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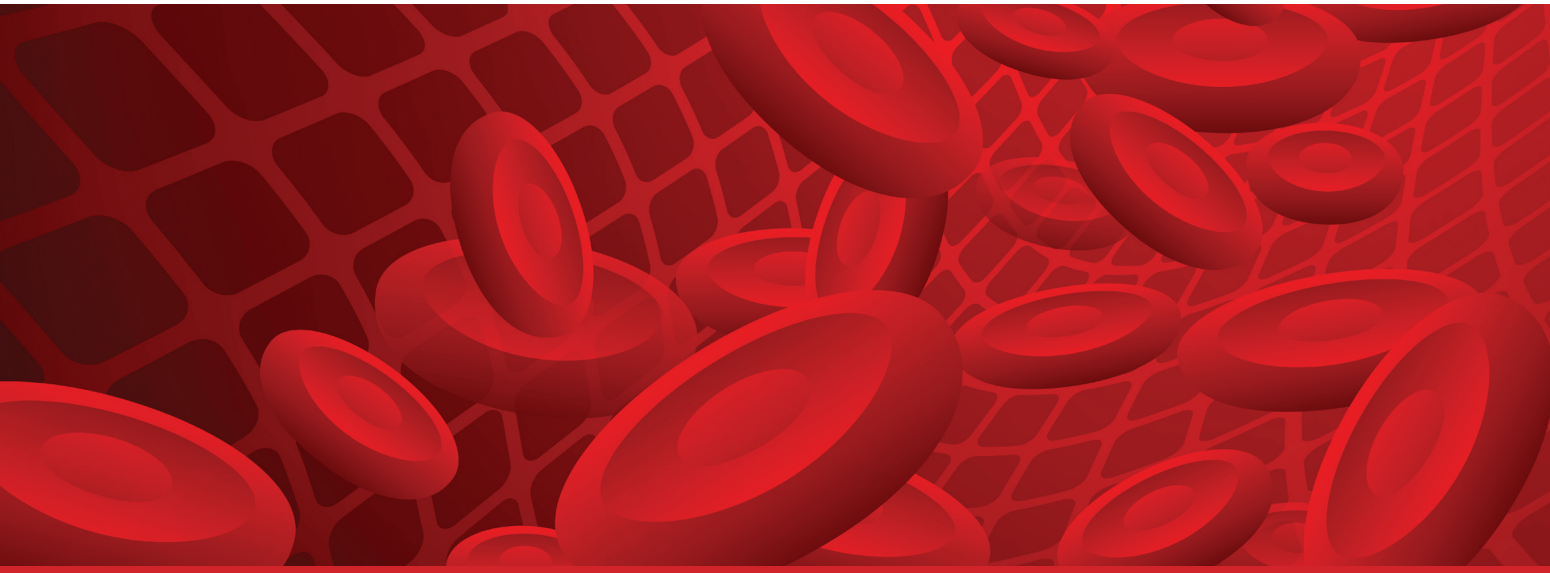

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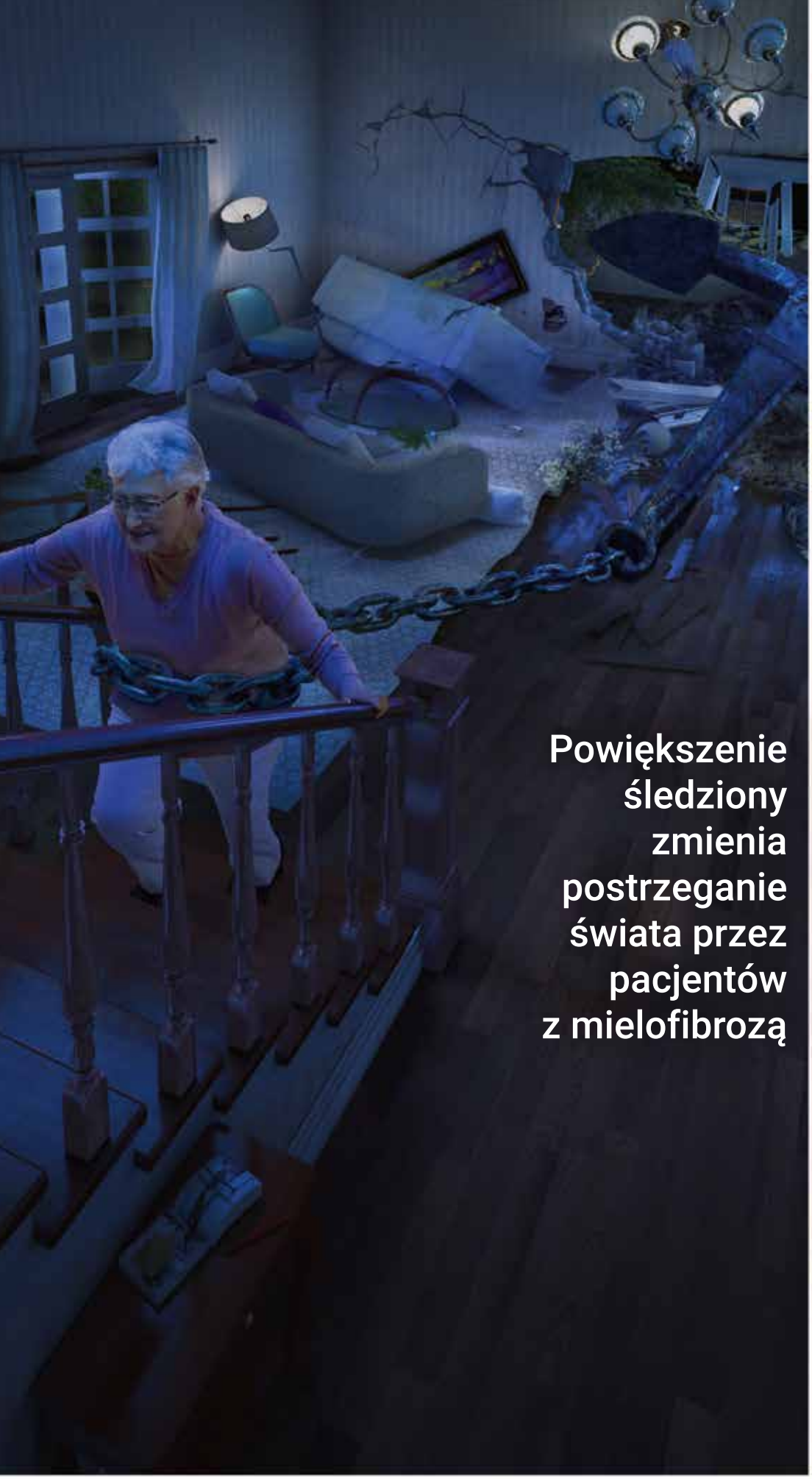

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Tabela 1: Zmniejszenie dawki w przypadku toksyczności hematologicznej, niehematologicznej i leczenia encefalopatii Wernickego

Toksyczność hematologiczna	**Zmniejszenie dawki**
Małopłytkowość stopnia 3. z aktywnym krwawieniem (liczba płytek krwi < 50 x 10^9/l) lub małopłytkowość stopnia 4. (liczba płytek krwi < 25 x 10^9/l)	Przerwać stosowanie produktu Inrebic do czasu ustąpienia objawów do stopnia ≤ 2. (liczba płytek krwi < 75 x 10^9/l) lub uzyskania wartości początkowych. Wznowić stosowanie w dawce dobowej mniejszej o 100 mg od ostatniej stosowanej dawki.
Neutropenia stopnia 4. (bezwzględna liczba neutrofili [ANC] < 0,5 x 10^9/l)	Przerywać stosowanie produktu Inrebic do czasu ustąpienia objawów do stopnia ≤ 2. (ANC < 1,5 x 10^9/l) lub uzyskania wartości początkowych. Wznowić w dawce dobowej mniejszej o 100 mg od ostatniej stosowanej dawki. Zgodnie z decyzją lekarza można zastosować czynniki wzrostu kolonii granulocytów.
Niedokrwistość stopnia 3. i wyższego, wskazana transfuzja (stężenie hemoglobiny < 8,0 g/dl)	Przerwać stosowanie produktu Inrebic, do czasu ustąpienia objawów do stopnia ≤ 2. (stężenie hemoglobiny ≤ 10,0 g/dl) lub uzyskania wartości początkowych. Wznowić stosowanie w dawce dobowej mniejszej o 100 mg od ostatniej stosowanej dawki.
Nawrót objawów toksyczności hematologicznej stopnia 4.	Zakończyć stosowanie produktu Inrebic zgodnie z decyzją lekarza.
Toksyczność niehematologiczna	**Zmniejszenie dawki**
Nudności, wymioty lub biegunka stopnia ≥ 3., nieodpowiadająca na leczenie wspomagające w ciągu 48 godzin	Przerwać stosowanie produktu Inrebic, do czasu ustąpienia objawów do stopnia ≤ 1. lub uzyskania wartości początkowych. Wznowić stosowanie w dawce dobowej mniejszej o 100 mg od ostatniej stosowanej dawki.
Objawy toksyczności stopnia ≥ 3. związane z aktywnością AlAT/ AspAT (> 5,0 do 20,0 x górna granica normy [GGN) lub stężeniem bilirubiny (> 3,0 do 10,0 GGN).	Przerwać stosowanie produktu Inrebic do czasu ustąpienia objawów do ≤ stopnia 1. (AspAT/AlAT [> GGN - 3,0 x GGN] lub bilirubina [> GGN - 1,5 x GGN]) lub do czasu uzyskania wartości początkowej. Wznowić stosowanie w dawce dobowej mniejszej o 100 mg od ostatniej stosowanej dawki. Monitorować aktywność AlAT, AspAT i stężenie bilirubiny (całkowitą i bezpośrednią) co 2 tygodnie przez co najmniej 3 miesiące po zmniejszeniu dawki. W przypadku ponownego wystąpienia objawów toksyczności stopnia 3. lub wyższego, zakończyć leczenie produktem Inrebic.
Aktywność amylazy i (lub) lipazy stopnia ≥ 3. (> 2,0 do 5,0 x GGN)	Przerwać stosowanie produktu Inrebic do czasu ustąpienia objawów do stopnia 1. (> GGN - 1.5 x GGN) lub do czasu uzyskania wartości początkowych. Wznowić stosowanie produktu leczniczego w dawce dobowej mniejszej o 100 mg od ostatniej stosowanej dawki. Monitorować aktywność amylazy i (lub) lipazy co 2 tygodnie przez co najmniej 3 miesiące po zmniejszeniu dawki. W przypadku ponownego wystąpienia objawów toksyczności stopnia 3. lub wyższego, zakończyć leczenie produktem Inrebic.
Stopień ≥ 3. innych objawów toksyczności niehematologicznych	Przerwać stosowanie produktu Inrebic do czasu ustąpienia objawów do stopnia ≤ 1. lub uzyskania wartości jak w punkcie wyjściowym. Ponownie rozpocząć stosowanie produktu leczniczego w dawce dobowej o 100 mg mniejszej od ostatniej stosowanej dawki.
Wyrównywanie niedoboru tiaminy i leczenie encefalopatii Wernickego	**Zmniejszenie dawki**
Dla stężeń tiaminy < zakres normalny (74 do 222 nmol/l), ale ≥ 30 nmol/l bez objawów przedmiotowych lub podmiotowych encefalopatii Wernickego	Przerwać stosowanie produktu Inrebic. Przyjmować doustnie 100 mg tiaminy na dobę do momentu wyrównania niedoboru*. Rozważyć wznowienie leczenia produktem Inrebic, gdy stężenie tiaminy będzie w granicach normy*.
Dla poziomów tiaminy < 30 nmol/l bez objawów przedmiotowych lub podmiotowych encefalopatii Wernickego	Przerwać stosowanie produktu Inrebic. Rozpocząć leczenie roztworem tiaminy do podania parenteralnego w dawkach terapeutycznych aż do przywrócenia stężenia tiaminy do normy*. Rozważyć wznowienie leczenia produktem Inrebic, gdy stężenie tiaminy będzie w granicach normy*.
W przypadku objawów podmiotowych lub przedmiotowych encefalopatii Wernickego, niezależnie od stężenia tiaminy	Przerwać stosowanie produktu Inrebic i natychmiast podać tiaminę parenteralnie w dawkach terapeutycznych.

* zakres normalny stężeń tiaminy może różnić się w zależności od metody oznaczenia stosowanej przez dane laboratorium

