protocol milestones and the actual dates were calculated. Treatment delay has been defined as any delay that occured between protocol checkpoints that has not already been registered earlier.

Based on assumption testing, study group description and intragroup association were conducted using chi^2 and U Mann-Whitney tests as well as Spearman's rank correlation coefficient. Associations between prognostic risk groups were declared using Kruskal–Wallis one-way analysis of variance. As all the analyses were preplanned, no correction for multiple comparisons was applied.

The log-rank test was used to compare the survival of two subgroups — patients with and without at least 1-day delay in treatment protocol as well as between protocols. Finally, the associations of treatment delay intervals with the event-free survival (EFS) and overall survival (OS) were evaluated using Kaplan-Meier curves and univariate Cox proportional hazards regression modelling. EFS and OS were calculated from date of diagnosis to date of first event. Regarding EFS the event was defined as relapse or death and regarding OS — death as a result of any cause. The observation time was ceased at last follow-up if no event occurred. All calculations were performed using R. Significance level was set to p-value less than 0.05.

In order to establish whether the poorer prognosis in treatment occurs due to the delays or because of the already present adverse conditions, we divided the control group according to risk groups patients belonged to at the onset of treatment (high risk, intermediate risk, standard risk) and evaluated the associations of treatment delays with OS and EFS within these groups. We have also analyzed the reasons for treatment delay when found in patients' documentation, in particular adverse conditions.

Finally, we tried to determine whether delay at any point of the induction phase of the treatment protocol had impact on the risk of death and the risk of relapse or death in the analyzed group of children. In order to authenticate our analysis we compared the delayed and non-delayed groups in search of any comorbid factors that may influence our analysis and to see if the groups are comparable.

Table I. Group characteristics

Characteristics	Number or median	Percentage (if applicable) [%]
Median age [years]	5 (IQR: 2.73–10.39)	
Sex:		
• girls	52	40.94
• boys	75	59.06
Risk group:		
• SR	28	22.05
• IR	68	54.54
• HR	31	24.41
Leukemia variant:		
• T-ALL	17	13.39
• BCP-ALL	110	86.61
Steroid response:		
• good steroid response	118	92.91
• poor steroid response	9	7.09
Median WBC at day 1 [/μL]	12,870 (IQR: 4,890–43,425)	
OS	84.8% (95% CI: 78.4–91.6%)	
EFS	82.1% (95% CI: 75.3–89.5%)	
Median follow-up time	5.25 (IQR: 2.09–7.82)	

IQR — interquartile range; SR — standard risk; IR — intermediate risk; HR — high risk; T-ALL — T-cell acute lymphoblastic leukemia; BCP-ALL — B-cell precursor acute lymphoblastic leukemia; WBC — white blood cells; OS — overall survival; EFS — event-free survival

Results

One hundred twenty-seven children, treated at the Department of Pediatrics, Oncology and Hematology between 2003 and 2015, were included in this analysis. The detailed characteristics of the study group were presented in Table I.

In the study group, median age of diagnosis was 5 years (interquartile range: 7.66 years) and was equal in both girls and boys (p = 0.53). Although the protocol was updated during the time of the study, the group of patients after and prior to the update of 2009 were similar in terms of all clinical characteristics (p >0.05).

Eighty children were treated using ALLIC BFM 2002 (group 2002) and forty-seven using ALLIC BFM 2009 (group 2009). The delays occurred in 84 cases (61.3%) out of which 56 in group 2002 and 28 in the group 2009. Median overall protocol delay was equal to 1 day (interquartile range: 5.25 days). The occurrence of delay was, however, not associated with the protocol (p = 0.29). Therefore, and since the number of children receiving treatment according to the latest protocol was insufficient to provide statistically significant data, both study groups were combined. Noteworthy, the overall number of delayed days was not correlated with age (rho = 0.02, p = 0.82) or associated with sex (p = 0.92).

The 5-year overall survival (OS) and event-free survival (EFS) of the analyzed group was 84.8% [95% confidence interval (CI): 78.4–91.6%] and 82.1% (95% CI: 75.3–89.5%) respectively. In the group 2002 5-year OS probability was equal to 81.3% (95% CI: 73.1–90.3%) while in group 2009 the 5-year OS was calculated as 93.2% (95% CI: 85.9–100%). Similar results were obtained for EFS. In the group 2002 5-year EFS was calculated as 78.8%

(95% CI: 70.3–88.2%) while in group 2009 it was calculated as 87.5% (95% CI: 75.4–100%). The difference in OS and EFS between protocols was not statistically significant ($p = 0.13$ and $p = 0.15$, log-rank test).

The differences in survival and hazard ratio between different risk subgroups of the study was summarized in Table II. The risk of death in patients belonging to the high-risk group was increased by 30% (HR 1.30, 95% CI: 1.08–1.57, $p < 0.01$) when delay occurred before the 8th day of treatment and by 25% (HR 1.25, 95% CI: 1.06–1.48, $p < 0.01$) when delay occurred before the 15th day. No statistically significant change in the risk of death was observed in patients experiencing delay before the 33rd day. The risk of death or relapse of the disease in the same group was increased by 31% (HR 1.31, 95% CI: 1.08–1.59, $p < 0.01$) and 26% (HR 1.26, 95% CI: 1.06–1.50, $p < 0.01$) in patients having their treatment postponed before the 8th and 15th respectively. No statistically significant change in the risk of death or relapse was observed among patients experiencing delays before the 33rd day. The results concerning patients belonging to the intermediate risk group were consistent with observations made in the high-risk group. However, analysis of the data showed that the results were statistically insignificant. The Cox proportional hazards model could not be calculated in the standard risk group since there were not enough cases of death or relapse post-induction phase among these patients, as shown in Table II.

A higher incidence of adverse initial condition was observed in the high-risk group of patients compared to the standard and intermediate risk groups combined. Disease complications were reported in 14 out of 31 patients in the high-risk group versus 15 out of 96 patients in the SR and IR groups (chi^2 test, $p < 0.001$).

Same observations were made regarding the 5-year overall survival and event-free survival of patients in respective risk groups (Table II). Although detrimental effect of delays was observed in groups of standard and intermediate risk, the results that were obtained proved to be statistically insignificant. However, in the high-risk group, interval before the 8th day once again proved to have the most detrimental effect on the outcome of treatment, lowering the 5-year OS by 44.1% ($p = 0.003$) and 5-year EFS by 48.6% ($p = 0.002$). The influence of intermission before the 15th and before the 33rd day wasn't statistically significant in the high-risk group of patients.

An increase in white blood cell count by one thousand was associated with a slight increase in the risk of death (HR 1.002, 95% CI 1–1.004, $p = 0.03$) and a slight increase in the risk of death or relapse (HR 1.003, 95% CI 1.001–1.004, $p = 0.004$). Steroid resistance was proven to have no statistically significant influence on the risk of death (HR 3.22, 95% CI: 0.93–11.13, $p = 0.06$). However, its impact on the risk of death or relapse was noted to be statistically significant (HR 5.61, 95% CI: 2.05–15.39, $p < 0.001$).

Delay in treatment was reported to be most impactful during the first 8 days of treatment, both for the 2002 and 2009 protocols ($p < 0.01$ for both protocols, regarding both OS and EFS). After analyzing the groups of patients from both protocols as a homogenous group, it was established that the risk of death due to delay before the 8th day of treatment increases by 30% (HR 1.30, 95% CI: 1.14–1.48, $p < 0.001$), whereas the death or relapse risk increases by 33% (HR 1.33, 95% CI: 1.16–1.53, $p < 0.001$).

Intermissions that occurred in latter days did not have such impact on the outcome of treatment. Delay before the 15th day of treatment was statistically significant regarding the hazard ratio of patients, with the risk of death for both groups combined elevated by 14% (HR 1.14, 95% CI: 1.01–1.28, $p = 0.03$) and the risk of death or relapse by 13% (HR 1.13, 95% CI: 1.01–1.27, $p = 0.03$).

Using the Kaplan-Meier survival and log-rank test, the risk of death (OS) and the risk of relapse or death (EFS) was found to be different between patients with and without delay in the 8th day of treatment ($p = 0.002$, Figure 2A and $p = 0.005$, Figure 2B respectively). These findings did not repeat in patients experiencing intermission in treatment before the 15th day or the 33rd day of treatment, where no statistically significant difference in OS and EFS was observed.

The occurrence of delay at any point of the induction phase in the treatment protocol was associated with a higher risk of death. However, its impact was not statistically significant (HR 3.99, 95% CI: 0.92–17.36, $p = 0.065$). Any postponement in drug administration resulted in a statistically significant elevated risk of relapse or death (HR 4.77, 95% CI: 1.11–20.49, $p = 0.036$). There was a noticeable difference in the 5-year OS and EFS of patients depending on the presence of delay. Children in which delay during the induction phase was reported had a statistically significant worse 5-year overall and event-free survival ($p = 0.046$, Figure 2C and $p = 0.02$, Figure 2D respectively).

Finally, the basic characteristics, shown in Table III, analyzed in comparisons between the delayed and the non-delayed before the 8th day group and the delayed and the non-delayed at any point of the induction phase group didn't show any statistically significant differences.