Szczególne grupy pacjentów: Zaburzenia czynności nerek: U pacjentów z ciężkimi zaburzeniami czynności nerek (klirens kreatyniny [CLcr] 15 ml/min do 29 ml/min według Cockcrofta-Gaulta [C-G]), dawka powinna zostać zmniejszona do 200 mg. Nie zaleca się modyfikacji dawki początkowej u pacjentów z łagodnymi lub umiarkowanymi zaburzeniami czynności nerek (CLcr 30 ml/min do 89 ml/min według C-G). Ze względu na potencjalny wzrost ekspozycji, pacjenci z wcześniej występującym umiarkowanym zaburzeniem czynności nerek, mogą wymagać co najmniej cotygodniowego monitorowania bezpieczeństwa i w razie konieczności zmian dawkowania w oparciu o działania niepożądane. *Zaburzenia czynności wątroby:* Nie badano farmakokinetyki produktu Inrebic u pacjentów z ciężkimi zaburzeniami czynności wątroby. Należy unikać stosowania produktu Inrebic u pacjentów z ciężkimi zaburzeniami czynności wątroby (klasa C w skali Child-Pugh lub stężenie bilirubiny całkowitej > 3 razy GGN i każde zwiększenie aktywności AspAT). Zmiana dawki początkowej nie jest konieczna u pacjentów z łagodnymi lub umiarkowanymi zaburzeniami czynności wątroby. *Pacjenci w podeszłym wieku:* U pacjentów w podeszłym wieku (> 65 lat) nie jest wymagane dostosowywanie dawki. *Dzieci i młodzież:* Nie określono dotychczas bezpieczeństwa stosowania ani skuteczności produktu leczniczego Inrebic u dzieci i młodzieży w wieku do 18 lat. Dane nie są dostępne. Sposób podawania: Podanie doustne. Nie należy otwierać, łamać ani żuć kapsułek. Kapsułki należy połykać w całości, najlepiej z wodą. Można je przyjmować z posiłkiem lub bez. Przyjmowanie z posiłkiem o dużej zawartości tłuszczu może zmniejszyć częstość występowania nudności i wymiotów, dlatego zaleca się przyjmowanie z posiłkiem. **Przeciwwskazania:** Nadwrażliwość na substancję czynną lub na którąkolwiek substancję pomocniczą. Ciąża. **Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania**: Encefalopatia, w tym encefalopatia Wernickego: Zgłaszano przypadki ciężkich i śmiertelnych encefalopatii, w tym encefalopatii Wernickego, u pacjentów przyjmujących produkt Inrebic. Encefalopatia Wernickego jest nagłym stanem neurologicznym spowodowanym niedoborem tiaminy (witamina B1). Objawy przedmiotowe i podmiotowe encefalopatii Wernickego mogą obejmować ataksję, zmiany stanu psychicznego i oftalmoplegię (np. oczopląs, podwójne widzenie). Wszelkie zmiany stanu psychicznego, dezorientacja lub upośledzenie pamięci powinny budzić obawy dotyczące potencjalnej encefalopatii, w tym encefalopatii Wernickego i wskazywać konieczność szybkiego przeprowadzenia pełnej oceny, w tym przeprowadzenia badania neurologicznego, oceny stężenia tiaminy i obrazowania. Stężenia tiaminy i stan odżywienia pacjentów należy oceniać przed rozpoczęciem leczenia produktem Inrebic, okresowo podczas leczenia (np. co miesiąc przez pierwsze 3 miesiące, a następnie co 3 miesiące) i zgodnie ze wskazaniami klinicznymi. Nie należy rozpoczynać leczenia produktem Inrebic u pacjentów z niedoborem tiaminy. Przed rozpoczęciem leczenia i w trakcie leczenia należy uzupełniać niedobór tiaminy. W przypadku podejrzenia encefalopatii, należy natychmiast przerwać leczenie produktem Inrebic i rozpocząć podanie parenteralne tiaminy podczas oceny pod kątem wszystkich możliwych przyczyn. Należy monitorować pacjenta do momentu ustąpienia lub poprawy objawów i uzupełnienia niedoboru tiaminy. Niedokrwistość, małopłytkowość i neutropenia: Leczenie produktem Inrebic może powodować niedokrwistość, małopłytkowość i neutropenię. Morfologię krwi należy wykonywać w punkcie początkowym, okresowo podczas leczenia i zgodnie z zaleceniami klinicznymi. Nie badano działania produktu Inrebic u pacjentów z początkową liczbą płytek krwi < 50 x 10^9/l oraz ANC < 1,0 x 10^9/L. *Niedokrwistość:* Niedokrwistość zazwyczaj występuje w ciągu pierwszych 3 miesięcy leczenia. U pacjentów ze stężeniem hemoglobiny poniżej 10,0 g/dl na początku leczenia prawdopodobieństwo wystąpienia niedokrwistości stopnia 3. lub wyższego podczas leczenia jest większe i powinno być uważnie monitorowane (np. raz w tygodniu przez pierwszy miesiąc, do czasu zwiększenia stężenia hemoglobiny). U pacjentów, u których wystąpi niedokrwistość, może być konieczna transfuzja krwi. Należy rozważyć zmniejszenie dawki u pacjentów, u których wystąpi niedokrwistość, szczególnie w przypadku osób, które będą wymagać transfuzji krwinek czerwonych. *Małopłytkowość*: Małopłytkowość zazwyczaj występuje w ciągu pierwszych 3 miesięcy leczenia. U pacjentów z małą liczbą płytek krwi (< 100 x 10^9/l) na początku leczenia bardziej prawdopodobne jest wystąpienie małopłytkowości stopnia 3. lub wyższego w trakcie leczenia i należy ich uważnie monitorować (np. raz w tygodniu przez pierwszy miesiąc, do czasu zwiększenia liczby płytek krwi). Małopłytkowość jest zazwyczaj odwracalna i można ją wyrównać poprzez leczenie wspomagające, takie jak przerwy w dawkowaniu, zmniejszenie dawki i (lub) transfuzje płytek krwi w razie potrzeby. Należy poinformować pacjentów o zwiększonym ryzyku wystąpienia krwawienia związanego z małopłytkowością. *Neutropenia*: Neutropenia była zazwyczaj odwracalna i była wyrównywana przez tymczasowe przerwanie stosowania produktu Inrebic. Zdarzenia ze strony układu pokarmowego: Nudności, wymioty i biegunka są najczęstszymi działaniami niepożądanymi u pacjentów przyjmujących produkt Inrebic. Większość działań niepożądanych była zdarzeniami stopnia 1. lub 2. i zazwyczaj występowały w ciągu pierwszych 2 tygodni leczenia. Podczas stosowania produktu Inrebic należy rozważyć odpowiednie profilaktyczne leczenie przeciwwymiotne (np. antagoniści receptora 5-HT3). Należy niezwłocznie włączyć leczenie biegunki lekami przeciwbiegunkowymi w momencie wystąpienia pierwszych objawów. W przypadku nudności, wymiotów i biegunki stopnia 3. lub wyższego, które nie reagują na leczenie wspomagające w ciągu 48 godzin, stosowanie produktu Inrebic należy przerwać do ustąpienia do stopnia 1. lub poziomu niższego lub wyjściowego. Ponownie rozpocząć stosowanie produktu leczniczego w dawce dobowej o 100 mg niższej od ostatniej stosowanej dawki. Stężenie tiaminy należy monitorować i uzupełniać zgodnie z potrzebami. Hepatotoksyczność: Podczas stosowania produktu Inrebic zgłaszano przypadki zwiększenia aktywności AlAT i AspAT oraz zgłoszono jeden przypadek niewydolności wątroby. Czynność wątroby powinna być monitorowana u pacjentów w punkcie początkowym, co najmniej raz w miesiącu przez pierwsze 3 miesiące, okresowo podczas leczenia i zgodnie ze wskazaniami klinicznymi. Po zaobserwowaniu objawów toksyczności pacjenci powinni być monitorowani co najmniej co 2 tygodnie aż do ustąpienia objawów. Wzrost aktywności AlAT i AspAT był zasadniczo odwracalny po wprowadzeniu zmian dawkowania lub zakończeniu leczenia. Zwiększona aktywność amylazy i (lub) lipazy: Odnotowano zwiększenie aktywności amylazy i (lub) lipazy podczas stosowania produktu Inrebic i zgłoszono jeden przypadek zapalenia trzustki. Aktywność amylazy i lipazy powinna być monitorowa u pacjentów w punkcie początkowym, co najmniej raz w miesiącu przez pierwsze 3 miesiące, okresowo podczas leczenia i zgodnie ze wskazaniami klinicznymi. Po zaobserwowaniu objawów toksyczności pacjenci powinni być monitorowani co najmniej co 2 tygodnie aż do ustąpienia objawów. W przypadku zwiększenia aktywności amylazy i (lub) lipazy stopnia 3. lub wyższego zaleca się wprowadzenie zmiany dawki. Podwyższone stężenie kreatyniny:

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Odnotowano zwiększenie stężenia kreatyniny podczas stosowania produktu Inrebic. Stężenie kreatyniny powinno być monitorowane u pacjentów w punkcie początkowym, co najmniej raz w miesiącu przez pierwsze 3 miesiące, okresowo podczas leczenia i zgodnie ze wskazaniami klinicznymi. W przypadku ciężkich zaburzeń czynności nerek (CLcr 15 ml/min do 29 ml/min według C-G) zaleca się zmianę dawki. Interakcje: Jednoczesne stosowanie produktu Inrebic z silnymi inhibitorami CYP3A4 zwiększa ekspozycję na produkt Inrebic. Zwiększona ekspozycja na produkt Inrebic może zwiększyć ryzyko wystąpienia działań niepożądanych. W przypadku silnych inhibitorów CYP3A4 należy rozważyć alternatywne metody leczenia, które nie wywołują silnego działania hamującego aktywności CYP3A4. Jeżeli nie można zastosować zamienników silnych inhibitorów CYP3A4, dawkę produktu Inrebic należy zmniejszyć podczas stosowania silnych inhibitorów CYP3A4 (np. ketokonazol, rytonawir). Należy uważnie monitorować pacjentów (np. co najmniej raz w tygodniu) pod kątem bezpieczeństwa stosowania. Długotrwałe stosowanie umiarkowanych inhibitorów CYP3A4 może wymagać ścisłego monitorowania bezpieczeństwa pacjentów, oraz, w razie konieczności, zmiany dawkowania w oparciu o występujące działania niepożądane. Leki hamujące jednocześnie CYP3A4 i CYP2C19 (np. flukonazol, fluwoksamina) lub połączenia leków hamujących CYP3A4 i CYP2C19 mogą zwiększyć ekspozycję na produkt Inrebic i należy unikać ich stosowania u pacjentów przyjmujących Inrebic. Leki umiarkowanie lub silnie indukujące CYP3A4 (np. fenytoina, ryfampicyna, efawirenz) mogą zmniejszyć ekspozycję na produkt Inrebic i należy unikać ich stosowania u pacjentów przyjmujących produkt Inrebic. Jeśli produkt Inrebic ma być stosowany razem z substratem CYP3A4 (np. midazolam, symwastatyna), CYP2C19 (np. omeprazol, S-mefenytoina) lub CYP2D6 (np. metoprolol, dekstrometorfan), należy w razie potrzeby modyfikować dawki leków stosowanych w skojarzeniu oraz ściśle monitorować bezpieczeństwo stosowania i skuteczność. Jeśli produkt Inrebic ma być stosowany razem z lekami, które są wydalane przy udziale transportera kationów organicznych (ang. *organic cation transporter*, OCT) OCT2 oraz transportera wielolekowego i wypływu toksyn (ang. *multidrug and toxin extrusion*, MATE) (MATE)1/2 K (np. metformina), należy zachować ostrożność i w razie potrzeby zmodyfikować dawkę. Nie badano jednoczesnego stosowania krwiotwórczych czynników wzrostu oraz produktu Inrebic. Bezpieczeństwo stosowania i skuteczność takiego połączenia nie są znane. Szczególne grupy pacjentów: *Pacjenci w podeszłym wieku:* Doświadczenie w stosowaniu u pacjentów w wieku 75 lat i powyżej jest ograniczone. W badaniach klinicznych, 13,8% (28/203) pacjentów leczonych produktem Inrebic było w wieku 75 lat i powyżej, w tej grupie ciężkie działania niepożądane i działania niepożądane prowadzące do przerwania leczenia występowały częściej. Substancje pomocnicze: Kapsułki produktu Inrebic zawierają mniej niż 1 mmol (23 mg) sodu na dawkę, to znaczy lek uznaje się za „wolny od sodu". **Działania niepożądane:** Podsumowanie profilu bezpieczeństwa: Ogólne informacje dotyczące bezpieczeństwa stosowania produktu Inrebic zebrano od 608 pacjentów, którzy otrzymywali stałe dawki Inrebic w badaniach klinicznych fazy 1, 2 i 3. Pierwotne lub wtórne włóknienie szpiku (JAKARTA, JAKARTA2, ARD11936): W badaniach klinicznych z udziałem pacjentów z pierwotnym włóknieniem szpiku (ang. *myelofibrosis*, MF), włóknieniem szpiku poprzedzonym czerwienicą prawdziwą (ang. *post polycythaemia vera myelofibrosis*, post-PV MF) lub włóknieniem szpiku poprzedzonym nadpłytkowością samoistną (ang. *post essential thrombocythemia myelofibrosis*, post-ET MF), przyjmujących produkt Inrebic w dawce 400 mg (N=203), w tym pacjentów po wcześniejszej ekspozycji na ruksolitynib (N=97; JAKARTA2) mediana ekspozycji wynosiła 35,6 tygodnia (przedział od 0,7 do 114,6 tygodni) a mediana liczby rozpoczętych cykli (1 cykl = 28 dni) wynosiła 9. Sześćdziesiąt trzy procent z 203 pacjentów było leczonych przez 6 miesięcy lub dłużej, a 38% przez 12 miesięcy lub dłużej. Wśród 203 pacjentów z MF leczonych dawką 400 mg produktu Inrebic w badaniach klinicznych, najczęstszymi niehematologicznymi działaniami niepożądanym były: biegunka (67,5%), nudności (61,6%) i wymioty (44,8%). Najczęstszymi hematologicznymi działaniami niepożądanymi były: niedokrwistość (99,0%) i małopłytkowość (68,5%), na podstawie badań laboratoryjnych (Tabela 2). Najczęstszymi ciężkimi działaniami niepożądanymi u pacjentów z MF leczonych dawką 400 mg były: niedokrwistość (2,5% na podstawie zgłaszanych działań niepożądanych, a nie badań laboratoryjnych) i biegunka (1,5%). Zakończenie udziału w badaniu ze względu na działania niepożądane, niezależnie od przyczyny, dotyczyło 24% pacjentów przyjmujących dawkę 400 mg produktu Inrebic. Tabelaryczne zestawienie działań niepożądanych: Działania niepożądane obserwowane w badaniach klinicznych przez cały czas trwania leczenia (Tabela 2) wymieniono według klasyfikacji układów i narządów MedDRA. W obrębie każdej klasy układów i narządów, działania niepożądane są wymienione według częstości występowania, zaczynając od działań obserwowanych najczęściej. Częstość występowania zdefiniowano 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); bardzo rzadko (<1/10 000) i nieznana (częstość nie może być określona na podstawie dostępnych danych).

Tabela 2: Wszystkie działania niepożądane produktu leczniczego według klasyfikacji układów i narządów oraz preferowanej terminologii

Klasyfikacja układów i narządów	Działanie niepożądane	Wszystkie stopnie Częstość
Zakażenia i zarażenia pasożytnicze	Zakażenie dróg moczowych	Bardzo często
Zaburzenia krwi i układu chłonnego	Niedokrwistość[a]	Bardzo często
	Małopłytkowość[a]	Bardzo często
	Neutropenia[a]	Bardzo często
	Krwawienie[b]	Bardzo często
Zaburzenia metabolizmu i odżywiania	Podwyższona aktywność lipazy[a]	Bardzo często
	Podwyższona aktywność amylazy[a]	Bardzo często
Zaburzenia układu nerwowego	Ból głowy	Bardzo często
	Encefalopatia Wernickego	Często
	Zawroty głowy	Często
Zaburzenia naczyniowe	Nadciśnienie	Często
Zaburzenia żołądka i jelit	Biegunka	Bardzo często
	Wymioty	Bardzo często
	Nudności	Bardzo często
	Zaparcia	Bardzo często
	Niestrawność	Często
Zaburzenia wątroby i dróg żółciowych	Zwiększona aktywność aminotransferazy alaninowej[a]	Bardzo często
	Zwiększona aktywność aminotransferazy asparaginianowej[a]	Bardzo często
Zaburzenia mięśniowo-szkieletowe i tkanki łącznej	Ból kości	Często
	Kurcze mięśni	Bardzo często
	Ból kończyn	Często
Zaburzenia nerek i dróg moczowych	Wzrost stężenia kreatyniny we krwi[a]	Bardzo często
	Dyzuria	Często
Zaburzenia ogólne i stany w miejscu podania	Zmęczenie/astenia	Bardzo często
Badania diagnostyczne	Zwiększenie masy ciała	Często

MedDRA (Medical dictionary of regulatory activities) = Słownik terminów medycznych dla czynności regulacyjnych
SMQ (Standardized MedDRA Quer) = standaryzowany wpise MedDRA (grupowanie kilku preferowanych terminów MedDRA w celu ujęcia koncepcji medycznej).
[a] Częstość opiera się na badaniach laboratoryjnych.
[b] Krwawienie obejmuje wszelkie rodzaje związane z małopłytkowością wymagającą interwencji klinicznej. Krwawienie ocenia się przy użyciu terminów związanych z krwotokami MedDRA SMQ (szeroki zakres).