Discussion

The results of this retrospective analysis suggest that the occurrence of delay in specific moments in early phases of treatment protocol may increase both the risk of death and the risk of relapse or death. This analysis was done on a representative group since all known risk factors are also applicable in children included in this study. Our results are contradictory to previous reports. In a retrospective study by Yeoh et al. [6] no difference in the risk of relapse in children with shorter or longer delays in therapy was

Table II. The effect of intervals on the 5 years overall survival and event-free survival, depending on the time of delay in reference to ALLIC BFM (Berlin–Frankfurt–Munster) protocol checkpoints

	Group size	Overall survival (5 years)	Risk of death (hazard ratio)	Number of deaths	Event-free survival (5 years)	Risk of death or relapse (hazard ratio)	Number of deaths or events
	HR: 31 children						
Interval before day 8	11	87.7% vs. 43.6% (p = 0.003)	1.30 (95% CI: 1.08–1.57, p <0.01)	6	82.7% vs. 34.1% (p = 0.002)	1.31 (95% CI: 1.08–1.59, p <0.01)	7
Interval before day 15	9	79.7% vs. 53.3% (p = 0.12)	1.25 (95% CI: 1.06–1.48, p < 0.01)	4	75.2% vs. 37.0% (p = 0.06)	1.26 (95% CI: 1.06–1.50, p < 0.01)	5
Interval before day 33	20	90.0% vs. 67.5% (p = 0.26)	1.02 (95% CI: 0.78–1.34, p = 0.88)	6	90.0% vs. 53.3% (p = 0.1)	1.04 (95% CI: 0.83–1.29, p = 0.72)	8
	IR: 68 children						
Interval before day 8	24	90.0% vs. 74.1% (p = 0.11)	1.51 (95% CI: 0.90–2.54, p = 0.12)	6	90.6% vs. 74.3% (p = 0.1)	1.51 (95%CI: 0.90–2.54, p = 0.12)	6
Interval before day 15	23	88.2% vs. 75.2% (p = 0.26)	1.11 (95% CI: 0.82–1.51, p = 0.49)	5	88.6% vs. 75.5% (p = 0.27)	1.11 (95% CI: 0.82–1.51, p = 0.49)	**5**
Interval before day 33	35	89.9% vs. 82.5% (p = 0.56)	1.10 (95% CI: 0.98–1.23, p = 0.12)	5	90.1% vs. 82.8% (p = 0.57)	1.01 (95%CI: 0.97–1.23, p = 0.12)	5
	SR: 28 children						
Interval before day 8	9	NA	NA	–	NA	NA	–
Interval before day 15	12	NA	NA	–	100% vs. 90.0% (p = 0.22)	0.98 (95% CI: 0.46–2.07, p = 0.96)	1
Interval before day 33	12	NA	NA	–	100% vs. 90.0% (p = 0.22)	0.94 (95%CI: 0.36–2.50, p = 0.91)	1

HR – high risk; CI – confidence interval; IR – intermediate risk; SR – standard risk; NA – not available

found. Moreover, a tendency for fewer relapses in patients who had a longer delay during the maintenance phase of treatment was noted [6]. Laughton et al. in another retrospective analysis reported that there is no significant association between delays at any measured time point and the risk of relapse [10]. However, the association between abandonment of therapy and the risk of death has not been investigated in any of the two mentioned studies. Koka et al. [11] in a study from 2014 investigated the influence of total delay of treatment on OS and reported that a period of interruption longer than 5 days during transition from M protocol to protocol II improved patients' OS comparing to shorter delays but no influence on EFS was noted. An association between treatment interruption and shorter OS or EFS was also rejected in a study by Wahl et al [12]. Meeske et al. [13] reported that females had significantly more

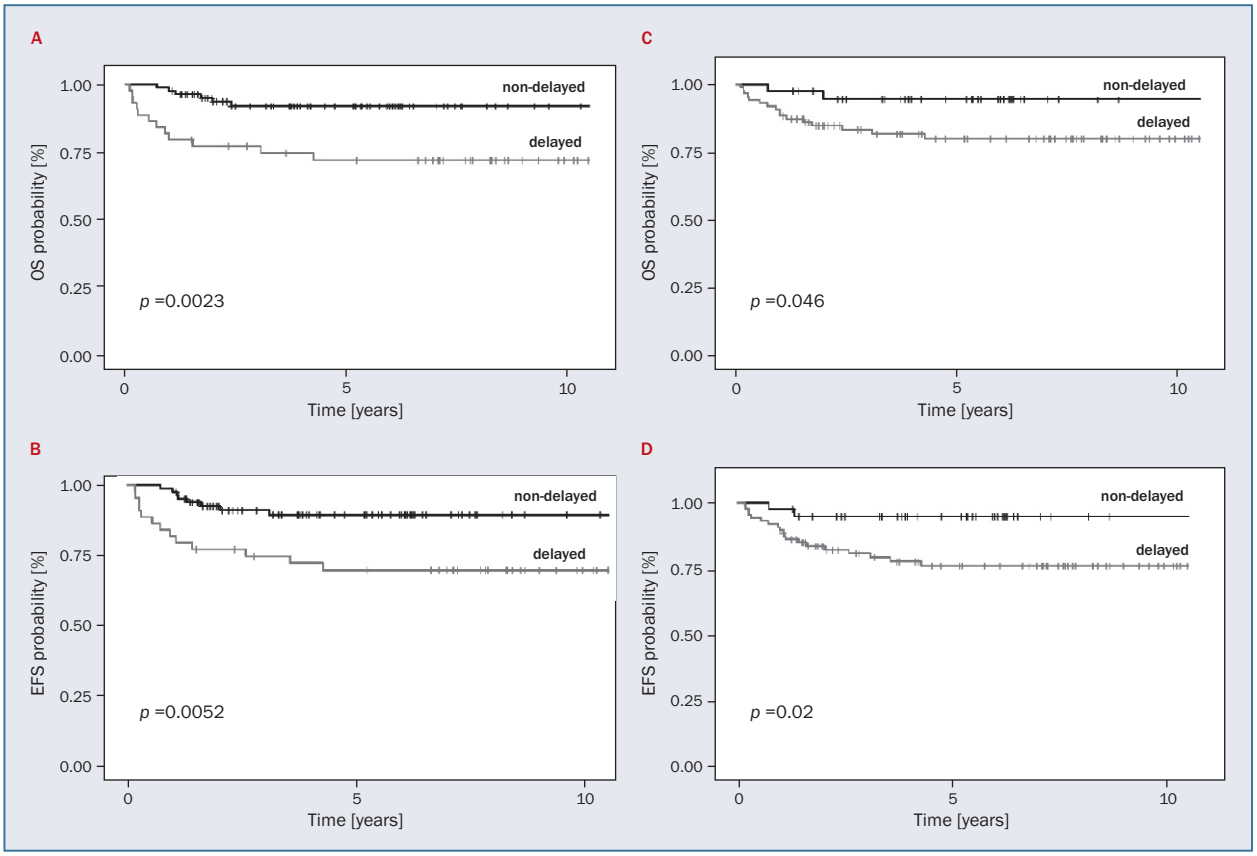

Figure 2. Graphs presenting the Kaplan-Meyer curves of overall survival (OS) and event-free survival (EFS) of patients in the whole group, depending on the occurrence of delay before the 8th day (**A, B**) and delay at any point during the induction phase (**C, D**). The presented *p* values are the result of the log-rank test

hospital days and delays in therapy than males. It should however be noted that some of the mentioned studies have major limitations. They include single center analyses with a relatively small number of patients. Considering the fact that, as mentioned above, the rates of abandonment of therapy or toxic deaths are low in high-income countries, a multiple center investigation is highly recommended for a chance of better understanding of treatment delays' influence on overall and event-free survival.

Our study demonstrates the importance of strict adherence to the protocol as even a single day of delay highly increases the risk of death and the risk of relapse or death. The first 33 days of treatment are a critical period due to the initial patient response to chemotherapy treatment, metabolic abnormalities and infections. Infections, neutropenia and febrile neutropenia can result in chemotherapy delay or changes of therapy and are commonly believed to contribute to worst outcome [14]. Prevention plays a key role in avoiding these complications. Another factor causing therapy abandonment is toxicity, which most commonly leads to early discontinuation [15].

As a retrospective observational study, our work is bound to several limitations. It should be noted that this is a single center study and a broader analysis on a bigger group of patients would be highly recommended. The sample size of patients belonging to the high-risk group is relatively small and potentially not representative enough, however, the results we obtained are alarming, as even smallest delays in this group may lead to dire consequences of higher risk of death or relapse. Furthermore, as we also have already demonstrated, initial conditions of patients also play a pivotal role in the prognosis, and it would be of great benefit to establish which of these two factors contributes more to the increased risk of death or relapse Therefore it would be wise to examine this relation further on a bigger group with a special focus on the initial patients' condition and the occurrence of delay. Another important aspect is no group division based on the protocol implemented. We decided that the differences between the two protocols are omittable for the purpose of our analysis.

The reasons for treatment interruptions in high-income countries are most commonly medical — meaning that patients with more severe disease are predestined to therapy delay because of contraindications. Postponement may be caused by complications such as infection, hypersensitivity reactions, kidney failure, thrombosis, bleeding or even

Table III. Comparison between children in which delay occurred before the 8th day of the protocol and those without such delay and between children in which delay occurred at any point of the induction phase (any-delay group) and those without any delay (no delay group) in the course of treatment

Parameter Characteristics	Delay before the 8th day Number/median	No delay before the 8th day Number /median	*P* value	Any delay Number/median	No delay Number/median	*P* value
Group size	44	83		87	40	
Median age [years]	5.88 (IQR: 2.53–2.55)	4.70 (IQR: 2.87–8.64)	0.49	5.29 (IQR: 2.53–0.64)	4.00 (IQR: 2.82–0.65)	0.99
Sex:			0.44			0.88
• girls	16	36		36	16	
• boys	28	47		51	24	
Risk group:			0.95			0.53
• SR	9	19		17	11	
• IR	24	44		47	21	
• HR	11	20		23	8	
Leukemia variant:			0.54			0.19
• T-ALL	7	10		14	3	
• BCP-ALL	37	73		73	37	
Steroid response:			0.93			0.17
• good steroid response	41	77		79	39	
• poor steroid response	3	6		8	1	
Protocol:			<0.001			0.21
• ALLIC BFM 2002	37	43		56	22	
• ALLIC BFM 2009	7	40		28	18	
Median WBC at day 1 [per μL]	17,010 (IQR: 4,900–5,000)	12,650 (IQR: 4,860–36,700)	0.70	14,175 (IQR: 5,400–46,745)	8,400 (IQR: 3,400–33,500)	0.13
OS	72.1%	92%	0.002	80.2%	94.7%	0.046
EFS	69.9%	89.4%	0.005	76.2%	94.9%	0.02
Median follow-up time	7.11 (IQR: 1.93–8.83)	4.53 (IQR: 2.09–6.27)	0.16	5.25 (IQR: 1.82–8.59)	5.28 (IQR: 3.34–6.22)	0.49

IQR — interquartile range; SR — standard risk; IR — intermediate risk; HR — high risk; ALLIC BFM (Berlin–Frankfurt–Munster); T-ALL — T-cell acute lymphoblastic leukemia; BCP-ALL — B-cell precursor acute lymphoblastic leukemia; BCP-ALL; WBC — white blood cells; OS — overall survival; EFS — event-free survival

the occurrence of weekend in the course of the calculated days of therapy protocol. Children with comorbidities, genetic diseases and those predestined to toxicity occurrence may present with lower OS and EFS which has been reported in some specific groups [16]. Distinguishing the most important factor contributing to worst survival may be troublesome in most cases. In our cohort, a difference in number of patients with delay in early phase of remission induction treatment according to treatment protocol was also noticed. This might suggest that a learning process of medical team in management of freshly diagnosed children with ALL could have an impact of delay in treatment. However, this needs to be validated on a large sample size.

Despite numerous investigations in the topic of children acute lymphoblastic leukemia, only a few analyses concerning chemotherapy delay and its association with survival have been conducted. The problem remains to be poorly understood and requires further multi center studies in order to determine its clinical importance.

Conclusion

The ALL treatment protocols have a very specific time regulation that should be strictly followed as delay in specific moments in early phases of treatment protocol may lead to worst patients' survival.

Authors' contributions

Wojciech Młynarski conceived the presented idea and supervised the project. Kaja Michalczyk, Maciej Cichosz, Maciej Zdunek gathered the necessary data, Wojciech Młynarski enabled the access to required databases and proposed the direction of investigation. Anna Puła conducted the statistical analysis (Kaplan-Meier curves, univariate Cox proportional hazards regression modelling). Anna Puła, Maciej Zdunek wrote the manuscript under supervision from Wojciech Młynarski.

Conflict of interest

The authors have no conflict of interest to declare.

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None.

Ethics

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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Kikuchi-Fujimoto disease: potential immune-mediated pathogenesis, a rare case and literature review

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Introduction

Kikuchi-Fujimoto is a rare, benign disease characterized by necrotizing lymphadenopathy. It is categorized as a reactive lymphadenopathy with paracortical hyperplasia. It usually presents with a painful enlarged cervical lymph node, but less frequently other superficial lymph nodes may also be involved. Early non-specific follicular hyperplasia with later prominent paracortical apoptosis surrounded by histiocytes and plasmacytoid monocytes with lack of neutrophils are the typical histopathological features. When the areas of necrosis and apoptosis are large, they may mimic other granulomatous lymphadenitis. The etiology of Kikuchi-Fujimoto disease is unclear. We here review a case of Kikuchi-Fujimoto disease and propose the immune-mediated pathogenesis for its etiology.

Case presentation

We present the case of a 25-year-old female of Caucasian descent who presented with acute tender unilateral (right) cervical lymphadenopathy that had started two weeks earlier without constitutional symptoms. The mass was first noticed with sore throat and cough and redness of the skin over it. The patient's past medical history was significant with having had asthma, recurrent bronchitis and multiple food allergies. A family history of diabetes was noted in her maternal grandfather. The patient described that the mass had gradually enlarged. The current unilateral neck pain was not continuous since the start, but was worsened by palpation. She denied any recent travel. On physical exam, her neck had a normal range of motion. There was a palpable, rubbery, well-circumscribed mass 2 × 1.7 × 1.5 cm close to the angle of the mandible on the right side of the neck. The mass was movable, with no adhesion to the skin or underlying soft tissue. On lab exam, white blood cell level and acute phase reactant were normal. Antinuclear antibodies (ANA) was negative. An excisional biopsy was performed. The mass appeared as a large lymph node. A portion of it was submitted for flow cytometry and the rest was submitted for histopathological review. Flow cytometry did not identify any clonal B- or T-cell populations. Histology showed sections of a lymph node with architectural distortion with areas of necrosis in both the paracortical and inter-follicular areas (Figures 1 and 2). Karyorrhexis, fibrin deposits and scattered histiocytic infiltration were noted. No neutrophils or eosinophils in the necrotic area were seen. Immunohistochemistry did not highlight any lymphoproliferative lesion. Mycobacterial and fungal stains were also negative. The diagnosis of Kikuchi-Fujimoto disease was confirmed after ruling out other possibilities.

Discussion

Kikuchi-Fujimoto disease is a rare, self-limited disease that is most frequently seen in young Asian women [1]. A literature review showed that concomitant asthma and other allergic related diseases (e.g. allergic rhinitis) with Kikuchi-Fujimoto disease have previously been seen [1–3]. Also, associations with other autoimmune diseases such as systemic lupus erythematosus (SLE) and Sjogren's syndrome have been noted [4, 5]. In up to 30% of cases, the onset of Kikuchi-Fujimoto disease starts before the onset of SLE [6].

Our current case also had a history of asthma. Even though the pathogenesis of Kikuchi-Fujimoto disease is unclear, an association between the host immune response and allergic reaction should be considered as one possible factor.

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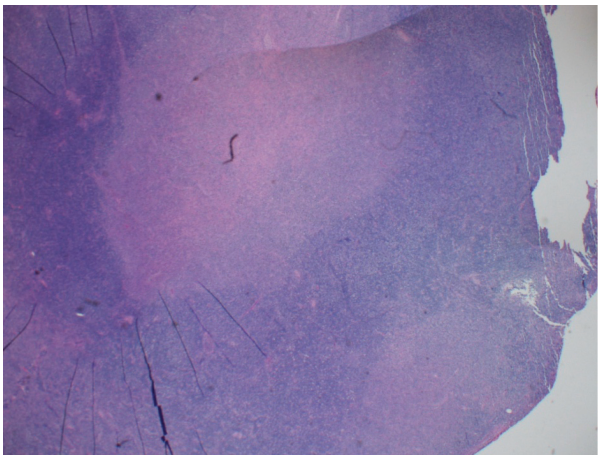

Figure 1. Lymph node with architectural distortion with pale areas (4× magnification)

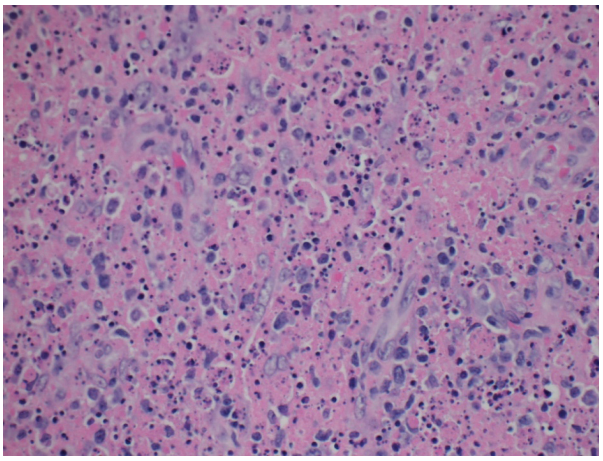

Figure 2. The pale areas composed of histocytes, eosinophilic granular material and abundant karyorrhectic debris with few plasmacytoid dendritic cells. No neutrophils present (40× magnification)

Authors' contributions

PSP — sole author.

Conflict of interest

There is no conflict of interest.

Financial support

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Ethics

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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YESCARTA® ▼
(aksykabtagen cyloleucel)

▼ 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.