Opis wybranych działań niepożądanych: *Encefalopatia, w tym encefalopatia Wernickego*: Ciężkie przypadki encefalopatii, w tym 1 potwierdzony przypadek encefalopatii Wernickego zgłoszono u 1,3% (8/608) pacjentów przyjmujących produkt Inrebic w badaniach klinicznych; 7 pacjentów przyjmowało produkt Inrebic w dawce 500 mg na dobę przed wystąpieniem objawów neurologicznych i występowały u nich czynniki predysponujące, takie jak niedożywienie, działania niepożądane ze strony żołądka i jelit oraz inne czynniki ryzyka, które mogą doprowadzić do niedoboru tiaminy. U jednego pacjenta leczonego produktem Inrebic w dawce 400 mg stwierdzono encefalopatię wątrobową. Większość zdarzeń ustąpiła z pewnymi pozostającymi objawami neurologicznymi, w tym utratą pamięci, zaburzeniami poznawczymi i zawrotami głowy, z wyjątkiem jednego przypadku śmiertelnego (1/608; 0,16%). Był to pacjent z rakiem głowy i szyi, przerzutami do mózgu, trudnościami z jedzeniem i utratą masy ciała, który otrzymywał fedratynib w dawce 500 mg w ramach badania w innym wskazaniu. *Toksyczny wpływ na układ pokarmowy:* Nudności, wymioty i biegunka są najczęstszymi działaniami niepożądanymi u pacjentów przyjmujących produkt Inrebic. U pacjentów z MF przyjmujących produkt Inrebic w dawce 400 mg, biegunka wystąpiła u 68% pacjentów, nudności u 62% pacjentów a wymioty u 45% pacjentów. Biegunka, nudności i wymioty stopnia 3. wystąpiły odpowiednio u 5%, 0,5% i 2% pacjentów. Mediana czasu do wystąpienia nudności, wymiotów i biegunki dowolnego stopnia wynosiła 2 dni, przy czym w 75% przypadków wystąpiły one w ciągu 3 tygodni od rozpoczęcia leczenia. Przerwy w przyjmowaniu i zmniejszenie dawki z powodu objawów toksyczności ze strony układu pokarmowego zgłoszono odpowiednio u 11% i 9% pacjentów. Stosowanie produktu Inrebic w dawce 400 mg zakończono z powodu wystąpienia objawów toksyczności ze strony układu pokarmowego u 4% pacjentów. *Niedokrwistość:* U 52% pacjentów z pierwotnym lub wtórnym włóknieniem szpiku leczonych produktem Inrebic w dawce 400 mg, wystąpiła niedokrwistość stopnia 3. Mediana czasu do pierwszego wystąpienia niedokrwistości stopnia 3. wynosiła około 60 dni, przy czym w 75% przypadków wystąpiła ona w ciągu 4 miesięcy od rozpoczęcia leczenia. 58% pacjentów leczonych produktem Inrebic w dawce 400 mg otrzymywało transfuzje krwinek czerwonych, a stosowanie produktu Inrebic w dawce 400 mg z powodu niedokrwistości zakończono u 1,5% pacjentów. *Małopłytkowość:* U pacjentów z pierwotnym lub wtórnym zwłóknieniem szpiku leczonych produktem Inrebic w dawce 400 mg, odpowiednio u 14% i 9% pacjentów wystąpiła trombocytopenia stopnia 3. i 4. Mediana czasu do pierwszego wystąpienia niedokrwistości stopnia 3. lub niedokrwistości stopnia 4. wynosiła około 70 dni, przy czym w 75% przypadków wystąpiła ona w ciągu 7 miesięcy od rozpoczęcia leczenia. 9% pacjentów leczonych produktem Inrebic w dawce 400 mg otrzymywało transfuzje płytek krwi. Krwawienie (związane z małopłytkowością), które wymagało interwencji klinicznej wystąpiło u 11% pacjentów. U 3% pacjentów zakończono leczenie z powodu małopłytkowości. *Neutropenia* Neutropenia stopnia 4. wystąpiła u 3,5% pacjentów, a u 0,5% pacjentów przerwano stosowania leku z powodu neutropenii. *Hepatotoksyczność*: Zwiększenie aktywności AlAT i AspAT (wszystkie stopnie) wystąpiły odpowiednio u 52% i 59% pacjentów, w tym stopnia 3. i 4. u odpowiednio 3% i 2% pacjentów przyjmujących produkt Inrebic w dawce 400 mg. Mediana czasu do wystąpienia zwiększenia aktywności transaminazy dowolnego stopnia wynosiła około 1 miesiąca, przy czym w 75% przypadków wystąpiło ono w ciągu 3 miesięcy od rozpoczęcia leczenia. *Zwiększenie aktywności amylazy i (lub) lipazy:* Zwiększenie aktywności amylazy i (lub) lipazy (wszystkie stopnie) wystąpiło odpowiednio u 24% i 40% pacjentów z MF. Większość tych zdarzeń była stopnia 1. lub 2., a odpowiednio u 2,5% i 12% pacjentów była stopnia 3. lub 4. Mediana czasu do pierwszego wystąpienia zwiększenia aktywności amylazy lub lipazy dowolnego stopnia 16 dni, przy czym w 75% przypadków, wystąpiła ono w ciągu 3 miesięcy od rozpoczęcia leczenia. Zakończenie leczenia z powodu zwiększenia aktywności amylazy i (lub) lipazy wystąpiło u 1,0% pacjentów przyjmujących produkt Inrebic w dawce 400 mg. *Zwiększone stężenie kreatyniny*: Zwiększone stężenie kreatyniny (wszystkie stopnie) wystąpiło u 74% pacjentów z MF przyjmujących produkt Inrebic w dawce 400 mg. Zwiększenie stężenia było zazwyczaj bezobjawowymi zdarzeniami stopnia 1. lub 2., przy czym zwiększenie stopnia 3. zaobserwowano u 3% pacjentów. Mediana czasu do pierwszego wystąpienia zwiększenia stężenia kreatyniny dowolnego stopnia wynosiła 27 dni, przy czym w 75% przypadków wystąpiła ona w ciągu 3 miesięcy od rozpoczęcia leczenia. Przerwanie i zmniejszenie dawkowania z powodu zwiększonego stężenia kreatyniny zgłoszono odpowiednio u 1% i 0,5% pacjentów. U 1,5% pacjentów przyjmujących produkt Inrebic w dawce 400 mg zakończono leczenie z powodu zwiększenia stężenia kreatyniny.

▼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.
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OBITUARY

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Tribute to Anna Waszczuk-Gajda

Joanna Drozd-Sokołowska

Department of Hematology, Transplantation and Internal Medicine, Medical University of Warsaw, Warszawa, Poland

It is with great sadness that we announce that our colleague and friend Dr. Anna Waszczuk-Gajda MD, PhD, aged 41, of Warsaw, Poland, passed away on July 13, 2022.

Anna was born in Łowicz, Poland. Even in her early high school years, she was scientifically very productive and won a silver medal at the 31st International Chemistry Olympiad held in Bangkok, Thailand. Anna graduated from the Medical University of Warsaw in 2005. As part of the student's exchange program, she additionally studied at the Free University of Berlin (2002/2003). From the beginning of her medical career, she worked within the Department of Hematology, Oncology, and Internal Medicine, of the Medical University of Warsaw, renamed more recently as the Department of Hematology, Transplantation and Internal Medicine.

Anna obtained a degree in internal medicine, hematology, and oncology. She additionally commenced her specialization in clinical transplantation. She successfully defended her dissertation with honours on infectious complications in hematological patients in 2011, under the supervision of Professor Wiesław Wiktor Jędrzejczak. Thereafter she became very actively involved in the clinical research conducted by the Polish Adult Leukemia Group, mainly within the MDS and Infections subcommittees, the Polish Myeloma Group, and the Polish Lymphoma Research Group.

Much of her scientific and clinical research effort was focused on plasma cell dyscrasias, in particular cohorts complicated by renal failure. She defended her habilitation on this issue in 2020, whilst already undergoing treatment. She continued her research focus on this issue as a member of the Chronic Malignancies Working Party of the EBMT.

She published actively on behalf of the CMWP, PMG, and PALG on various aspects of plasma cell dyscrasia treatment and its complications over the years and added greatly to the available knowledge in this arena.

Until the final stages of her medical career, she remained very interested in the compendium of infectious complications in hematology, including in the HCT setting. Her own disease prompted her to analyse hematological problems in solid tumor oncology to prevent patients from being disqualified from both novel and established treatments based on their hematological parameters.

Anna was truly an excellent clinician, always very dedicated to the patients she was responsible for and remained a true advocate for excellence in all aspects of haemato-oncology and stem cell transplantation practice. Moreover, Anna had a unique way of 'looking at us, her colleagues and her friends. She was always able to find virtuous features within all of us, features that made us unique. She was compassionate, a true friend and active and empathetic listener, sharing fondness and warm words when needed which made our day-day work and, ultimately, our lives better. We will miss her greatly and will strive to continue her work and spirit.

She is survived by her beloved husband, son and mother.

ZAPOWIEDŹ WYDAWNICZA

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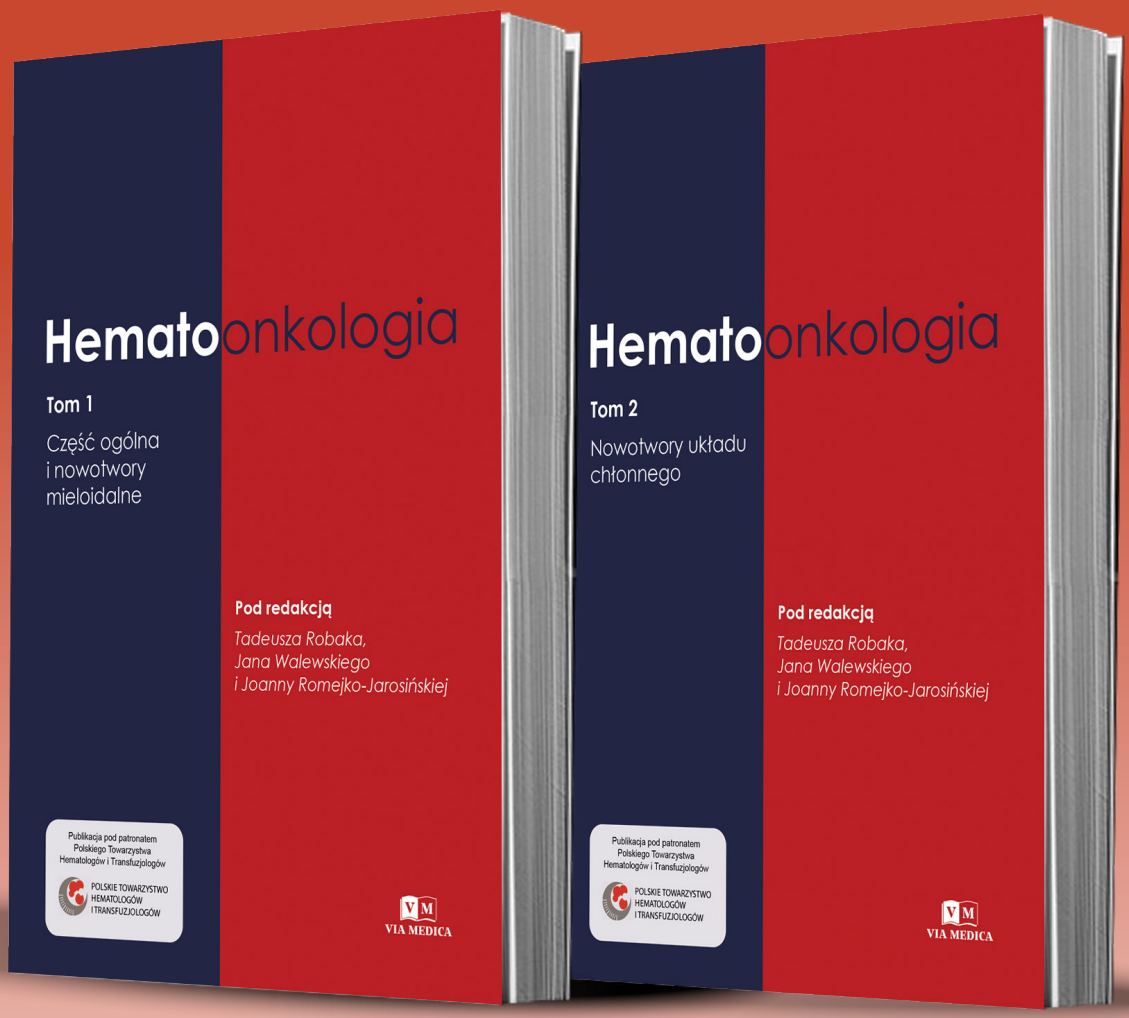

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EDITORIAL

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30th Congress of the Polish Society of Hematologists and Transfusiologists: in the shadow of international conflicts

Jan Styczyński*, Agata Marjańska

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On 8, 9 and 10 September, members of the Polish Society of Hematology and Transfusion Medicine (PTHiT, *Polskie Towarzystwo Hematologii i Transfuzjologii*) will have the opportunity to meet together at the 30th Congress of the Society, which will be held for the first time in Bydgoszcz, and organized for the first time by a pediatric center. This meeting was initially planned for September 2021, but due to the coronavirus disease 2019 (COVID-19) pandemic, we organized only 'Highlights 2021', and published an issue of 'Acta Haematologica Polonica' featuring educational papers prepared for the Congress [1].

The past two years have demonstrated the deep interconnectedness of everything we do. Not only the pandemic, but also the war in Ukraine, have reminded us that we live in a global environment, and we have to cope with its consequences every day, including in hematology wards. Refugees from Ukraine have been given the chance to start new lives in Poland in 2022. We have faced also the continuing challenge of refugees from Syria.