1. NAZWA PRODUKTU LECZNICZEGO: Yescarta, 0,4-2 $\times$ 10^8 komórek, dyspersja do infuzji. **2. SKŁAD JAKOŚCIOWY I ILOŚCIOWY: 2.1 Opis ogólny:** Yescarta (aksykabtagen cyloleucel) to genetycznie zmodyfikowane autologiczne limfocyty T skierowane przeciw CD19 stosowane w immunoterapii. Aby przygotować produkt Yescarta, od pacjenta pobiera się limfocyty T, które są następnie genetycznie modyfikowane w warunkach *ex vivo* metodą transdukcji retrowirusowej w celu uzyskania ekspresji chimerowego receptora antygenowego (ang. *chimeric antigen receptor*, CAR) zawierającego mysi jednołańcuchowy fragment Fv anty-CD19 połączony z domeną kostymulującą CD-28 i domeną sygnalizacyjną CD3-zeta. Żywotne limfocyty CAR-T anty-CD19 są namnażane i z powrotem wprowadzane za pomocą infuzji do organizmu pacjenta, gdzie mogą rozpoznawać i eliminować komórki docelowe prezentujące CD19. **2.2 Skład jakościowy i ilościowy:** Każdy worek do jednorazowej infuzji ze swoistym dla danego pacjenta produktem Yescarta zawiera około 68 ml dyspersji limfocytów CAR-T anty-CD19, co umożliwia otrzymanie docelowej dawki wynoszącej 2 $\times$ 10^6 żywotnych limfocytów CAR-T anty-CD19/kg masy ciała (zakres od 1 $\times$ 10^6 do 2 $\times$ 10^6 limfocytów/kg) z maksymalną liczbą limfocytów CAR-T anty-CD19 wynoszącą 2 $\times$ 10^8. <u>Substancje pomocnicze o znanym działaniu:</u> Każdy worek z produktem Yescarta zawiera 300 mg sodu. Pełny wykaz substancji pomocniczych, patrz punkt 6.1 ChPL. **3. POSTAĆ FARMACEUTYCZNA:** Dyspersja do infuzji. Klarowna do opalizującej dyspersja w kolorze od białego do czerwonego. **4. SZCZEGÓŁOWE DANE KLINICZNE: 4.1 Wskazania do stosowania:** Produkt Yescarta jest wskazany w leczeniu nawrotowego lub opornego na leczenie chłoniaka rozlanego z dużych komórek B (ang. *diffuse large B-cell lymphoma*, DLBCL) i pierwotnego chłoniaka śródpiersia z dużych komórek B (ang. *primary mediastinal large B-cell lymphoma*, PMBCL) u dorosłych pacjentów, którzy uprzednio otrzymali co najmniej dwie linie leczenia systemowego. **4.2 Dawkowanie i sposób podawania:** Produkt Yescarta musi być podawany w kwalifikowanym ośrodku leczniczym przez lekarza mającego doświadczenie w leczeniu złośliwych nowotworów krwi oraz przeszkolonego w zakresie podawania i leczenia pacjentów produktem Yescarta. Na wypadek wystąpienia zespołu uwalniania cytokin (ang. *cytokine release syndrome*, CRS) przed infuzją musi być dostępna przynajmniej 1 dawka tocilizumabu i sprzęt ratunkowy. Ośrodek, w którym odbywa się leczenie musi mieć zapewniony dostęp do dodatkowej dawki tocilizumabu w ciągu 8 godzin od uprzedniego podania każdej dawki. W wyjątkowej sytuacji braku dostępności tocilizumabu uwzględnionym w wykazie produktów leczniczych zagrożonych brakiem dostępności Europejskiej Agencji Leków przed rozpoczęciem infuzji muszą być dostępne odpowiednie, alternatywne leki do leczenia CRS zamiast tocilizumabu. <u>Dawkowanie:</u> Yescarta to produkt przeznaczony wyłącznie do stosowania autologicznego (patrz punkt 4.4). Pojedyncza dawka produktu Yescarta zawiera 2 $\times$ 10^6 żywotnych limfocytów CAR-T na kilogram masy ciała (lub maksymalnie 2 $\times$ 10^8 żywotnych limfocytów CAR-T dla pacjentów o masie ciała równej 100 kg i większej) w około 68 ml dyspersji w worku do infuzji. Należy potwierdzić dostępność produktu Yescarta przed rozpoczęciem limfodeplecji. *Leczenie wstępne (chemioterapia limfodeplecyjna):* W 5., 4. i 3. dniu przed infuzją produktu Yescarta należy zastosować chemioterapię limfodeplecyjną, składającą się z cyklofosfamidu w dawce 500 mg/m^2 podawanego dożylnie i fludarabiny w dawce 30 mg/m^2 podawanej dożylnie. *Premedykacja:* Zaleca się podanie paracetamolu w dawce 500-1000 mg doustnie i difenhydraminy w dawce 12,5 do 25 mg dożylnie lub doustnie (lub równoważnej) na około 1 godzinę przed infuzją produktu Yescarta. Nie zaleca się podawania ogólnoustrojowych kortykosteroidów w ramach profilaktyki, ponieważ mogą mieć wpływ na działanie produktu Yescarta. *Monitorowanie:* Po infuzji pacjentów należy monitorować codziennie przez pierwsze 10 dni po infuzji pod kątem objawów przedmiotowych i podmiotowych potencjalnego CRS, zdarzeń neurologicznych i innych toksyczności. Lekarze powinni rozważyć hospitalizację pacjenta przez pierwsze 10 dni po infuzji lub w momencie pojawienia się pierwszych objawów przedmiotowych lub podmiotowych CRS i (lub) zdarzeń neurologicznych. Po pierwszych 10 dniach od infuzji o monitorowaniu pacjenta zdecyduje lekarz. Pacjentów należy poinformować o konieczności pozostania w pobliżu kwalifikowanej placówki klinicznej przez co najmniej 4 tygodnie po infuzji. <u>Specjalne grupy pacjentów:</u> *Pacjenci z zakażeniem ludzkim wirusem niedoboru odporności (ang. human immunodeficiency virus, HIV), wirusowym zapaleniem wątroby typu B (ang. hepatitis B virus, HBV) oraz wirusowym zapaleniem wątroby typu C (ang. hepatitis C virus, HCV):* Brak doświadczenia klinicznego ze stosowaniem u pacjentów z aktywnym zakażeniem HIV, HBV lub HCV. *Dzieci i młodzież:* Nie określono jeszcze bezpieczeństwa stosowania ani skuteczności produktu leczniczego Yescarta u dzieci i młodzieży w wieku poniżej 18 lat. Dane nie są dostępne. *Osoby w podeszłym wieku:* Nie jest wymagane dostosowywanie dawki u pacjentów w wieku 65 lat i starszych. Skuteczność leczenia była zgodna ze skutecznością leczenia w całej leczonej populacji pacjentów. <u>Sposób podawania:</u> Produkt Yescarta jest podawany drogą infuzji dożylnej. Produktu Yescarta nie wolno naświetlać. NIE używać filtra do deplecji leukocytów. *Środki ostrożności, które należy podjąć przed użyciem lub podaniem produktu leczniczego:* Ten produkt leczniczy zawiera genetycznie zmodyfikowane ludzkie komórki krwi. Fachowy personel medyczny przygotowujący produkt Yescarta powinien stosować odpowiednie środki ostrożności (nosić rękawice i okulary), aby uniknąć potencjalnego przeniesienia chorób zakaźnych. *Przygotowanie do infuzji:* Zweryfikować zgodność tożsamości pacjenta (ang. *identity,* ID) z oznaczeniami na kasecie z produktem Yescarta. Nie wolno wyjmować worka z produktem Yescarta z metalowej kasety, gdy brak zgodności informacji na etykiecie dotyczącej danego pacjenta z danymi pacjenta, dla którego przeznaczony jest ten produkt. Po potwierdzeniu ID pacjenta wyjąć worek z produktem Yescarta z metalowej kasety. Sprawdzić, czy dane pacjenta na etykiecie metalowej kasety są zgodne z danymi na etykiecie worka. Przed rozmrożeniem sprawdzić, czy worek z produktem nie ma jakichkolwiek uszkodzeń. W razie uszkodzenia worka postępować zgodnie z lokalnymi wytycznymi dotyczącymi postępowania z odpadami materiałów pochodzenia ludzkiego (lub niezwłocznie przekazać informację do firmy Kite). Umieścić worek do infuzji w drugim worku. Rozmrozić produkt Yescarta w temperaturze wynoszącej około 37°C w kąpieli wodnej lub metodą suchego rozmrażania do momentu, gdy w worku infuzyjnym nie będzie widocznego lodu. Delikatnie wymieszać zawartość worka, aby rozprowadzić grudki materiału komórkowego. Jeśli nadal widoczne są grudki materiału komórkowego, kontynuować delikatne mieszanie zawartości worka. Powinno to doprowadzić do rozproszenia małych grudek materiału komórkowego. Produktu Yescarta nie należy myć, wirować ani powtórnie odtwarzać zawiesiny na nowych nośnikach przed infuzją. Rozmrażanie powinno trwać około 3 do 5 minut. Po rozmrożeniu produkt Yescarta zachowuje trwałość w temperaturze pokojowej (od 20°C do 25°C) do 3 godzin. Infuzję produktu Yescarta należy jednak rozpocząć w ciągu 30 minut od rozmrożenia. *Podawanie:* Tylko do stosowania autologicznego. Tocilizumab oraz sprzęt ratunkowy powinny być dostępne przed infuzją i podczas monitorowania. W wyjątkowej sytuacji braku dostępności tocilizumabu uwzględnionym w wykazie produktów leczniczych zagrożonych brakiem dostępności Europejskiej Agencji Leków przed rozpoczęciem infuzji muszą być dostępne odpowiednie, alternatywne leki do leczenia CRS zamiast tocilizumabu. Nie wolno używać filtra do deplecji leukocytów. Zaleca się założenie centralnego dostępu żylnego w celu podania produktu Yescarta. Ponownie zweryfikować ID pacjenta w celu potwierdzenia zgodności z oznaczeniami pacjenta na worku z produktem Yescarta. Przed infuzją wypełnić zestaw do infuzji roztworem chlorku sodu (0,154 mmol sodu/ml). Cała zawartość worka z produktem Yescarta powinna zostać podana w infuzji w ciągu 30 minut metodą grawitacyjną lub z użyciem objętościowej pompy infuzyjnej. Delikatnie masować worek podczas infuzji produktu Yescarta, aby zapobiec tworzeniu się grudek materiału komórkowego. Po podaniu w infuzji całej zawartości worka, przepłukać zestaw do infuzji roztworem chlorku sodu (0,154 mmol sodu/ml) z tą samą prędkością infuzji, aby upewnić się, że produkt Yescarta został podany w całości. Instrukcja dotycząca postępowania, przypadkowego narażenia oraz usuwania tego produktu, patrz punkt 6.6 ChPL.