This issue of 'Acta Haematologica Polonica' shows not only progress in the work within the Society [2], but also achievements in other countries which are exposed to much more severe problems than we face in Poland. Papers by Troyanovska et al. from Ukraine [3], by Hamdan et al. from Syria [4], and by Sharma from India [5], are published in this issue. We have also a paper from Portugal [6].

The increasing internationalization of the activity of our Society, of our Congress, and of 'Acta Haematologica Polonica' are natural processes arising out of our everyday work, international cooperation, and international expectations [7–11].

Authors' contributions

Both authors contributed equally to the concept and content of the paper.

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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REVIEW ARTICLE

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Supportive care in multiple myeloma

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Abstract

Multiple myeloma is one of the most commonly diagnosed blood cancers. Due to the introduction of new therapies in recent years, there has been significant progress in treating myeloma. Even so, with the introduction of new groups of drugs, there have been some adverse events. In addition to anti-myeloma treatment, patients require supportive therapies. This article presents the principles of supportive treatment in emergencies and discusses the toxicity associated with the use of new groups of drugs.

Key words: adverse events, management, multiple myeloma, supportive care

Acta Haematologica Polonica 2022; 53, 4: 227–240

Introduction

Multiple myeloma (MM) is one of the most frequently diagnosed hematological neoplasms [1]. In Poland, c.2,600 new MM cases are reported annually, and it is the third most frequently diagnosed hematological neoplasm [2]. The introduction of thalidomide, bortezomib and lenalidomide to therapy has prolonged the survival of patients with myeloma [3, 4]. The more recent use of pomalidomide, carfilzomib, ixazomib, daratumumab, isatuximab, selinexor, belantamab, mandolin, and chimeric antigen receptor-T (CAR-T) will most likely prolong the survival of patients with MM. In addition to anti-MM therapy, the standard of care requires supportive therapies to prevent and treat organ damage early.

The method of treating MM has been changing dynamically in recent years. In Europe, patients qualified for high-dose (HD) chemotherapy followed by autologous stem cell transplantation (ASCT) are treated with 3–4 cycles of remission-inducing chemotherapy, followed by high-dose (HD) chemotherapy followed by ASCT. As recommended by the European Hematology Association–European Society for Medical Oncology (EHA-ESMO), first-line chemotherapy protocols include VRd (bortezomib, lenalidomide, dexamethasone) and DaraVTD (daratumumab, bortezomib, thalidomide, dexamethasone). Other methods of induction therapy include the VTD (bortezomib, thalidomide, dexamethasone) and the VCD (bortezomib, cyclophosphamide, dexamethasone) protocols.

However, in patients not qualified for ASCT, the following chemotherapy protocols are recommended for treating newly diagnosed myeloma (NDMM): DaraRd (daratumumab, lenalidomide, dexamethasone); DaraVMP (daratumumab, bortezomib, melphalan, prednisone); and VRd. Other first-line treatment options include the VMP (bortezomib, melphalan, prednisone) and the Rd (lenalidomide, dexamethasone) protocols. Figure 1 shows the treatment algorithm for patients with newly diagnosed myeloma recommended by the EHA-ESMO [5]. After achieving remission, all patients are expected to relapse. The duration of

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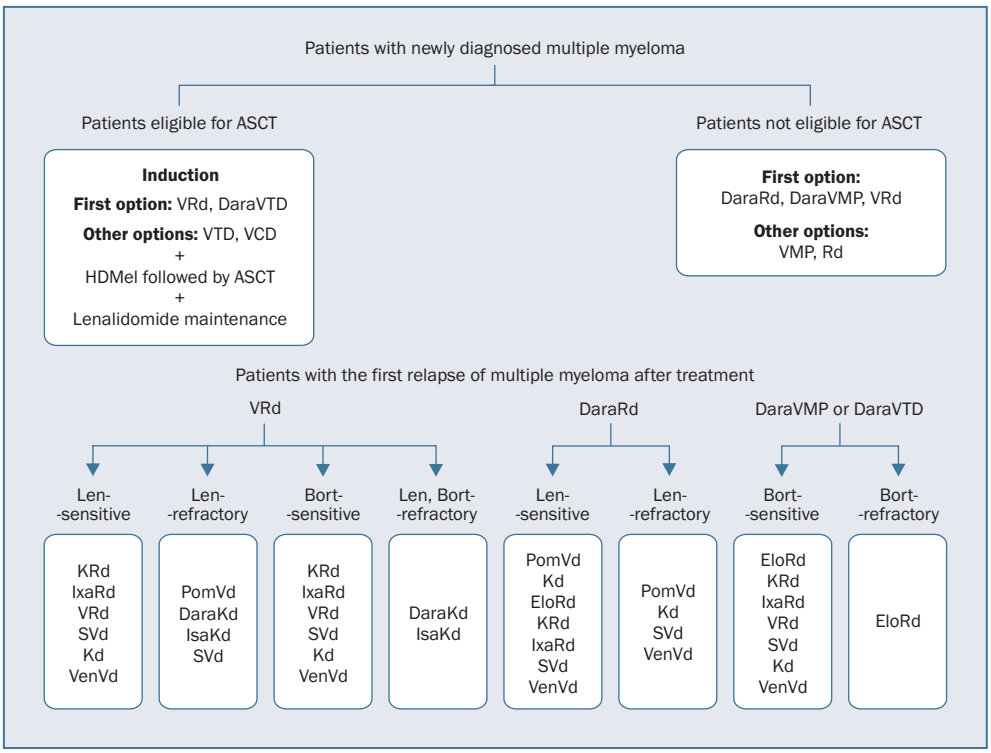

Figure 1. Multiple myeloma treatment recommendations according to European Hematology Association–European Society for Medical Oncology; ASCT — autologous stem cell transplantation; Bort — bortezomib; DaraKd — daratumumab, carfilzomib, dexamethasone; DaraRd — daratumumab, lenalidomide, dexamethasone; DaraVMP — daratumumab, bortezomib, melphalan, prednisone; DaraVTD — daratumumab, bortezomib, thalidomide, dexamethasone; EloRd — elotuzumab, lenalidomide, dexamethasone; HDMel — high-dose melphalan; IsaKd — isatuximab, carfilzomib, dexamethasone; IxaRd — ixazomib, lenalidomide, dexamethasone; Kd — carfilzomib, dexamethasone; KRd — carfilzomib, lenalidomide, dexamethasone; Len — lenalidomide; PomVd — pomalidomide, bortezomib, dexamethasone; Rd — lenalidomide, dexamethasone; SVd — selinexor, bortezomib, dexamethasone; VCD — bortezomib, cyclophosphamide, dexamethasone; VenVd — venetoclax, bortezomib, dexamethasone; VMP — bortezomib, melphalan, prednisone; VRd — bortezomib, lenalidomide, dexamethasone; VTD — bortezomib, thalidomide, dexamethasone

remission decreases with each subsequent relapse. Treating relapsed/refractory MM (RRMM) depends on many factors, including time of remission, treatment applied, response to previous therapy, the aggressiveness of the relapse, and the patient's performance status. . Among the newest options for treating RRMM are belantamab mafodotin (BM) and CAR-T [5].

Multiple myeloma is a malignant tumor that worsens patients' quality of life due both to the disease itself and to the consequences of adverse events (AEs) associated with the treatment used. Clinical symptoms of MM include impaired immune system function, impaired hematopoiesis, diseases of the skeletal system, and organ failure including kidney, heart, and nervous system [6]. Depending on the symptoms, patients with MM often require supportive treatment, including renal replacement therapy, treatment of hypercalcemia, analgesic treatment, and treatment of pathological bone fractures. An additional component of treating patients with MM is the treatment of the AEs that develop during anti-MM therapy.

In this article, we summarize the principles of supportive treatment and the principles of the prevention and treatment of the adverse events observed in the most commonly used methods of anti-MM treatment. Table I lists the most common AEs observed during the treatment of NDMM [7–11]. Tables II [12–19] and III [20–24] summarize the most common AEs observed in treating RRMM.

Prevention and supportive treatment in patients with MM

Treatment of hyperviscosity syndrome

Hyperviscosity syndrome (HVS) is a life-threatening condition found in c.2–6% of MM patients [25]. Clinical symptoms are most often seen when the concentration of monoclonal (M) protein in the immunoglobulin (Ig) M class is at least 30 g/L, IgA — 40 g/L, and IgG — 60 g/L (mean concentration of M protein: >40 g/L). The most common clinical symptoms of HVS are neurological symptoms including headache, dizziness, impaired consciousness,

Table I. Incidence of serious adverse events (grade >3) in treatment of newly diagnosed multiple myeloma identified in pivotal phase III clinical trials

Trial	IFM2013-04 [7]		CASSIOPEIA [8]		SWOG S0777 [9]		MAIA [10]		ALCYONE [11]	
Regimen	VCD	VTD	VTD	DaraVTD	Rd	VRd	DaraRd	Rd	DaraVMP	VMP
Hematological adverse events, grade >3 [%]										
Neutropenia	33	19	15	28	21	19	50	35	40	39
Thrombocytopenia	11	5	7	11	14	18	NA	NA	34	38
Anemia	9	4	NA	NA	16	13	12	20	16	20
Non-hematological adverse events, grade >3 [%]										
Infections	NA	NA	20	22	14	19	32	23	23	15
Peripheral neuropathy	Grade 2–4: 13	Grade 2–4: 22	9	9	11	35	NA	NA	<2	4
Venous thromboembolism	2	2	NA	NA	9	8	NA	NA		
Skin rash	NA	NA	NA	NA	4	4	NA	NA	NA	NA
Secondary malignancy (any grade)	NA	NA	2	2	3	3	9	7	NA	NA
IRR (all grades)				4			3		4	

DaraRd — daratumumab, lenalidomide, dexamethasone; DaraVMP — daratumumab, bortezomib, melphalan, prednisone; DaraVTD — daratumumab, bortezomib, thalidomide, dexamethasone; IRR — infusion-related reactions; NA — not available; Rd — lenalidomide, dexamethasone; VCD — bortezomib, cyclophosphamide, dexamethasone; VMP — bortezomib, melphalan, prednisone; VRd — bortezomib, lenalidomide, dexamethasone; VTD — bortezomib, thalidomide, dexamethasone

visual disturbances, central nervous system bleeding, somnolence, and coma. Other symptoms include coronary pain, dyspnea, pulmonary hypertension, and bleeding disorder symptoms. The treatment of HVS in MM involves plasmapheresis. In addition, anti-MM therapy should start as soon as possible, and be repeated for 3–5 consecutive days [26, 27].

Prevention and treatment of MM anemia

Anemia develops due to direct AE of clonal plasmacytes, chronic inflammation, kidney disease, and myelosuppressive effects of drugs. Anemia is found in at least 60–70% of NDMM patients and in more than 40% of patients who are RRMM [28]. Treatment of MM-related anemia includes red blood cell (RBC) transfusions and the use of erythropoiesis-stimulating agents (ESAs; epoetin, darbepoetin alfa). Red blood cell transfusions cause a rapid but transient increase in hemoglobin (Hb) level; therefore, this is recommended for the acute treatment of symptomatic anemia or in high-risk patients with asymptomatic anemia [29]. Importantly, the use of ESAs increases the risk of thromboembolic events, especially in patients treated with immunomodulatory drugs (IMiDs) combined with dexamethasone [30, 31]. On the other hand, a sustained increase in Hb concentration and a reduction in the need for RBC transfusion is achieved after using ESA [30]. For this reason, treatment with ESA should be administered only in accordance with international guidelines and having carried out a risk-benefit assessment.

Infection prevention while treating MM

Patients with MM have an increased risk of infection, especially in the early stages of diagnosis. This is due to the impairment of both humoral immunity (functional hypogammaglobulinemia) and cellular immunity and the applied anti-MM therapy, which has a myelosuppressive effect [32]

Bacterial infections

The risk of bacterial infections in patients with MM is significantly greater than in the healthy population [33]. This mainly concerns active NDMM patients, especially the elderly and people with recurrent infections. According to the ESMO and the European Myeloma Network (EMN), all MM patients should receive prophylactic antibiotic therapy during the first three months of anti-MM therapy. This is especially true for patients treated with lenalidomide and pomalidomide. As part of antibacterial prophylaxis, trimethoprim–sulfamethoxazole (TMP/SMX), amoxycillin, or quinolone is recommended [34–36]. The guidelines of the Stratification for Myeloma and Risk-Adapted Therapy (mSMART) and the International Myeloma Working Group (IMWG) also recommend prophylactic use of TMP/SMX during induction therapy of MM.

Viral infections

An increased risk of reactivation of Varicella-Zoster virus (VZV) is observed in patients with MM. Prophylaxis with acyclovir or its derivatives (famcyclovir, pencyclovir, and

Table II. Incidence of serious adverse events (grade >3) in treatment of relapsed/refractory multiple myeloma in pivotal phase III clinical trials

Trial	ASPIRE [12]		TOURMALINE-MM1 [13]		POLLUX [14]		ELO-QUE NT-2 [15]		ENDEA-VOR [16]		CASTOR [17]		CANDOR [18]		CLARION [19]	
Regimen	Rd	KRd	Rd	IxaRd	Rd	DaraRd	Rd	EloRd	Kd	Vd	Vd	DaraVd	Kd	DaraKd	KMP	VMP
Hematological adverse events, grade >3 [%]																
Neutropenia	27	31	24	23	42	55	45	36	NA	NA	5	14	6	8	23	29
Thrombocytopenia	13	17	9	19	16	15	21	21	9	9	33	46	16	24	15	21
Anemia	17	19	13	9	21	18	21	20	14	10	16	15	14	17	17	14
Non-hematological adverse events, grade >3 [%]																
Pneumonia	12	16	NA	2	10	15	26	33	6	7	10	10	8	13	10	7
Peripheral neuropathy	3	3	2	2	NA	NA	NA	NA	1	5	7	4	0	1	<1	8
Diarrhea	4	5	NA	NA	4	10	5	6	0	<1	1	4	<1	4		
Cardiac disorders	4	7	2	3	NA	NA	8	5	6	<3	NA	NA	11	7	10	4
Hypertension	2	4	1	3	NA	NA	NA	NA	9	3	<1	7	14	18	9	3
IRR (all grades)						5		1				9				

DaraKd – daratumumab, carfilzomib, dexamethasone; DaraRd – daratumumab, lenalidomide, dexamethasone; DaraVd – daratumumab, bortezomib, dexamethasone; EloRd – elotuzumab, lenalidomide, dexamethasone; IRR – infusion-related reactions; IxaRd – ixazomib, lenalidomide, dexamethasone; Kd – carfilzomib, dexamethasone; KMP – carfilzomib, melphalan, prednisone; KRd – carfilzomib, lenalidomide, dexamethasone; NA – not available; Rd – lenalidomide, dexamethasone; Vd – bortezomib, dexamethasone; VMP – bortezomib, melphalan, prednisone

valacyclovir) is recommended in all MM patients treated with proteasome inhibitors (PIs) and monoclonal antibodies (MoAbs) [37, 38]. It is recommended to use prophylactic doses, usually 50% of the therapeutic dose.