4.3 Przeciwwskazania: Nadwrażliwość na substancję czynną lub którąkolwiek substancję pomocniczą wymienioną w punkcie 6.1 ChPL. Należy uwzględnić przeciwwskazania dotyczące chemioterapii limfodeplecyjnej. **4.4 Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania:** <u>Identyfikowalność:</u> Należy bezwzględnie przestrzegać wymogów identyfikowalności produktów leczniczych stosowanych w zaawansowanych terapiach komórkowych. Aby zapewnić identyfikowalność nazwę produktu leczniczego, numer serii oraz imię i nazwisko leczonego pacjenta należy przechowywać przez okres 30 lat po upłynięciu terminu ważności produktu. <u>Ogólne:</u> Produkt Yescarta jest przeznaczony wyłącznie do stosowania autologicznego i nie wolno podawać go innym pacjentom. Przed infuzją: tożsamość pacjenta musi być zgodna z danymi identyfikacyjnymi na worku infuzyjnym i kasecie z produktem Yescarta. Nie należy podawać infuzji produktu Yescarta, gdy informacja na etykiecie dotyczącej danego pacjenta nie jest zgodna z danymi pacjenta, dla którego przeznaczony jest produkt. Pacjentów należy monitorować codziennie przez pierwsze 10 dni po infuzji w celu wykrycia przedmiotowych i podmiotowych objawów potencjalnego CRS, zdarzeń neurologicznych i innych toksyczności. Lekarze powinni rozważyć hospitalizację pacjenta przez pierwsze 10 dni po infuzji lub w momencie wystąpienia pierwszych objawów przedmiotowych/podmiotowych CRS i (lub) zdarzeń neurologicznych. Po pierwszych 10 dniach po infuzji o monitorowaniu pacjenta zdecyduje lekarz. Należy poinformować pacjentów o konieczności pozostawania w pobliżu kwalifikowanego ośrodka leczniczego przez co najmniej 4 tygodnie po infuzji oraz o konieczności uzyskania natychmiastowej pomocy medycznej w razie wystąpienia przedmiotowych lub podmiotowych objawów CRS lub neurologicznych działań niepożądanych. W zależności od stopnia nasilenia danego działania niepożądanego należy rozważyć monitorowanie parametrów życiowych i czynności narządów. <u>Powody odroczenia leczenia:</u> Ze względu na zagrożenia związane z leczeniem produktem Yescarta podanie infuzji należy wstrzymać, jeśli u pacjenta występuje którykolwiek z następujących stanów: utrzymujące się ciężkie działania niepożądane (w szczególności działania dotyczące płuc, serca lub niedociśnienie), w tym związane z wcześniejszymi chemioterapiami; czynne, niekontrolowane zakażenie; czynna choroba przeszczep przeciwko gospodarzowi (ang. *graft-versus-host disease*, GVHD). <u>Badania serologiczne:</u> Przed pobraniem komórek do wytworzenia produktu Yescarta, należy wykonać badania przesiewowe na obecność HBV, HCV i HIV (patrz punkt 4.2). <u>Oddawanie krwi, narządów, tkanek i komórek:</u> Pacjenci leczeni produktem Yescarta nie powinni być dawcami krwi, narządów, tkanek ani komórek do przeszczepienia. <u>Choroba współistniejąca:</u> Pacjenci z czynnym zaburzeniem OUN lub z zaburzeniami czynności nerek, wątroby, płuc lub serca mogą być bardziej podatni na skutki działań niepożądanych opisanych poniżej i wymagają szczególnej uwagi. <u>Pierwotny chłoniak ośrodkowego układu nerwowego (OUN):</u> Brak doświadczenia związanego ze stosowaniem produktu Yescarta u pacjentów z pierwotnym chłoniakiem OUN. W związku z tym nie określono stosunku ryzyka do korzyści leczenia produktem Yescarta dla tej populacji. <u>Zespół uwalniania cytokin:</u> U prawie wszystkich pacjentów wystąpił CRS któregoś stopnia. W przypadku stosowania produktu Yescarta bardzo często stwierdzano ciężkie przypadki CRS, w tym reakcje zagrażające życiu i prowadzące do zgonu, a czas do ich wystąpienia wynosił od 1 do 12 dni (patrz punkt 4.8). O leczeniu CRS decyduje lekarz na podstawie występujących u pacjenta objawów klinicznych oraz zgodnie z algorytmem postępowania w CRS przedstawionym w tabeli 1. W leczeniu CRS o nasileniu umiarkowanym lub ciężkim, związanego z podaniem produktu Yescarta, stosowano terapię opartą na inhibitorze receptora interleukiny 6 (IL-6), takim jak tocilizumab. Ośrodek, w którym odbywa się infuzja produktu Yescarta, musi przystępując do niej dysponować co najmniej 1 dostępną do podania dawką tocilizumabu dla każdego pacjenta. Ośrodek, w którym odbywa się leczenie, musi mieć dostęp do dodatkowej dawki tocilizumabu w ciągu 8 godzin od podania każdej z uprzednich dawek. W wyjątkowej sytuacji braku dostępności tocilizumabu uwzględnionym w wykazie produktów leczniczych zagrożonych brakiem dostępności Europejskiej Agencji Leków ośrodek leczniczy musi mieć dostęp do odpowiednich, alternatywnych leków do leczenia CRS zamiast tocilizumabu. Pacjentów należy codziennie monitorować w kwalifikowanej placówce klinicznej przez co najmniej 10 dni po infuzji pod kątem objawów przedmiotowych i podmiotowych CRS. Po upływie pierwszych 10 dni od infuzji o monitorowaniu pacjentów zdecyduje lekarz. Należy poinformować pacjentów o konieczności pozostawania w pobliżu kwalifikowanej placówki klinicznej przez co najmniej 4 tygodnie po infuzji oraz o konieczności uzyskania natychmiastowej pomocy medycznej w razie wystąpienia objawów przedmiotowych lub podmiotowych CRS. Opracowano algorytmy postępowania mające na celu łagodzenie niektórych objawów CRS występujących u pacjentów przyjmujących produkt Yescarta. Obejmują one stosowanie tocilizumabu lub tocilizumabu z kortykosteroidami w przypadkach CRS o nasileniu umiarkowanym, ciężkim lub zagrażającym życiu, jak przedstawiono w tabeli 1. Pacjentów, u których wystąpi CRS w stopniu 2. lub wyższym (np. niedociśnienie, brak odpowiedzi po podaniu płynów lub hipoksja wymagająca podania dodatkowego tlenu), należy monitorować z wykorzystaniem ciągłej telemetrii kardiologicznej oraz pulsoksymetrii. U pacjentów z ciężkim CRS należy rozważyć wykonanie echokardiogramu w celu oceny czynności serca. W przypadku ciężkiego lub zagrażającego życiu CRS należy rozważyć wdrożenie intensywnej terapii w ramach leczenia wspomagającego. Produktu Yescarta nie należy podawać pacjentom, u których występuje czynne zakażenie lub choroba zapalna, dopóki stany te nie ustąpią. Wiadomo, że CRS jest związany z niewydolnością narządów docelowych (np. wątroby, nerek, serca i płuc). Ponadto w przebiegu CRS może dojść do nasilenia występujących zaburzeń tych narządów. U pacjentów z istotnymi klinicznie zaburzeniami kardiologicznymi należy stosować standardy opieki w stanach krytycznych oraz rozważyć takie środki, jak echokardiografia. W celu rozpoznania CRS należy wykluczyć inne przyczyny ogólnoustrojowej odpowiedzi zapalnej, w tym zakażenie. W razie wystąpienia gorączki neutropenicznej należy dokonać oceny pod kątem zakażenia i zastosować antybiotyki o szerokim spektrum działania, płyny oraz leczenie podtrzymujące zgodnie z istniejącymi wskazaniami medycznymi. W przypadku pacjentów z ciężkim lub nieodpowiadającym na leczenie CRS należy rozważyć możliwość wystąpienia limfohistiocytozy hemofagocytarnej/zespołu aktywacji makrofagów (ang. *haemophagocytic lymphohistiocytosis/macrophage activation syndrome*, HLH/MAS). Produkt Yescarta nadal rozprzestrzenia się i utrzymuje w organizmie po podaniu tocilizumabu oraz kortykosteroidów. Nie zaleca się stosowania antagonistów czynnika martwicy nowotworu (ang. *tumour necrosis factor*, TNF) w leczeniu CRS związanego z zastosowaniem produktu Yescarta. **Tabela 1: Algorytm postępowania w zespole uwalniania cytokin (CRS).** Nasilenie CRS[a]: <u>Stopień 1.:</u> Objawy wymagają zastosowania tylko leczenia objawowego (np. gorączka, nudności, zmęczenie, ból głowy, ból mięśni, złe samopoczucie). *Tocilizumab:* W razie braku poprawy po 24 godzinach postępować jak w stopniu 2. *Kortykosteroidy:* N/A. <u>Stopień 2.:</u> Objawy wymagają umiarkowanej interwencji, po której ustępują. Zapotrzebowanie na tlen wynoszące mniej niż 40% FiO_2 lub hipotensja odpowiadająca na podanie płynów lub małej dawki jednego leku wazopresyjnego, lub toksyczność narządowa 2. stopnia[b]. *Tocilizumab:* Podać tocilizumab[c] w dawce 8 mg/kg dożylnie przez 1 godzinę (nie przekraczać dawki 800 mg). W razie potrzeby podawać tocilizumab co 8 godzin, gdy brak odpowiedzi na dożylne podanie płynów lub rośnie zapotrzebowanie na tlenoterapię. Nie podawać więcej niż 3 dawki w ciągu 24 godzin; maksymalna całkowita liczba dawek to 4 dawki, jeśli brak poprawy klinicznej dotyczącej objawów przedmiotowych i podmiotowych CRS lub jeśli brak odpowiedzi na drugą lub kolejną dawkę tocilizumabu, należy rozważyć zastosowanie alternatywnych sposobów leczenia CRS. *Kortykosteroidy:* Leczenie jak w stopniu 3., gdy brak poprawy w ciągu 24 godzin od podania tocilizumabu. <u>Stopień 3.:</u> Objawy wymagają poważnej interwencji, po której ustępują. Zapotrzebowanie na tlen przekraczające lub równe 40% FiO_2 lub hipotensja wymagająca podania dużej dawki leku wazopresyjnego albo zastosowania wielu leków wazopresyjnych, lub toksyczność narządowa 3. stopnia, albo hipertransaminazemia 4. stopnia. *Tocilizumab:* Leczenie jak w stopniu 2. *Kortykosteroidy:* Podać metyloprednizolon dożylnie w dawce 1 mg/kg dwa razy na dobę lub równoważną dawkę deksametazonu (np. 10 mg dożylnie co 6 godzin). Kontynuować podawanie kortykosteroidów do momentu, gdy zdarzenie zostanie zakwalifikowane jako zdarzenie stopnia 1. lub mniejszego, a następnie stopniowo zmniejszać dawkę. Gdy brak poprawy, zastosować leczenie jak w stopniu 4. (poniżej). <u>Stopień 4.:</u> Objawy zagrażające życiu. Pacjent wymaga zastosowania respiratora lub ciągłej hemodializy żylno-żylnej, lub toksyczność narządowa 4. stopnia (z wyjątkiem hipertransaminazemii). *Tocilizumab:* Leczenie jak w stopniu 2. *Kortykosteroidy:* Podawać metyloprednizolon dożylnie w dawce dobowej 1000 mg przez 3 dni, gdy jest poprawa – stosować leczenie jak powyżej. Rozważyć podanie innych leków immunosupresyjnych, gdy brak poprawy lub pogorszenie stanu. N/A = brak/nie dotyczy. *(a) Lee et al 2014. (b) Leczenie neurologicznych działań niepożądanych – patrz Tabela 2. (c) Szczegółowe informacje można znaleźć w charakterystyce produktu leczniczego tocilizumabu.* <u>Neurologiczne działania niepożądane:</u> U pacjentów leczonych produktem Yescarta bardzo często obserwowano ciężkie neurologiczne działania niepożądane, które mogą zagrażać życiu lub prowadzić do zgonu (patrz punkt 4.8). Pacjenci z zaburzeniami OUN w wywiadzie, takimi jak drgawki lub niedokrwienie naczyniowo-mózgowe, mogą być narażeni na większe ryzyko. Zgłaszano przypadki zakończonego zgonem i ciężkiego obrzęku mózgu u pacjentów leczonych produktem Yescarta. Pacjentów należy monitorować pod kątem objawów przedmiotowych i podmiotowych neurologicznych działań niepożądanych (Tabela 2). Po infuzji pacjentów należy monitorować w kwalifikowanej placówce opieki zdrowotnej co najmniej codziennie przez pierwsze 10 dni pod kątem objawów przedmiotowych i podmiotowych toksyczności neurologicznej. Po tych pierwszych 10 dniach o monitorowaniu pacjenta zdecyduje lekarz. Pacjentów należy poinformować o konieczności pozostania w pobliżu kwalifikowanej placówki klinicznej przynajmniej przez 4 tygodnie po infuzji i natychmiastowego zwrócenia się po pomoc medyczną, jeśli wystąpią objawy przedmiotowe lub podmiotowe toksyczności neurologicznej. W zależności od stopnia nasilenia danego działania niepożądanego należy rozważyć monitorowanie parametrów życiowych i wydolności narządów. Pacjentów, u których wystąpi toksyczność neurologiczna stopnia 2. lub wyższego, należy monitorować z wykorzystaniem ciągłej telemetrii kardiologicznej oraz pulsoksymetrii. W razie ciężkiej lub zagrażającej życiu toksyczności neurologicznej należy wdrożyć intensywną terapię wspomagającą. Należy rozważyć podanie leków przeciwdrgawkowych niemających działania uspokajającego w ramach profilaktyki przeciwdrgawkowej zgodnie ze wskazaniami klinicznymi dla działań niepożądanych 2. lub wyższego stopnia. Opracowano algorytmy postępowania mające na celu złagodzenie neurologicznych działań niepożądanych występujących u pacjentów przyjmujących produkt Yescarta. Obejmują one stosowanie tocilizumabu (w razie współistniejącego CRS) i (lub) kortykosteroidów w przypadku umiarkowanych, ciężkich lub zagrażających życiu neurologicznych działań niepożądanych, jak przedstawiono w tabeli 2. **Tabela 2: Algorytmy postępowania dotyczące objawów neurologicznych działań niepożądanych.** <u>Stopień 2.:</u> Rozważyć podanie leków przeciwdrgawkowych bez działania uspokajającego (tj. lewetyracetam) w ramach profilaktyki przeciwdrgawkowej. *Współistniejący CRS:* Podać tocilizumab jak w tabeli 1 dla CRS stopnia 2. Gdy brak poprawy w ciągu 24 godzin po podaniu tocilizumabu: podać deksametazon dożylnie w dawce 10 mg co 6 godzin, jeśli pacjent nie przyjmuje już innych kortykosteroidów. Kontynuować podawanie deksametazonu, dopóki zdarzenie nie zostanie zakwalifikowane jako zdarzenie stopnia 1. lub mniejszego, a wówczas stopniowo zmniejszać dawkę. *Bez współistniejącego CRS:* Podawać deksametazon dożylnie w dawce 10 mg co 6 godzin. Kontynuować podawanie deksametazonu, dopóki zdarzenie nie zostanie zakwalifikowane jako zdarzenie stopnia 1. lub mniejszego, a wówczas stopniowo zmniejszać dawkę. <u>Stopień 3.:</u> Rozważyć podanie leków przeciwdrgawkowych bez działania uspokajającego (tj. lewetyracetam) w ramach profilaktyki przeciwdrgawkowej. *Współistniejący CRS:* Podać tocilizumab jak w tabeli 1 dla CRS stopnia 2. Dodatkowo z pierwszą dawką tocilizumabu podać deksametazon dożylnie w dawce 10 mg, powtarzając co 6 godzin. Kontynuować podawanie deksametazonu, dopóki zdarzenie nie zostanie zakwalifikowane jako zdarzenie stopnia 1. lub mniejszego, a wówczas stopniowo zmniejszać dawkę. *Bez współistniejącego CRS:* Podawać deksametazon dożylnie w dawce 10 mg co 6 godzin. Kontynuować podawanie deksametazonu, dopóki zdarzenie nie zostanie zakwalifikowane jako zdarzenie stopnia 1. lub mniejszego, a wówczas stopniowo zmniejszać dawkę. <u>Stopień 4.:</u> Rozważyć podanie leków przeciwdrgawkowych bez działania uspokajającego (tj. lewetyracetam) w ramach profilaktyki przeciwdrgawkowej. *Współistniejący CRS:* Podać tocilizumab jak w tabeli 1 dla CRS stopnia 2. Wraz z pierwszą dawką tocilizumabu podać metyloprednizolon dożylnie w dobowej dawce 1000 mg oraz kontynuować podawanie metyloprednizolonu dożylnie w dobowej dawce 1000 mg przez 2 kolejne dni; w przypadku poprawy stosować leczenie jak powyżej. Gdy brak poprawy, rozważyć podanie metyloprednizolonu 1000 mg dożylnie 3 razy na dobę lub alternatywne leczenie[a]. *Bez współistniejącego CRS:* Podawać metyloprednizolon dożylnie w dawce dobowej 1000 mg przez 3 dni, gdy poprawa – stosować leczenie jak powyżej. Gdy brak poprawy, rozważyć podanie metyloprednizolonu 1000 mg dożylnie 3 razy na dobę lub alternatywne leczenie[a]. *(a) Alternatywne leczenie obejmuje (między innymi): anakinrę, siltuksymab, ruksolitynib, cyklofosfamid, immunoglobuliny podawane dożylnie* (*ang. intravenous immunoglobulin,* IVIG) *oraz globulinę anty-tymocytarną* (*ang. anti-thymocyte globulin,* ATG). <u>Zakażenia i gorączka neutropeniczna:</u> Podczas stosowania produktu Yescarta bardzo często obserwowano ciężkie zakażenia (patrz punkt 4.8). Pacjentów należy monitorować pod kątem objawów przedmiotowych i podmiotowych zakażenia przed, w trakcie i po podaniu produktu Yescarta w infuzji oraz zastosować odpowiednie leczenie. Należy zastosować profilaktykę przeciwbakteryjną zgodnie z obowiązującymi standardowymi wytycznymi. Po infuzji produktu Yescarta u pacjentów stwierdzano gorączkę neutropeniczną (patrz punkt 4.8) i może ona występować jednocześnie z CRS. W przypadku wystąpienia gorączki neutropenicznej należy ocenić, czy nie jest to zakażenie, i zastosować antybiotyki o szerokim spektrum działania, płyny oraz leczenie objawowe zgodnie ze wskazaniami medycznymi. <u>Reaktywacja HBV:</u> U pacjentów leczonych lekami skierowanymi przeciwko limfocytom B może dojść do reaktywacji HBV, w niektórych przypadkach prowadzącej do piorunującego zapalenia wątroby, niewydolności wątroby i zgonu. Przed pobraniem komórek do wytworzenia produktu Yescarta należy przeprowadzić badanie przesiewowe w kierunku HBV, HCV i HIV. <u>Przedłużająca się cytopenia:</u> Po chemioterapii limfodeplecyjnej i infuzji produktu Yescarta u pacjentów przez kilka tygodni może występować cytopenia. Odnotowano bardzo częste występowanie przedłużającej się cytopenii stopnia 3. lub wyższego, w tym małopłytkowość, neutropenię i niedokrwistość, po infuzji produktu Yescarta. Należy monitorować wyniki badań morfologii krwi po infuzji produktu Yescarta. <u>Hipogammaglobulinemia:</u> U pacjentów leczonych produktem Yescarta może wystąpić aplazja limfocytów B, prowadząca do hipogammaglobulinemii. Hipogammaglobulinemię obserwowano bardzo często u pacjentów leczonych produktem Yescarta. Należy monitorować stężenie immunoglobulin po leczeniu produktem Yescarta oraz stosować leczenie obejmujące profilaktykę zakażeń, profilaktykę antybiotykową oraz immunoglobulinową terapię zastępczą. <u>Reakcje nadwrażliwości:</u> Po infuzji produktu Yescarta mogą wystąpić reakcje alergiczne. Ciężkie reakcje nadwrażliwości, w tym reakcja anafilaktyczna, mogą być spowodowane obecnością dimetylosulfotlenku (ang. *dimethylsulfoxide*, DMSO) lub resztkowej gentamycyny w produkcie Yescarta. <u>Wtórne nowotwory złośliwe:</u> U pacjentów leczonych produktem Yescarta mogą rozwinąć się wtórne nowotwory złośliwe. Pacjentów należy monitorować przez całe życie pod kątem wtórnych nowotworów złośliwych. W razie pojawienia się wtórnego nowotworu złośliwego należy skontaktować się z firmą w celu uzyskania instrukcji dotyczących pobrania od pacjenta próbek do badań. <u>Zespół rozpadu guza (ang. *tumour lysis syndrome*, TLS):</u> Rzadko obserwowano występowanie TLS, który może mieć ciężką postać. W celu zminimalizowania ryzyka wystąpienia TLS pacjenci ze zwiększonym stężeniem kwasu moczowego lub dużą łączną masą guza powinni otrzymywać allopurynol lub inne leczenie profilaktyczne przed infuzją produktu Yescarta. Pacjentów należy monitorować pod kątem przedmiotowych i podmiotowych objawów TLS, a objawy należy leczyć zgodnie ze standardowymi wytycznymi. <u>Wcześniejsze leczenie terapią anty-CD19:</u> Doświadczenie związane ze stosowaniem produktu Yescarta u pacjentów, którzy wcześniej otrzymali leczenie celowane przeciwko CD19, jest ograniczone. Nie zaleca się stosowania produktu Yescarta, jeśli u pacjenta nastąpił nawrót choroby bez ekspresji CD19 po uprzedniej terapii anty-CD19. <u>Substancje pomocnicze:</u> Ten produkt leczniczy zawiera 300 mg sodu na worek infuzyjny, co odpowiada 15% maksymalnego dziennego dopuszczalnego spożycia sodu, wynoszącego 2 g dla osoby dorosłej, zgodnie z zaleceniami WHO. Oczekuje się, że pacjenci zostaną wpisani do rejestru pacjentów, na podstawie którego prowadzona będzie obserwacja w celu lepszego poznania długoterminowego bezpieczeństwa stosowania i skuteczności produktu Yescarta. **4.8 Działania niepożądane:** <u>Podsumowanie profilu bezpieczeństwa:</u> Dane dotyczące bezpieczeństwa opisane w tym punkcie odzwierciedlają skutki narażenia na produkt Yescarta w badaniu fazy I/II ZUMA-1, w którym 108 pacjentów z nawrotowym/opornym chłoniakiem nieziarniczym (NHL) z limfocytów B otrzymywało limfocyty CAR-T w zalecanej dawce w zależności od masy ciała. Mediana okresu obserwacji wyniosła 27,4 miesiąca. Do najbardziej poważnych i najczęstszych działań niepożądanych należały CRS (93%), encefalopatia (58%) oraz zakażenia (39%). Ciężkie działania niepożądane wystąpiły u 56% pacjentów. Do najczęstszych działań niepożądanych należały: encefalopatia (22%), zakażenia nieswoistymi patogenami (16%), zakażenia bakteryjne (6%), gorączka neutropeniczna (6%), zakażenia wirusowe (5%) i gorączka (5%). Najczęściej występujące działania niepożądane stopnia 3. lub wyższego obejmowały encefalopatię (31%), zakażenia nieswoistymi patogenami (19%), CRS (11%), zakażenie bakteryjne (9%), afazję (7%), zakażenie wirusowe (6%), stan majaczeniowy (6%), hipotensję (6%) i nadciśnienie (6%). <u>Tabelaryczna lista działań niepożądanych:</u> Działania niepożądane zgłaszane w badaniach klinicznych oraz po wprowadzeniu produktu do obrotu przedstawiono poniżej. Działania te są wymienione według klasyfikacji układów i narządów oraz częstości występowania. Częstości występowania określone są w następujący sposób: bardzo często (≥ 1/10), często (≥ 1/100 do < 1/10), niezbyt często (≥ 1/1000 do < 1/100), rzadko (≥ 1/10 000 do < 1/1000) i bardzo rzadko (< 1/10 000). W obrębie każdej grupy o określonej częstości występowania działania niepożądane wymieniono zgodnie ze zmniejszającym się nasileniem. **Tabela 3: Działania niepożądane związane ze stosowaniem produktu Yescarta.