The outcomes of treating MM patients with coronavirus disease 2019 (COVID-19) are relatively poor, with mortality ranging from 30% to 55% [39, 40]. Survival rates have improved with the advent of vaccines and new drugs including remdesivir, dexamethasone, and anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies. Nevertheless, the immune response to the applied vaccines in patients with MM is inconsistent, and is generally lower than in the general population [41].

Vaccinations

Vaccinations are essential in protecting immunocompromised MM patients from common pathogens such as influenza and pneumococcus. Vaccination against the influenza virus, Streptococcus pneumonia, and Hemophilus influenza is recommended in patients with MM [42]. Patients undergoing ASCT should be revaccinated [43].

Prophylactic use of intravenous immunoglobulins

In severe humoral immunodeficiency, one may consider treatment with intravenous immunoglobulins (IVIg) at 0.4 g/kg body weight every four weeks. This applies to selected patients with recurrent bacterial infections and Ig deficiency [44–47].

Prophylaxis of neutropenia during MM treatment

Prophylactic use of granulocyte colony-stimulating factor (G-CSF) is recommended in patients with MM treated with chemotherapy protocols associated with a high risk of febrile neutropenia (FN) and in patients with additional risk factors [48]. Additionally, G-CSF is recommended in patients who develop grade 3/4 neutropenia and/or FN due to treatment [49]. In clinical practice, G-CSF's intermittent or short-term use at an amount of 30 MU is usually sufficient. After an increase in the absolute neutrophil count (ANC) ≥1.0 G/L, treatment with the current doses may continue; if not, the start of treatment should be delayed until an increase in the ANC ≥1.0 G/L and the quantity of the drug should be reduced accordingly [50].

Prevention and treatment of venous thromboembolism in patients with MM

Venous thromboembolism (VTE) is a common complication. It is usually observed in the initial phase of MM treatment,

Table III. Incidence of serious adverse events of pomalidomide in treatment of relapsed/refractory multiple myeloma identified in pivotal phase III clinical trials

Trial	MM-003 [20]		OPTIMISMM [21]		APOLLO [22]		ICARIA-MM [23]		ELOQUENT-3 [24]	
Regimen	Dex	Pd	Vd	PVd	Pd	DaraPd	Pd	IsaRd	Pd	EloPd
Hematological adverse events, grade ≥3 [%]										
Neutropenia	16	48	9	41	51	68	71	85	27	13
Thrombocytopenia	26	21	29	28	18	17	25	34	5	8
Anemia	37	33	14	14	21	17	29	35	21	20
Non-hematological adverse events, grade ≥3 [%]										
Febrile neutropenia	0	10	NA	NA	3	9	NA	NA	20	10
Infections	10	14	1	1	23	28	<1	5	22	13
Pneumonia			7	11	7	13	21	23	9	5
Peripheral neuropathy	NA	NA	4	9	NA	NA	NA	NA	NA	NA
Venous thromboembolism	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Skin rash	NA	NA	NA	NA	NA	NA	NA	NA	2	0
Cardiac disorders	NA	NA	NA	NA	NA	NA	NA	NA	4	7
IRR (all grades)						2		3		1

DaraPd — daratumumab, pomalidomide, dexamethasone; Dex — dexamethasone; EloPd — elotuzumab, pomalidomide, dexamethasone; IRR — infusion-related reactions; IsaRd — isatuximab, pomalidomide, dexamethasone; NA — not available; Pd — pomalidomide, dexamethasone; PVd — pomalidomide, bortezomib, dexamethasone; Vd — bortezomib, dexamethasone

Table IV. Thrombosis risk factors and recommendations for use of antithrombotic prophylaxis according to International Myeloma Working Group guidelines

Risk factors		
Treatment-specific	**Patient-specific**	**Myeloma-specific**
Immunomodulatory drugs	Age	Active uncontrolled disease
High-dose dexamethasone	Previous VTE	Hyperviscosity
Erythropoietin	Infection	
Anthracyclines	Surgical procedures	
Multiagent chemotherapy	Cardiovascular comorbidities	
	Immobilization	
	Inherited thrombophilia	
	Central venous catheter	
Recomendations for thromboprophylaxis		
Risk factor	**Number of risk factors**	**Therapy**
Treatment-specific	>1	LMWH or warfarin
Patient-specific	1	ASA
Myeloma-specific	1	ASA
Patient- or myeloma-specific	>2	LMWH or warfarin

VTE — venous thromboembolism; LMWH — low molecular weight heparin; ASA — acetylsalicylic acid

and decreases in the period of MM remission or recurrence. VTE risk factors are presented in Table IV [51].

An increased risk of VTE has been observed during treatment with IMiDs used both as monotherapy and combined with dexamethasone and other drugs such as carfilzomib and adriamycin or ESA [52, 53]. According to the IMWG recommendations, in patients with at least one treatment-specific, or at least two patient-specific or MM, risk factors for VTE, treatment with low-molecular-weight heparin (LMWH) or warfarin (target international normalized ratio 2–3) is recommended. However, acetylsalicylic acid (ASA) treatment is recommended in lower-risk patients. The

optimal duration of antithrombotic prophylaxis has not yet been established. It is often recommended for 4–6 months, while ASA can be used chronically. The risk of developing VTE with lenalidomide maintenance treatment is low, and thromboprophylaxis is not required [52, 54, 55].

If a thromboembolic complication occurs, anti-MM treatment may be temporarily interrupted and restarted with concomitant therapy with warfarin or LMWH. New oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban) are valuable in VTE treatment [56, 57].

Application of dialysis therapy in patients with MM

Renal impairment (RI) is diagnosed in 20–40% of patients with MM, with 2–4% requiring renal dialysis [58]. Kidney involvement occurs due to excessive secretion of serum-free light chains (sFLC) leading to foundry nephropathy, hypercalcemia, acute tubular necrosis, or acquired Fanconi syndrome. Current data supports high-cutoff hemodialysis (HCO-HD) combined with anti-MM therapy. In combination with anti-MM therapy, HCO-HD leads to a sustained reduction in FLC concentration in 67% of patients and leads to independence from dialysis in 63% of patients [59].

Prevention and treatment of bone disease in course of MM

Osteolytic lesions can cause skeletal-related severe events (SREs) such as hypercalcemia, pain, and fractures requiring surgery or radiotherapy. Osteolytic changes are detected by X-ray examination of the skeletal system in at least 80% of MM patients [60]. SREs are found in 40% of NDMM patients and in more than 20% of patients with RRMM. At MM diagnosis, pathological fractures and compression fractures are diagnosed in 26% and 22% of patients, respectively. In 58% of patients with NDMM, pain is present during bone disease [28]. As a result of compression of the nerves in the spinal cord, neurological symptoms may develop, including decreased sensation or numbness in the extremities. Spinal cord compression caused by a MM tumor or bone fractures that compress the spinal cord can occur. Local and systemic treatment is used in the treatment of bone changes. Radiotherapy can treat pain or pressure on the spinal cord. In the case of compression fractures of the vertebrae, kyphoplasty is performed, and surgery is performed in the case of fractures of long bones or instability of the spine. Two groups of drugs are used to treat systemic treatment and prevent the occurrence of SREs: bisphosphonates (BP) and denosumab, an inhibitor of the kappa-B nuclear ligand–receptor RANKL (receptor activator for nuclear factor κB ligand). Pamidronic acid (PA) and zoledronic acid (ZA) are the BPs used to treat bone disease [61]. Particular caution should be exercised when treating BPs in patients with MM and RI (creatinine clearance: 30–60 mL/min). Zoledronic acid is a BP recommended for use in all MM patients, regardless of the presence of bone disease in imaging tests. In addition, this drug is recommended for use in patients with asymptomatic biochemical recurrence of MM. The use of ZA is limited in patients with RI [62, 63]. In such cases, an alternative may be denosumab, a MoAb that inhibits RANKL activation. The effectiveness of denosumab is comparable to that of ZA at the time of the first SRE [64]. Hypocalcemia is more frequent with denosumab treatment than with ZA treatment (17% vs. 12%), but conversely renal adverse events are less frequent (10% vs. 17%). For this reason, denosumab is recommended for treating MM patients with RI [65–67]. Another indication for denosumab treatment is BPs-resistant hypercalcemia.

It is worth noting that since its approval the use of denosumab in MM has increased rapidly, irrespective of renal function or BP intolerance, mainly due to the advantages of subcutaneous administration. Denosumab, like ZA, does not show anti-MM activity in the case of disease recurrence, but is effective in inhibiting bone resorption markers.

Other treatments for bone disease in the course of MM include surgery, vertebroplasty, and radiotherapy.

Surgical treatment is indicated in the case of high-risk long bone fractures and compression fractures of the vertebrae. Vertebroplasty and balloon kyphoplasty effectively reduce pain resulting from compression fractures of the vertebrae. Radiotherapy is the treatment of choice for solitary plasmacytoma. More than 90% of patients respond to topical therapy. Low-dose radiotherapy (8 Gy × × 1 fx or 10–30 Gy × 2–3 fx) can be used for uncontrolled bone pain, impending spinal compression, and pathological fractures [67].

Prevention and treatment of peripheral neuropathy in course of MM

Peripheral neuropathy (PNP) can be seen in MM and can also develop with IMiDs, PIs, and histone deacetylase inhibitor (HDACi) treatment, an incidence rising to 19% in NDMM [68]. Thalidomide can cause severe and, in most cases irreversible, PNP, especially in patients with existing PNP. Thalidomide-induced PNP appears to be cumulative and persistent toxicity, unlike bortezomib-induced PNP, which typically occurs within the first five treatment cycles and is rarely observed later [69]. PNP development is more likely to occur during treatment with intravenous bortezomib than with subcutaneous administration. The most common PNP is sensory, very rarely motor. We have clearly defined guidelines for dose reduction of bortezomib based on the intensity of PNP. Anticonvulsants (gabapentin and pregabalin), antidepressants, and analgesics mainly treat PNP and neuropathic pain symptoms.

Other anti-MM agents, including other PIs (ixazomib, carfilzomib), and other IMiDs (lenalidomide, pomalidomide), are less likely to cause neurotoxicity [70].

Occurrence and treatment of skin lesions during MM therapy

Skin changes, including rashes, are among the most commonly observed AEs during treatment with IMiDs. Rash (of any grade) has been reported in approximately a quarter of lenalidomide-treated patients and most often develops within the first month of treatment [71]. Such rashes have been rarely observed and are primarily mild during treatment with bortezomib. In combination with antihistamines, topical corticosteroids treat mild and moderate rash [72]. In contrast, the discontinuation of lenalidomide treatment and the initiation of systemic corticosteroid therapy is recommended to treat a severe rash. The changes usually go away after one or two weeks, and most patients tolerate re-treatment with lenalidomide and switching from dexamethasone to prednisone. The reappearance of rash is a contraindication to lenalidomide treatment [72].

Prophylaxis and treatment of cardiovascular complications

Cardiovascular diseases are diagnosed in over 60% of patients at the time of MM diagnosis, the most common being cardiac arrhythmias, ischemic disease, and congestive heart failure. Additionally, more than 70% of patients develop cardiac complications during the treatment of newly diagnosed and recurrent MM [73]. Drugs used in treating MM with AEs on the heart are anthracycline antibiotics, IMiDs, or PIs. Acute cardiac events during treatment with doxorubicin include arrhythmias and ECG abnormalities. Left ventricular failure and the development of congestive heart failure occur in c.1–2% of patients and increase with cumulative dose of the drug [74]. The pegylated liposomal form of doxorubicin reduces cardiotoxicity compared to the classic form. In contrast, using pegylated liposomal doxorubicin in combination with bortezomib causes cardiac severe adverse events in 2% of patients [75].

Immunomodulatory drugs can induce cardiac arrhythmias, including sinus bradycardia and atrioventricular block, and increase the risk of thromboembolic events. Thalidomide causes sinus bradycardia in 5% of patients [76]. Another serious complication of treatment with thalidomide is the development of pulmonary arterial hypertension (PAH), which occurs in 4.8% of patients and correlates with structural heart disease and PAH [77]. In phase III clinical trials with IMiDs (lenalidomide, pomalidomide) in combination with dexamethasone, heart failure (grade ≥3) was found in 2–8% of patients [12–15, 24]. On the other hand, the use of thalidomide in combination with bortezomib and dexamethasone in inducing treatment causes serious cardiac events (grade ≥3) in 8% of patients [78].

The causes of cardiotoxicity caused by PIs are still not fully understood. One of the mechanisms may be the inhibition of the sarcomeric turnover protein, resulting in the death of myocytes [79]. The incidence of heart failure (all grades) in patients treated with bortezomib ranges from 2% to 17.9%, depending on the clinical trial [80]. Carfilzomib is a PI used in Europe to treat RRMM. In phase III studies, heart failure (grade ≥3) was observed in 2–4% of carfilzomib-treated patients [12, 16, 81] and in 0–7.5% of bortezomib-treated patients [9, 82–84]. In the ENDEAVOR study, heart failure (grade ≥3) was observed in 2.8% of patients treated with carfilzomib in combination with dexamethasone and in 0.7% of patients treated with bortezomib plus dexamethasone [16]. In patients treated with ixazomib, the development of arterial hypertension has been found in 5% of patients [85]. In the TOURMALINE-MM1 study, in a group of patients treated with Ixa-Rd (ixazomib, lenalidomide, dexamethasone) versus Rd, heart failure, arrhythmias, hypertension, and myocardial ischemia were found in 4% of both groups, 16% versus 15%, 6% versus 5%, and 1%, respectively versus 2% of patients [13].

In Europe, bortezomib is approved for the treatment of both NDMM and RRMM, while carfilzomib and ixasomib are used to treat RRMM.

Angiotensin-converting enzyme (ACE) inhibitors and beta-blockers are drugs recommended for treating symptomatic heart failure with reduced ejection fraction. An additional option is using a mineralocorticoid receptor antagonist; an angiotensin receptor nepresin inhibitor, and ivabradine. If optimal pharmacological treatment is not practical, cardioverter-defibrillator implantation may be considered [86].

Arterial hypertension is diagnosed in 38% of patients at the time of myeloma diagnosis [87]. It is found relatively often in patients treated with PIs. In phase III studies, in a group of patients with RRMM, the development of arterial hypertension (grade ≥3) was found in 0–4% of patients treated with bortezomib, in 3–15% of patients treated with carfilzomib [12, 16, 81], and in 5% of patients treated with ixasomib in combination with Rd [85].