** *Zakażenia i zakażenia pasożytnicze:* Bardzo często: zakażenia nieswoistymi patogenami, zakażenie wirusowe, zakażenie bakteryjne. Często: zakażenie grzybicze. *Zaburzenia krwi i układu chłonnego:* Bardzo często: leukopenia, neutropenia, niedokrwistość, małopłytkowość. Często: koagulopatia. *Zaburzenia układu immunologicznego:* Bardzo często: zespół uwalniania cytokin, hipogammaglobulinemia. Często: nadwrażliwość, histiocytoza hemofagocytarna. *Zaburzenia metabolizmu i odżywiania:* Bardzo często: odwodnienie, zmniejszone łaknienie, hipofosfatemia, hiponatremia, zmniejszenie masy ciała. Często: hipokalcemia, hipoalbuminemia. *Zaburzenia psychiczne:* Bardzo często: majaczenia, lęk. Często: bezsenność. *Zaburzenia układu nerwowego:* Bardzo często: encefalopatia, ból głowy, drżenie, zawroty głowy, afazja. Często: ataksja, neuropatia, drgawki, dyskalkulia, mioklonie. Niezbyt często: obrzęk rdzenia kręgowego, zapalenie rdzenia kręgowego, porażenie czterokończynowe. *Zaburzenia serca:* Bardzo często: tachykardia, arytmia. Często: zatrzymanie akcji serca, niewydolność serca. *Zaburzenia naczyniowe:* Bardzo często: niedociśnienie, nadciśnienie. Często: zakrzepica, zespół przesiąkania włośniczek. *Zaburzenia układu oddechowego, klatki piersiowej i śródpiersia:* Bardzo często: kaszel, duszność, hipoksja, wysięk opłucnowy. Często: obrzęk płuc. *Zaburzenia żołądka i jelit:* Bardzo często: biegunka, nudności, wymioty, zaparcia, ból brzucha, suchość w jamie ustnej. Często: dysfagia*. *Zaburzenia skóry i tkanki podskórnej:* Często: wysypka. *Zaburzenia układu mięśniowo-szkieletowego i tkanki łącznej:* Bardzo często: zaburzenia ruchowe, ból kończyn, ból pleców, ból stawów, ból mięśni. *Zaburzenia nerek i dróg moczowych:* Często: niewydolność nerek. *Zaburzenia ogólne i stany w miejscu podania:* Bardzo często: zmęczenie, gorączka, obrzęk, dreszcze. *Badania diagnostyczne:* Bardzo często: zwiększone stężenie aminotransferazy alaninowej, zwiększone stężenie aminotransferazy asparaginowej. Często: zwiększone stężenie bilirubiny. W tabeli 3 ujęto wyłącznie przypadki cytopenii, które spowodowały (I) wystąpienie nowych lub zaostrzenie istniejących następstw klinicznych, (II) wymagały leczenia lub (III) modyfikacji aktualnego leczenia. * Dysfagię zgłaszano w ramach toksycznego działania na układ nerwowy i encefalopatii. <u>Opis wybranych działań niepożądanych:</u> *Zespół uwalniania cytokin:* CRS wystąpił u 93% pacjentów. U jedenastu procent (11%) pacjentów wystąpił CRS stopnia 3. lub wyższego (ciężki, zagrażający życiu oraz prowadzący do zgonu). Mediana czasu do wystąpienia CRS wynosiła 2 dni (zakres od 1 do 12 dni), a mediana czasu trwania 7 dni (zakres od 2 do 29 dni). U dziewięćdziesięciu ośmiu procent pacjentów (98%) doszło do ustąpienia CRS. Najczęściej występujące objawy przedmiotowe i podmiotowe związane z CRS obejmowały gorączkę (83%), niedociśnienie (44%), tachykardię (24%), hipoksję (23%) i dreszcze (20%). Ciężkie działania niepożądane, które mogą być związane z CRS, obejmowały: ostre uszkodzenie nerek, migotanie przedsionków, tachykardię komorową, zatrzymanie akcji serca, niewydolność serca, zespół przesiąkania włośniczek, niedociśnienie, hipoksję i HLH/MAS. Wskazówki dotyczące monitorowania i leczenia – patrz punkt 4.4. *Neurologiczne działania niepożądane:* Neurologiczne działania niepożądane wystąpiły u 67% pacjentów. U trzydziestu dwóch procent (32%) pacjentów wystąpiły działania niepożądane stopnia 3. lub wyższego (ciężkie lub zagrażające życiu). Mediana czasu do wystąpienia działań niepożądanych wynosiła 5 dni (zakres od 1 do 17 dni). Mediana czasu trwania wynosiła 13 dni (zakres: od 1 do 191 dni). U większości pacjentów neurologiczne działania niepożądane ustąpiły, z wyjątkiem 4 pacjentów, u których niepożądane działania neurologiczne utrzymywały się do momentu zgonu; zgony te były spowodowane innymi przyczynami. Najczęstszymi objawami przedmiotowymi i podmiotowymi związanymi z neurologicznymi działaniami niepożądanymi były: encefalopatia (58%), ból głowy (40%), drżenie (31%), zawroty głowy (21%), afazja (18%) i stan majaczeniowy (17%). Zgłaszano ciężkie działania niepożądane, w tym encefalopatię (22%), afazję (4%), stan majaczeniowy (4%) i drgawki (1%), u pacjentów, którym podawano produkt Yescarta. Inne neurologiczne działania niepożądane były zgłaszane rzadziej w badaniach klinicznych i obejmowały dysfagię (5%), zapalenie rdzenia kręgowego (0,2%) i porażenie czterokończynowe (0,2%). W okresie po wprowadzeniu produktu do obrotu zgłoszono wystąpienie obrzęku rdzenia kręgowego, w kontekście neurotoksyczności. Wskazówki dotyczące monitorowania i leczenia – patrz punkt 4.4. *Gorączka neutropeniczna i zakażenia:* Gorączkę neutropeniczną zaobserwowano u 36% pacjentów po infuzji produktu Yescarta. Zakażenia wystąpiły u 39% pacjentów w badaniu ZUMA-1. Zakażenia stopnia 3. lub wyższego (ciężkie, zagrażające życiu lub prowadzące do zgonu) wystąpiły u 26% pacjentów. Zakażenia nieswoistymi patogenami oraz zakażenia bakteryjne i wirusowe stopnia 3. lub wyższego wystąpiły u, odpowiednio, 19%, 9% i 6% pacjentów. Najczęstszym miejscem zakażenia były drogi oddechowe. Wskazówki dotyczące monitorowania i leczenia – patrz punkt 4.4. *Przedłużająca się cytopenia:* Neutropenia (w tym gorączka neutropeniczna), niedokrwistość i małopłytkowość stopnia 3. lub wyższego wystąpiły u, odpowiednio, 80%, 45% i 40% pacjentów. Przedłużająca się (utrzymująca się w dniu 30. lub pojawiająca się w dniu 30. lub później) neutropenia, małopłytkowość i niedokrwistość stopnia 3. lub wyższego wystąpiła u, odpowiednio, 26%, 24% i 10% pacjentów. Utrzymująca się neutropenia, małopłytkowość i niedokrwistość stopnia 3. lub wyższego po dniu 93. wystąpiła u, odpowiednio, 11%, 7% i 3% pacjentów. Wskazówki dotyczące leczenia – patrz punkt 4.4. *Hipogammaglobulinemia:* W badaniu ZUMA-1 hipogammaglobulinemia wystąpiła u 16% pacjentów. Łącznie 33 (31%) ze 108 pacjentów otrzymywało dożylne leczenie immunoglobulinami w momencie przeprowadzania analizy po 24 miesiącach. Wskazówki dotyczące leczenia – patrz punkt 4.4. <u>Immunogenność:</u> Immunogenność produktu Yescarta oceniano za pomocą testu immunoenzymatycznego (ELISA) wykrywającego przeciwciała wiążące FMC63, z których wywodzą się przeciwciała anty-CD19 CAR. U trzech pacjentów przed leczeniem produktem Yescarta badanie przeciwciał anty-FMC63 dało wynik dodatni. Wpływ tych przeciwciał na skuteczność lub bezpieczeństwo stosowania nie był dostrzegalny. <u>Specjalne grupy pacjentów:</u> Doświadczenie dotyczące stosowania produktu Yescarta u pacjentów w wieku 75 lat i starszych jest ograniczone. Na ogół bezpieczeństwo stosowania oraz skuteczność były podobne jak w przypadku pacjentów w wieku ≥ 65 lat i < 65 lat leczonych produktem Yescarta. Wyniki były zgodne z wynikami uzyskanymi w grupach pacjentów z oceną w skali Eastern Cooperative Oncology Group (ECOG) 0 i 1 oraz według płci. <u>Zgłaszanie podejrzewanych działań niepożądanych:</u> 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, PL-02 222 Warszawa, tel.: +48 22 49 21 301, faks: +48 22 49 21 309, strona internetowa: https://smz.ezdrowie.gov.pl.* Działania niepożądane można także zgłaszać za pośrednictwem przedstawiciela podmiotu odpowiedzialnego w Polsce: Gilead Sciences Poland Sp. z o.o., tel.: +48 22 262 87 02 lub e-mail: DrugSafety.Poland@gilead.com. **7. PODMIOT ODPOWIEDZIALNY POSIADAJĄCY POZWOLENIE NA DOPUSZCZENIE DO OBROTU:** Kite Pharma EU B.V., Tufsteen 1, 2132 NT Hoofddorp, Holandia. **8. NUMER POZWOLENIA NA DOPUSZCZENIE DO OBROTU:** EU/1/18/1299/001. **WYDANE PRZEZ:** Komisję Wspólnot Europejskich. **OGÓLNA KATEGORIA DOSTĘPNOŚCI:** Rpz. **9. DATA WYDANIA PIERWSZEGO POZWOLENIA NA DOPUSZCZENIE DO OBROTU I DATA PRZEDŁUŻENIA POZWOLENIA:** Data wydania pierwszego pozwolenia na dopuszczenie do obrotu: 23 sierpnia 2018. **10. DATA ZATWIERDZENIA LUB CZĘŚCIOWEJ ZMIANY TEKSTU CHARAKTERYSTYKI PRODUKTU LECZNICZEGO:** 01/2022. Szczegółowe informacje o tym produkcie leczniczym są dostępne na stronie internetowej Europejskiej Agencji Leków http://www.ema.europa.eu.