Arterial hypertension develops in 5% of patients treated with daratumumab and in less than 7% of patients treated with daratumumab plus bortezomib and dexamethasone [88]. In the treatment of grade I hypertension, thiazides are recommended, and grade II a diuretic plus an ACE inhibitor or an angiotensin receptor blocker or a beta-blocker is the recommendation [89].

Prevention and treatment of most common AEs observed during treatment with MoAbs

In 2015, the US Food and Drug Administration (FDA) approved the first anti-CD38 monoclonal antibody for treating

MM, daratumumab. Another anti-CD38 MoAb is isatuximab. Isatuximab, based on the results of the phase III ICARIA-MM study, has been approved by the FDA and European Medicines Agency (EMA) for use in combination with Pd in the therapy of RRMM. The anti-SLAM7 monoclonal antibodies (elotuzumab) and anti-B-cell maturation antigen are also used to treat MM (anti-BCMA, belantamab mafodotin). Many clinical trials have been carried out with these drugs in recent years, and they are currently used to treat NDMM and RRMM.

Reactions related to infusion of MoAbs

Daratumumab treatment in monotherapy and combination therapy has a favorable safety profile. Most infusion-related reactions (IRR, 96%) are observed with the first infusion. The most commonly observed AEs are fatigue, nausea, anemia, back pain, cough, upper respiratory tract infection, thrombocytopenia, and neutropenia. Reactions related to daratumumab infusion have been observed in 48% of patients and include nasal congestion, cough, allergic rhinitis, throat irritation, and dyspnea. Antihistamines, corticosteroids, and acetaminophen have been used to treat infusion-related reactions [90]. In the POLLUX clinical trial, daratumumab IRR were observed in 47.7% of patients; they were most often mild and occurred during the first infusion [14]. A similar incidence of IRR was seen in the CASTOR study, which used daratumumab in combination with bortezomib and dexamethasone (DVd). Daratumumab IRR occurred in 45.3% of patients and occurred mainly during the first infusion [17]. In both the POLLUX and the CASTOR studies, dexamethasone 20 mg intravenously/orally or an equivalent long-acting corticosteroid, acetaminophen 650–1,000 mg intravenously/orally, and an intravenous/oral antihistamine (diphenhydramine in 25–50 mg or equivalent) were used.

Rarely, mild (grade I/II) AEs develop during treatment with elotuzumab. The most common symptoms are chills, fatigue, fever, cough, headache, anemia, nausea, and back pain. One of the most frequently reported AEs is an IRR, found in fewer than 60% of patients during the first elotuzumab infusion in a Phase I study. With subsequent infusions of elotuzumab, IRRs were observed in half of them. No severe IRR was observed after changing the infusion rate of elotuzumab and using methylprednisolone, diphenhydramine, and acetaminophen. Grade I/II infusion reactions resolved spontaneously, usually within 24 hours [91].

In the phase III clinical trial, ELOQUENT-2, which compared EloRd (elotuzumab, lenalidomide, dexamethasone) to Rd, diphenhydramine (dose: 25–50 mg) or its equivalent, ranitidine (dose: 50 mg) or equivalent, and acetaminophen (dose: 650–1,000 mg) were used before starting the elotuzumab infusion. Infusion-related reactions were reported in 33 patients, including 29 with grade I/II. Most infusion-related reactions (70%) were observed after the first dose of elotuzumab [15]. To prevent an IRR to elotuzumab, the administration of diphenhydramine and ranitidine or their equivalents, as well as acetaminophen, is recommended c.30–60 minutes before the start of elotuzumab infusion and administration of elotuzumab 10 mg/kg body weight (in 250 mL), starting with flow 0.5 mL/min [92].

Infusion-related reactions with belantamab mafodotin (BM) are rare and usually grade I/II. If grade II or higher infusion reactions occur during the BM infusion, the infusion rate should be reduced or stopped, depending on the severity of the symptoms. If a grade II or higher IRR occurs, premedication should be initiated before the next infusion. If a grade II IRR occurs, the infusion should be interrupted, supportive treatment started, and when symptoms resolve, infusion should be continued at a rate reduced by at least 50%. However, if grade III/IV IRRs occur, the infusion should be stopped and supportive care given. After symptoms have resolved, the infusion can be continued at a reduced rate of at least 50%. If an anaphylactic or life-threatening infusion-related reaction occurs, the infusion should be stopped and appropriate emergency measures started [93].

Prevention and treatment of keratopathy during BM therapy

Belantamab mafodotine is an antibody-drug conjugate approved for the treatment of RRMM. It is an agent against the B-cell maturation antigen (BCMA). Treatment with BM is associated with a high incidence of ocular complications, including keratopathy (≥20%) [85]. In the Phase I DREAMM-1 clinical trial, 53% of patients in the first part, and 63% of patients with MM in the second part of the study, had corneal AEs [94]. In contrast, in the randomized phase II clinical trial, DREAMM-2, keratopathy (grade III/IV) was observed in 31% of RRMM patients treated with BM 2.5 mg/kg body weight monotherapy and 34% of RRMM patients treated with BM in 3.4 mg/kg body weight [95, 96]. In the DREAMM-6 study, 83% of patients experienced keratopathy in the combination of BM with bortezomib and dexamethasone in RRMM [97]. To reduce the risk of keratopathy incidence, an ophthalmological examination to assess vision is recommended before initiating treatment with BM and then again during treatment (assessment of AEs). Dose reduction or interruption of therapy with BM depends on the severity of ocular toxicity, including blurred vision, dry eyes, and corneal ulceration. BM should be discontinued if ocular toxicity is severe. BM dose modifications based on AEs in the cornea are summarized in Table V [93].

Adverse events in CAR-T therapy

The introduction to therapy of CAR-T has significantly changed the prognosis of patients with B-cell malignances,

Table V. Belantamab mafodotin dose modifications based on corneal adverse events

Category	Eye examination findings		Belantamab mafodotin dose modification
	Corneal examination finding(s)	Change in BCVA	
Mild	Mild superficial keratopathy	Decline from baseline of 1-line on Snellen Visual Acuity	Continue treatment at current dose
Moderate	Moderate superficial keratopathy	Decline from baseline of 2 or 3 lines (and Snellen Visual acuity not worse than 20/200)	Withhold treatment until improvement in examination findings and BCVA to mild severity or better Consider resuming treatment at a reduced dose of 1.9 mg/kg body weight
Severe	Severe superficial keratopathy Corneal epithelial defect	Change in BCVA: decline from baseline of more than three lines	Withhold until improvement in examination findings and BCVA to mild severity or better For worsening symptoms that are unresponsive to appropriate management, consider discontinuation

BCVA — best corrected visual acuity

including patients with MM. CAR-T can cause numerous AEs, including life-threatening ones such as cytokine-release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) [98]. CRS (grade III/IV) is found in 6–38% of patients and ICANS (grade III/IV) in 3–12% of patients [99–102]. The main symptoms of CRS include pyrexia, hypotension, hypoxia, and organ toxicity, which may result in organ failure. However, the main symptoms of ICANS are a disturbance in concentration, cognitive impairment, confusion, agitation, tremors, lethargy, aphasia, delirium, somnolence, convulsions, motor weakness, and paresis or signs of intracerebral pressure. ICANS development most often occurs during or after CRS and in c.10% of cases up to four weeks after CAR-T infusion.

For early detection, it is recommended to perform a neurological assessment at least twice daily using the immune effector cell-associated encephalopathy (ICE) screening tool [98]. It is currently believed that pro-inflammatory interleukin-6 (IL-6) plays a crucial role in the pathogenesis of CRS [103]. A recent study identified mbaIL-6 expression on the surface of T cells that was associated with the rapid clearance of IL-6 from the cell culture supernatant. T lymphocytes co-expressing mbaIL-6 and anti-CD19 CAR neutralized macrophage-derived IL-6, retaining antitumor activity *in vitro* and the xenograft model. Another strategy is to turn on 'suicidal' switches such as constructs containing CAR and inducible caspase 9. The administration of a small molecule that dimerizes inducible caspase 9 resulted in CAR-T specific apoptosis and depletion [104].

Other side effects during CAR-T treatment are hemophagocytosis and prolonged cytopenia. Neutropenia (grade III/IV) has been reported in 85–100% of patients and thrombocytopenia (grade III/IV) in 28–69% of patients [99–102].

Conclusions

In the past, dosages of anti-MM drugs and durations of treatment were determined by AEs, especially myelosuppression or PNP. The introduction of new anti-MM drugs has led to the development of highly effective treatment regimens for MM. Better understanding of the role of drug toxicity in early and late AEs is important due to the shift from short-term to chronic treatment. Treatment of a patient with MM should be based not only on the characteristics of the disease, but also on patient factors including age, general condition, comorbidities, and AEs of previous treatment.

In the treatment of MM, a very important role is played by the management of AEs, including regular monitoring and prompt and appropriate intervention in the event of treatment-related AEs, based on scientific knowledge, applicable guidelines, and clinical experience.

Authors' contributions

GC, AJ, DHV — wrote and critically revised manuscript.

Conflict of interest

None.

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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; and Uniform Requirements for manuscripts submitted to biomedical journals.

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A living drug: application of CAR-T therapy for lymphoid malignancies and beyond

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Abstract

The ongoing development of novel personalized cancer therapies has resulted in the implementation of T-cells enriched with synthetic chimeric antigen receptors, known as chimeric antigen receptors T-cell (CAR-T) cells, into clinical practice. CAR-T cells are able to recognize and bind specific antigens present on the surface of target cells — so-called tumor-associated antigens. This innovative method has been approved for the treatment of hematological malignancies and may also serve as a bridge to hematopoietic stem cell transplantation. The production of the drug containing modified T-cells consists of several steps — leukapheresis, T-cell activation, transduction and expansion of the final CAR-T cells. Activation of CAR-T cells occurs through a pathway independent of the major histocompatibility complex, which is often associated with uncontrolled responses from the immune system and adverse reactions such as cytokine release syndrome. CAR-T therapy can only be performed in certified centers, and requires close cooperation between experienced specialists of different medical disciplines. This is what determines its effectiveness. Every step from collection and cryopreservation, through transport and modification, to thawing and infusion is strictly controlled because it has a critical impact on the quality and efficiency of the drug. Despite its proven benefits, CAR-T therapy remains available only to patients who meet well-defined criteria. These however are liable to change with the emergence of new indications.

Key words: CAR-T, efficacy, CRS, ICANS, side effects

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Introduction

The ongoing quest to develop more effective methods of cancer treatment has recently resulted in the implementation of a therapeutic modality based on the patient's cells, which combines the achievements of gene-, cell-, and immunotherapies.

Chimeric antigen receptors T cell (CAR-T) therapy, i.e. the use of T lymphocytes enriched with synthetic chimeric antigen receptors (CAR), has shown significant efficacy in the treatment of certain hematological malignancies, including mainly refractory and relapsed leukemias and lymphomas [1].

The motivation to engineer CAR-T cells was the antibody dependent cellular cytotoxicity (ADCC) process. This begins with the coating of the target cell by an antibody, which bridges a natural killer (NK) cell containing a Fc receptor (FcR). The activation of NK cells results in their degranulation, leading to the release of perforin, granzymes, and granulysins, followed by apoptosis of the target cell [2, 3]. In the late 1980s, the first studies were published describing the activation of T-cells without the involvement of major histocompatibility complex (MHC), i.e. through the combination of T-cell receptor (TCR) with variable antibody fragments [4, 5]. Three decades later, in

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Table I. Food and Drug Administration (FDA)-approved chimeric antigen receptors T-cell (CAR-T) cell therapies (source [6])

Brand name (generic name)	Indications	Target	Date of approval
Kymriah™ (tisagenlecleucel)	r/r DLBCL r/r B-ALL up to 25 years	CD19	August 30, 2017
Yescarta™ (axicabactagene ciloleucel)	r/r DLBCL r/r PMBCL r/r FL	CD19	October 18, 2017
Tecartus™ (brexucabtagene autoleucel)	r/r MCL r/r B-ALL	CD19	July 24, 2020/October 1, 2021
Breyanzi® (lisocabtagene maraleucel)	r/r LBCL	CD19	February 5, 2021
Abecma® (idecabtagene vicleucel)	r/r MM	BCMA	March 26, 2021
Carvykti™ (ciltacabtagene autoleucel)	r/r MM	BCMA	February 28, 2022

r/r – relapsed/refractory; DLBCL – diffuse large B-cell lymphoma; B-ALL – B-cell acute lymphoblastic leukemia; PMBCL – primary mediastinal large B-cell lymphoma; FL –follicular lymphoma; MCL – mantle cell lymphoma; LBCL – large B-cell lymphoma; MM – multiple myeloma; BCMA – B-cell maturation antigen

2017, the US Food and Drug Administration (FDA) approved the two first drugs for relapsed or refractory (r/r) malignancies: for B-cell acute lymphoblastic leukemia (B-ALL) – Kymriah™ (Novartis) and for diffuse large B-cell lymphoma (DLBCL) – Yescarta™ (KitePharma). Since then, six CAR-T-based immunotherapies have been approved (see Table I) [6].

Structure of CAR-T

The transmembrane CAR-T cells' receptor has a modular structure and is classically composed of five parts, which determine its durability and efficacy:

1) extracellular antigen-binding domain – a key component responsible for CAR specificity by recognizing a well-defined antigen, such as CD19, without the involvement of the MHC. It is derived from the single-chain variable fragment of the antibody (scFv), which is built from light and heavy regions linked by a peptide fragment;
2) hinge region – a linking element whose length and flexibility affect CAR functionality;
3) transmembrane domain – a hydrophobic fragment responsible for signal transduction into the cell and for receptor stability;
4) intracellular costimulatory domain – co-responsible for signal transduction. This structure reduces the risk of lymphocyte anergy, thus preserving the functionality, proliferation and survival of CAR-T cells. The drug Kymriah™ contains the 4-1BB domain, and Yescarta™ contains CD28. Studies indicate that the use of 4-1BB is associated with a later and smaller peak of expansion and higher longevity of CAR-T cells relative to those with the CD28 domain, which rapidly reach a maximum of activity, and subsequently become exhausted. It has been observed that the use of the 4-1BB domain promotes the differentiation of cells into central memory T-cells (T_{CM}), whereas the CD28 domain affects the differentiation into effector memory T-cells (T_{EM});
5) intracellular signalling domain – responsible for signal transduction into the cell, usually contains the TCR CD3ζ complex [7–10] (see Figure 1).

Subsequent modifications of CAR have led to the development of their five generations. The first generation lacks a costimulatory domain, making it insufficiently effective. The second generation contains one costimulatory domain, and the third generation contains two. The fourth generation has been further enriched with the ability to produce proteins such as cytokines – interleukins (IL) and chemokines, and the fifth generation with the expression of interleukin-2 receptor (IL-2R) β domain, which stimulates the STAT3/STAT5 signaling pathway. Currently, second generation CARs have been used in clinical practice [11].

Production of CAR-T cells and application in clinical practice

The production of a CAR-T cell drug is a multi-step process, and requires the collaboration of many specialists. Once the number of peripheral blood lymphocytes exceeds 0.3 × 10^3/μL, a patient eligible for CAR-T therapy is referred for leukapheresis targeting unmobilized CD3+ T-cells. This procedure is performed in transplant centers that routinely perform apheresis to collect hematopoietic stem cells from mobilized peripheral blood [12]. It is important to maintain an interval between the use of certain drugs indicated by the manufacturer and the apheresis, the so-called wash out period. For example, bendamustine impairs CAR-T cell production, but there are many others [13].

The main factors affecting the efficiency of leukapheresis are the patient's health status and age. In patients being treated for malignancies, lymphopenia, as a consequence of chemotherapy, may hinder the collection of sufficient numbers of cells [14]. An example is the concentration of memory T-cells in patients with ALL and non-Hodgkin lymphoma (NHL), which decreases with each course of standard treatment [15]. The possible contamination of

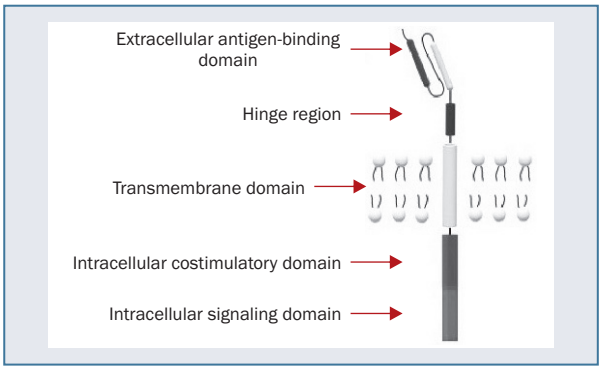

Figure 1. Schematic diagram of chimeric antigen receptors (CAR) structure [7–10]

the material by erythrocytes, monocytes and granulocytes can also be a problem [12]. The collected product should contain as many T-cells as possible. This has a beneficial effect on the efficiency of CAR-T cell production, and also reduces the possibility of accidental transduction of other populations, including tumor cells, inducing resistance to therapy. In infants and young children, the smaller volume of circulating blood remains an additional challenge [16].

Bearing these limitations in mind, methods of purifying the material after apheresis can be used in the production of CAR-T therapy drug. One of these involves the selection of T lymphocytes, or their specific subpopulations, using magnetic beads conjugated with antibodies. This allows the separation of a pure population of required cells from a heterogeneous population of leukocytes [15]. A fully automated closed system CliniMACS Prodigy® (Miltenyi Biotec, Germany) using appropriate antibodies combined with microbeads is commercially available [17]. T-lymphocyte selection is mainly performed on material collected from patients with a high number of tumor cells in the peripheral blood, e.g. from untreated patients with chronic lymphocytic leukemia (CLL). Selection is also used in the later steps of drug production. Using anti-CD3, anti-CD4 or anti-CD8 antibodies, a final cell product with a specific CD4+/ /CD8+ lymphocyte ratio can be obtained, which positively influences the antitumor activity of CAR-T cells [18]. Furthermore, research to develop subcutaneous implants is in progress. They would be coated with antigens specific to receptors present on desired T-lymphocyte subpopulations, so that *in vivo* they could specifically capture cells necessary for CAR-T production. After a few days, such implants would be removed from the patient's body, thus replacing traditional apheresis [14].

The collected material is delivered to the Cell Bank and to the Hematological Laboratory, where CD3+ cell count and viability is determined by flow cytometry. After confirming the appropriate quality, the product is prepared for transport to the Cell Engineering Laboratory. Cells collected during leukapheresis can be transported unfrozen or frozen, although fresh lymphocytes have a short period of sufficiently high viability, and so in most cases cryopreservation of cell suspension in liquid nitrogen is recommended, using 5–10% dimethylsulfoxide (DMSO) as a cryoprotectant [15].

Proper cryopreservation of material with adequate cellularity is critical to maintaining product quality, and must be done under controlled conditions with a slow rate of temperature decrease. The transport of cells in an adapted dewar, a kind of vessel with a vacuum space between liquid nitrogen and the outer walls, is a critical moment for maintaining the viability of the required cytotoxic T-cells. Currently, pharmaceutical companies which are distributors of the drug in Poland cooperate with laboratories located in Switzerland, the United States of America (USA) and France, among others [19].

In pharmaceutical manufacture, the material is firstly thawed and washed to remove anticoagulants added during leukapheresis with the use of counterflow centrifugation. The T lymphocytes are then activated, which is a necessary step for subsequent transduction and expansion *ex vivo* [20]. The most common way to activate T lymphocytes is by stimulation using soluble anti-CD3 monoclonal antibodies or immobilized — on the surface of flasks or paramagnetic beads — anti-CD3 and anti-CD28 antibodies. The anti-CD3 antibodies are responsible for the proliferative signal, and the anti-CD28 antibodies are responsible for the costimulatory signal. Flasks form a relatively small surface area for T-cells to adhere to, so paramagnetic beads are more commonly used. The suspension containing such microbeads should then be exposed to a magnetic field in order to remove them from the finished product, which will be administered to the patient [15, 18]. Another way to activate T-cells uses retronectin, a recombinant fragment of human fibronectin that enhances gene transfer efficiency in retroviral transduction. Retronectin, combined with anti-CD3 and anti-CD28 monoclonal antibodies, is a promising method for proliferating less differentiated T-cell subpopulations, which may be beneficial for long-term persistence of CAR-T cells *in vivo*. However, retronectin activation should be performed with caution, especially in patients with a high percentage of tumor cells in the peripheral blood, as it may stimulate persistent malignant B cells within the cell product, especially if T-cell selection was not performed at the initial production step [18, 21].

In the next step, the CAR transgene is delivered into cells using lentiviral or retroviral vectors. The high transduction efficiency with these viruses requires the previously mentioned activation of T lymphocytes. Especially for retroviruses, which transduce only dividing cells, proliferation is essential for gene transfer [22]. Lentiviral vectors are usually produced by transient transfection using large amounts of plasmid DNA, making them more expensive than retroviruses which can be produced using stable packaging cell

lines [23]. However, it is important that viral vectors introduce genetic material into the genome in a manner that is random, otherwise we pose the risk of silencing a random gene or causing insertional oncogenesis [14].

Recent years have also seen the development of non-viral T-cell transfection techniques, which use transposon/transposase systems. A transposon is a DNA sequence that has the ability to change position within the genome via transposase-mediated excision and insertion [24]. To date, four transposons have been described: Sleeping Beauty (SB) and Frog Prince, which were reconstructed from inactive transposons derived from the fish and frog genomes, respectively; Tol2, which is the only vertebrate transposon of natural origin; and piggyBac (PB), which is derived from the insect *Trichoplusia ni*. SB and PB have high transposase activity in mammalian cells, with higher activity for PB and involving larger chromatin loops than in SB. In addition, PB does not leave gene excision marks, so that possible genome damage is less likely. Transposition involving PB is also simple to reproduce *in vitro* [25]. Targeted CAR transgene insertion can also be performed using the CRISPR-Cas9 genome editing system. Preclinical studies have shown promise in using this system to ablate the endogenous αβ TCR receptor on the surface of T-cells, and thus reduce the prevalence of graft-versus-host disease (GvHD) [26–28]. These modifications allow for the expression of CAR, which gives the T-cells the ability to recognize a specific antigen. In hematological malignancies, where CAR-T therapy is predominantly used, the receptor for the CD19 antigen is most frequently used [1].

The ready, genetically modified lymphocytes are expanded in static or dynamic dishes or culture devices until the required therapeutic dose is reached. Ready-made culture media adapted to multiple cells of adaptive cell therapy, supplemented with e.g. IL-7 and IL-15 or human serum, are used. Cultures are monitored for bioanalytes — pH, glucose, lactate, electrolytes, pO_2, pCO_2, humidity — and for cell proliferation and volume change. This step can take place before or after gene transduction, depending on the drug manufacturer, and lasts approximately 10 days [20, 29]. Finally, cells are harvested and cryopreserved for further distribution. The frozen drug is received by the hospital pharmacy, which is responsible for its storage at a temperature ≤–130°C and subsequent delivery to the department. The completed product is intended only for a single autologous application in a particular patient [30].

The complete process of CAR-T cell production usually takes about four weeks (17 to 60 days). During this time, the patient may be considered for bridging therapy in the form of classical chemotherapy or immunotherapy and radiation therapy, based on disease burden. Promising results have been observed with the use of polatuzumab, but this requires further studies [31]. The lymphodepletion phase is between day –5 and day –3, and a regimen containing

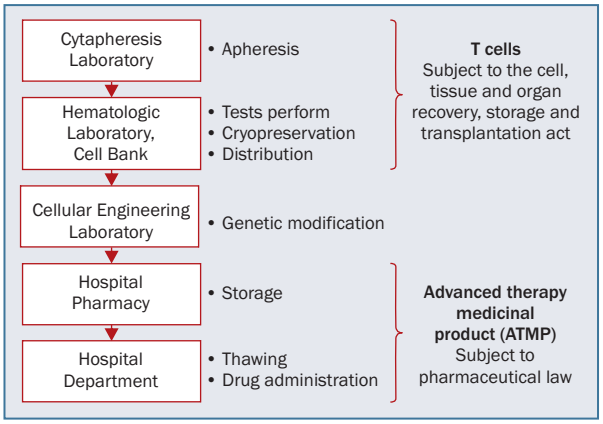

Figure 2. Schematic of collaboration in implementation of chimeric antigen receptors T-cell (CAR-T) therapy

fludarabine/cyclophosphamide, which increases the expansion of CAR-T CD19 cells, is used. On the day of infusion, the drug is thawed in a 37°C water bath at the patient's bedside, as is done in cryopreserved hematopoietic stem cell transplantation, and immediately administered as an intravenous infusion. Additionally, premedication of oral paracetamol and intravenous diphenhydramine, or another H1 antihistamine, may be considered, but prophylactic use of systemic corticosteroids is not recommended — there is a possibility of drug interference.

A requirement for the use of the product is access to at least one dose of tocilizumab, which has an immunosuppressive effect. After the infusion, until at least day 10, the patient is hospitalized and thereafter for at least four weeks is obliged to remain near the center for close observation [19, 32, 33]. Figure 2 presents a schematic showing collaboration in the implementation of CAR-T therapy.

Mechanism of action

Modified CAR-T cells are able to recognize and bind specific antigens present on the surface of target cells, mainly tumor cells — tumor-associated antigens (TAAs) — however, it should be noted that normal antigen-presenting cells may also be targeted. Upon binding to the antigen, a signaling cascade activating CAR-T is induced through a conformational change. The release of perforins and granzymes, using immunological synapse, leads to the activation of cytotoxic mechanisms. Expression of Fas ligand (FasL) and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) on the surface of CAR-T, by binding receptors containing the so-called death domain, induces apoptosis. Among others, caspase 8 and caspase 3 are involved in this process. Secretion of proinflammatory cytokines (IL-2, interferon-γ, tumor necrosis factor-α) activates other cells of the immune system. The reason for the superiority of the described processes in the therapy of hematological

malignancies compared to solid tumors is the lack of physical barriers — the localization of tumor cells and migrating T lymphocytes is usually the same — and the lack of an immunosuppressive microenvironment, which hinders the infiltration of CAR-T cells into the tumor site [34, 35].

CAR-T available for Polish patients

The cost of administering the drug exceeds $350,000 [36]. In Poland, CAR-T therapy has been reimbursed for patients with relapsed/refractory (r/r) B-ALL up to 25 years since September 2021 and for patients with r/r DLBCL since May 1 2022. A patient who meets the reimbursement criteria, in accordance with the relevant drug program (B.93), may apply through an accredited center for eligibility for treatment, which is subject to a final decision by the CAR-T Coordination Team.

The number of clinical trials for CAR-T therapy in 2022 was about 1,000, of which less than 10% are being conducted in Europe [37]. Despite excellent research facilities, European countries, compared to the USA or China, have complicated and time-consuming regulatory regulations, resulting in delays in clinical application of trials, as well as funding problems [38]. In Poland, the development of CAR-NET adoptive therapy is possible thanks to a grant from the Medical Research Agency worth more than $220,000, which will be implemented by a consortium between 2021–2026. This aims to improve therapeutic efficacy and significantly reduce the cost of CAR-T therapy, which would enable its application on a larger scale, rather than as before in the form of single cases often financed by public donations.

Difficulties associated with use of CAR-T therapy

Activation of CAR-T cells through an MHC-independent pathway may be associated with uncontrolled immune responses and some adverse reactions. The main ones include cytokine release syndrome (CRS), neurotoxicity with encephalopathy, headache, slurred speech and hallucinations, and also infections. Some patients develop transaminases increase, hypogammaglobulinemia, disseminated intravascular coagulation (DIC), and macrophage activation syndrome (MAS). These abnormalities are usually the manifestations of the expansion of CAR-T cells, which, after interaction with the patient's immune cells, activate each other, leading to increased toxicity [10].

CRS and ICANS

Binding of the CAR-T cell to the target TAA results in a cascade of reactions, including the production of proinflammatory cytokines. While desirable in limited amounts, in excess they can lead to serious clinical symptoms and threaten the patient's life. Symptoms of CRS include fever, decreased blood pressure, muscle and joint pain, accelerated heart rate, and tachypnea. The severity of CRS is assessed using a 5-grade classification. In extreme cases, CRS can lead to shock and multiorgan failure similar to hemophagocytic lymphohistiocytosis (HLH) or MAS. It is supposed that the severity of CRS correlates with previous allotransplantations, the percentage of blasts in the bone marrow before lymphodepletion, the dose of CAR-T cells, and the type of costimulatory domain used. An especially life-threatening condition is the rare blood-brain barrier injury leading to the development of immune effector cell-associated neurotoxicity syndrome (ICANS) with seizures, aphasia, brain edema, hypoxia, and elevated IL-15 levels. For treatment, in addition to IL-6 inhibitors, corticosteroids are used for patients with concomitant CRS. Preclinical studies on mouse models also indicate the involvement of IL-1 in the pathogenesis of CRS, and therefore the benefit of administering IL-1R antagonists or modification of 4th generation CAR-T to allow its release into the circulation. Another solution may be the inactivation of CAR-T cells by enriching them, e.g. with CD20 antigens, and then, in cases of CRS, administering rituximab; however, it should be remembered that this way of eliminating CAR-T cells will not be immediate [10, 39, 40].