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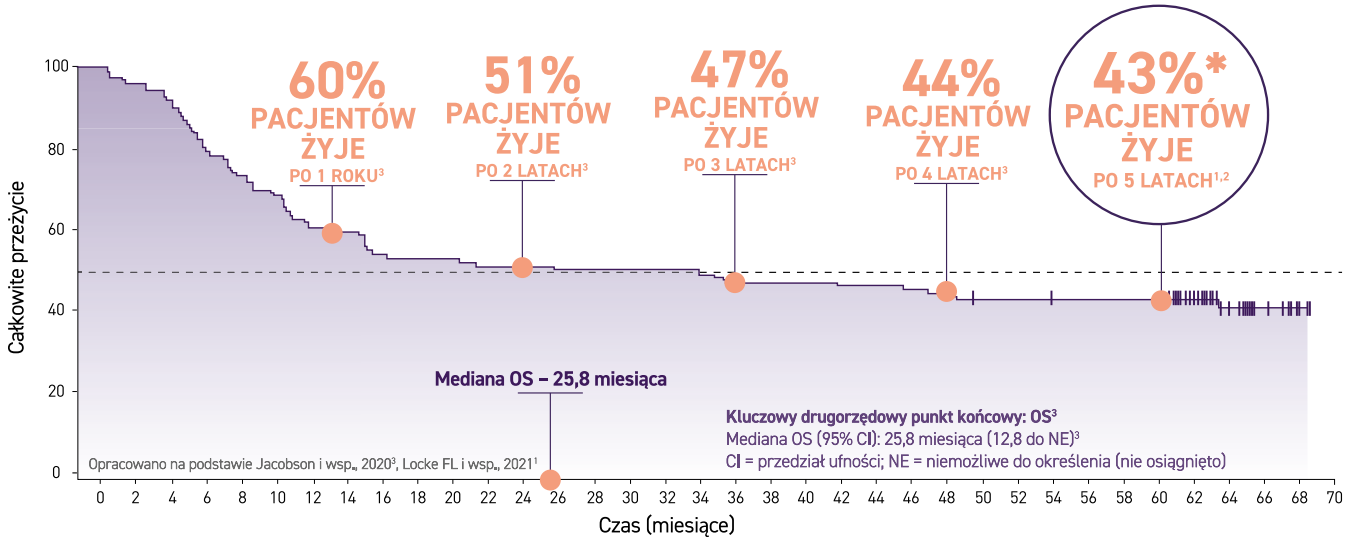
DZIŚ SĄ RZECZYWISTOŚCIĄ

5-LETNIE CAŁKOWITE PRZEŻYCIE (OS) WYNIOSŁO 43%[1,2]*
w badaniu rejestracyjnym Zuma-1



Pacjenci narażeni																																
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* Wartości szacunkowe wg Kaplana-Meiera dla 5-letniego wskaźnika OS wyniosły 42,6%.

Piśmiennictwo: 1. Locke FL et al. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. N Engl J Med 2021. doi: 10.1056/NEJMoa2116133. 2. Jacobson C et al. Long-term (4- and 5-year) overall survival in ZUMA-1, the pivotal study of axicabtagene ciloleucel in patients with refractory large B-Cell lymphoma (LBCL), Poster 1764 at ASH 2021. 3. Jacobson C et al. Poster presented at: American Society for Hematology Annual Meeting (Virtual); December 5-8, 2020.

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