On-target/off-tumor effect

Antigens (Ag) present on the surface of cancer cells are also found on some regular cells. The use of therapies targeting such Ag therefore runs the risk of attacking non-cancerous tissues. Due to the high heterogeneity of tumor cells, both inside cancerous and inter-individual, it is challenging to develop a unique set of TAAs to target CAR-T cells. This phenomenon is also an impediment when trying to develop bispecific CARs. One way to protect non-malignant cells may be to exploit the difference in expression of the same Ags on normal and cancer cells.

The administration of CAR-T cells whose scFv will have low affinity, and thus whose activation requires a high density of Ag on the surface of target cells, may prevent the destruction of normal tissues with low Ag expression [10, 41, 42].

Antigen loss

The complete or partial loss of Ag expression by tumor cells may be due to the proliferation of clones already present that lack specific Ag, or to the effect of treatment — the result of such a kind of selective pressure is the resistance of the patient to mono-targeted CAR-T therapy based on a single TAA. Some patients treated with anti-CD19 CAR-T cells may relapse with CD19- tumor cells due to mutations

or alternative gene splicing. Research is currently in progress to develop CAR-T cells that have CARs directed against several different Ags, including CD20 and CD22, to delay or avoid the difficulties associated with Ag loss [1, 10, 42].

T-cell exhaustion

An important factor limiting the efficacy of CAR-T therapy is T-cell exhaustion. CAR-T cell depletion is characterized by impaired effector function and increased expression of inhibitory receptors, such as the programmed death-receptor 1 (PD-1), due to chronic antigenic stimulation usually resulting from an ongoing chronic infection or from the neoplastic process itself. Aging or exhausted CAR-T cells are characterized by impaired proliferation and persistence *in vivo*. Strategies to detect, prevent, or reverse the effects of T-cell exhaustion — such as checkpoint blockade through ligand inhibition – are needed to enhance the efficacy of CAR-T therapy. One of them may include programmed death-ligand 1 (PD-L1) or PD-L2 by using nivolumab and pembrolizumab (anti-PD-1) [43–45].

Future of CAR-T therapy

Therapy of solid tumors

The effects of CAR-T therapy for solid tumors are currently not satisfying and are not associated with long-term responses. The problem of cancer cells heterogeneity precludes the success of available generations of CAR-T cells. In addition, the immunosuppressive microenvironment, including the extracellular matrix, constitutes a specific barrier and significantly limits the infiltration of CAR-T cells, leading to their depletion. Tumor cells are also characterized by increased expression of, among others, PD-L1, responsible for activation of signaling pathways impairing T-cell function.

In the future, determination of the type of abnormal immune response may be used to enrich CAR-T cells with, for example, receptors for specific ILs and chemokines produced by the tumor microenvironment. With such modifications, cytokines released by cancer cells will serve as chemoattractants for CAR-T cells [41, 46].

Allogeneic CAR-T cells

All CAR-T cell products on the market or in clinical trials are autologous, i.e. are produced from T-cells from the same patient, so if they are manufactured from dysfunctional T-cells, they may not be effective. CAR-T therapy might be the only treatment for patients with resistant and relapsing forms of the disease, but it should be kept in mind that in patients with leukopenia it can be difficult or impossible to obtain sufficient numbers of cells. The CAR-T vein-to-vein process time is also an issue — patients in poor condition may not survive the waiting period required for genetic modification.

The solution to these obstacles is offered by potentially lymphocytes from a healthy allogeneic donor; however, as in the case of transplantation, this is associated with the risk of rejection of CAR-T by the host or the development of GvHD. Accordingly, one of the concepts is to modify CAR-T cells and turn off the mediators of GvHD — the TCRs. Researchers also aim to develop universal allogeneic CAR-Ts, ready to be administered to patients with a specific disease — in other words, 'off-the-shelf CAR-T' [41, 47, 48].

Summary

CAR-T therapy is performed only in specialized centers with extensive experience in allotransplantation, which have received appropriate accreditation at several levels. The whole procedure is complicated, not only in terms of the sophistication of the genetic modifications performed, but also given its logistical difficulties. Despite its remarkable innovativeness, due to some adverse reactions, high costs and limited number of eligible centers, currently it is not the gold standard of treatment, but this may change.

The development of CAR-T therapy is of enormous interest, and thanks to the cooperation of bioengineers and clinicians it will undergo more and more innovative improvements in response to real needs and problems arising in clinical practice. It is possible that this therapy, along with immune checkpoint inhibitors and bispecific antibodies, will become the standard of care for hematooncology patients.

Authors' contributions

AS, AK — analyzed data, conceived and wrote manuscript, drew figures. GH, NGR — analyzed data, conceived and wrote manuscript, critical review. All authors contributed to the article and approved the submitted version.

Conflict of interest

GH — Speaker's fee and Advisory Board for Novartis (GH). AS, AK, NRG — none.

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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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Anemia of critical illness: a narrative review

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Abstract

The prevalence of anemia in patients admitted to the intensive care unit (ICU) reaches 66%. Moreover, numerous patients develop anemia during ICU hospitalization. In fact, anemia is the most common hematologic disease in the ICU.

The majority of patients hospitalized in the ICU present with acute systemic inflammation, so called systemic inflammatory response syndrome (SIRS). These patients may develop anemia of inflammation (AI). In crtitically ill patients AI may present acutely (acute systemic inflammation) or chronically (comorbidities associated with prolonged systemic inflammation), here we describe both presentations of AI as 'anemia of critical illness' (ACI). The second most frequent type of anemia in critically ill patients is iron-deficiency anemia (IDA). A mixed type of anemia (ACI + IDA) may also be present in these patients.

The three major pathophysiological mechanisms leading to ACI are: iron restriction, decreased erythropoiesis, and decreased erythrocyte lifespan. Cytokines synthesized during SIRS induce the production of hepcidin that inhibits the only transmembrane iron exporter (ferroportin) present in the duodenum and macrophages.

Etiological classification of anemia in critically ill patients poses a significant challenge to clinicians, as there is a multitude of tests available, and there are various reference ranges for these tests reported in the literature in the patient population in question. Pure ACI or mixed ACI + IDA can be diagnosed using a single laboratory test — complete blood count with analysis of reticulocytes — which provides Hb concentration in erythrocyte and reticulocyte.

The management of ACI incorporates discontinuation with erythropoiesis-stimulating agent causing anemia, reduction of iatrogenic blood loss, parenteral iron, and combined therapy of parenteral iron with erythropoiesis-stimulating agents in approved indications.

Key words: anemia of inflammation, anemia of critical illness, critically ill patients, hepcidin, iron-deficiency anemia, intensive care unit, reticulocyte hemoglobin equivalent

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Introduction

The prevalence of anemia in patients admitted to the intensive care unit (ICU) reaches 60–66% [1, 2]. Moreover, numerous patients develop anemia during ICU hospitalization, which is caused by disease processes, but may also be iatrogenic (e.g. phlebotomy, extracorporeal treatment procedures). By day 3 of ICU hospitalization, up to 90% of patients are anemic [3]. Lower hemoglobin (Hb) concentrations are associated with higher mortality rates and longer stays in the ICU, and in hospital in general [4].

The majority of patients hospitalized in the ICU present with acute systemic inflammation (SI), so called systemic inflammatory response syndrome (SIRS). These patients may develop anemia of inflammation (AI). AI, previously known as anemia of chronic disease (ACD), is also the most common

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Table I. Prevalence of anemia of inflammation in chronic conditions

Study	Year	Patient population	Anemia [%]
Birgegård et al. [9]	2006	Cancer (lymphoma + multiple myeloma)	72.9
Macciò et al. [7]	2015	Cancer (solid tumors)	63
Ambrosy et al. [10]	2019	Heart failure	57.1
Coiffier et al. [11]	2001	Cancer (chemotherapy)	54.1
Gaskell et al. [12]	2008	Older people (>65 years)	17-47
St Peter et al. [13]	2018	Chronic kidney disease (dialysis)	6.7–22.2
Boutou et al. [14]	2013	Chronic obstructive pulmonary disease	15.6

type of anemia in hospitalized chronically ill patients [5] and may be present in the following conditions: infection, autoimmune disease [6], cancer [7], chronic kidney disease (CKD), congestive heart failure, chronic obstructive pulmonary disease, pulmonary arterial hypertension, chronic liver disease, obesity, advanced atherosclerosis, and old age [8]. The prevalence of AI in different chronic conditions is presented in Table I [7, 9–14]. Patients with the aforementioned diseases are frequently hospitalized in the ICU. These factors make AI the most common type of anemia in critically ill patients [15]. In critically ill patients AI can present acutely (acute systemic inflammation) or chronically (comorbidities associated with prolonged systemic inflammation), so we decided to call both presentations of AI in critically ill patients 'anemia of critical illness' (ACI). The second most frequent type of anemia in critically ill patients is iron-deficiency anemia (IDA). A mixed type of anemia (ACI + IDA) may also be present in these patients.

Moreover, deficiency of vitamin B12, folic acid, and vitamin D, may also be present in critically ill patients.

The aim of this work was to summarize the current knowledge on the pathophysiology, diagnosis, and management of ACI, and to present our perspectives on this important topic.

Pathophysiology

There are three major pathophysiological mechanisms leading to ACI: iron restriction, decreased erythropoiesis, and decreased erythrocyte lifespan.

Iron-restricted erythropoiesis

The activation of immune cells leads to synthesis of cytokines. The most important here are interleukin (IL) 6 and 1β as they induce the production of hepcidin in the liver, which is the master regulator of the iron metabolism [16]. Hepcidin is a 25-amino acid protein that exerts its effects by inhibiting the only transmembrane iron exporter — ferroportin, either through internalization [17] or direct occlusion [18]. These ILs also decrease production of the only iron-transporting protein — transferrin. Bacterial lipopolysaccharide (LPS) and interferon gamma (IFN-γ) also block the transcription of ferroportin [19]. Ferroportin is present in the duodenum where dietary iron is absorbed, and in macrophages from where over 90% of daily iron comes from. All these mechanisms lead to iron-restricted erythropoiesis (IRE) and its typical laboratory profile: low iron, low transferrin, and high ferritin.

Decreased erythropoiesis

This effect is mainly caused by decreased erythropoietin (EPO) production. EPO is produced by fibroblasts in the renal cortex. Decreased EPO is caused by the negative effect of IL-1 and tumor necrosis factor alpha (TNF-α) on EPO expression [20], and decreased erythropoietin biological activity caused by IL-1 and IL-6 [21]. Erythropoietin is responsible for proliferation and differentiation of erythrone and induces erythroferrone that inhibits hepcidin synthesis. Numerous cytokines (mainly IFN-γ) induce apoptosis of erythroid progenitor cells in the stem.

Decreased erythrocyte lifespan

This effect is caused by: enhanced phagocytosis by hepatic and splenic macrophages caused by deposition of antibody and complement on erythrocytes, activation of macrophages, and mechanical damage from fibrin deposits in microvasculature [22]. An overview of the pathophysiology of AI is presented in Figure 1 [23]. The organs involved are the bone marrow, liver, duodenum and kidneys, the most important regulator being hepcidin.

There can be other causes of anemia in critically ill patients, including mineral (iron) and vitamin (vitamin B12, folic acid, vitamin D) deficiency. Iron deficiency (ID) leads to impaired erythropoiesis, vitamin B12 and folic acid deficiency (megaloblastic anemia) leads to impaired erythropoiesis and hemolysis, and vitamin D increases hepcidin concentration leading to even greater IRE.

Etiological classification of anemia

The World Health Organization defines anemia as a condition in which the number of erythrocytes, or their oxygen-carrying capacity, is insufficient to meet the body's

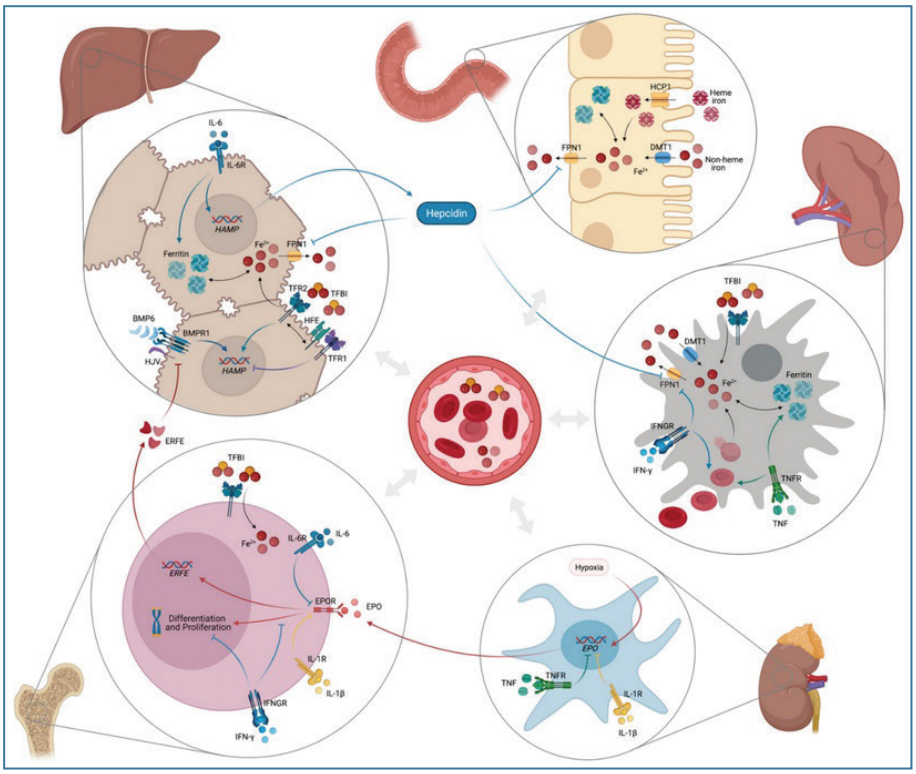

Figure 1. Pathophysiology of anemia of inflammation ['Pathophysiology of anemia of inflammation (created with Biorender)' by Lanser et al. (no modification), available at: https://doi.org/10.3390/nu13113732, under licence CC BY 4.0]

physiological needs [24]. The diagnostic criterion for anemia is a Hb concentration <12 g/dL for women and <13 g/dL for men. In clinical scenarios with potential blood loss (e.g. the perioperative period), there is a consensus to use a Hb cut-off value of <13 g/dL for both sexes, as women have lower blood volumes, yet bleed as much as men [25, 26].

Exclusion of nutrient deficiencies

ACI is a diagnosis of exclusion, so as a first step other causative/contributory factors of anemia ought to be excluded. These include at least mineral (iron) and vitamin (vitamin B12, folic acid, vitamin D) deficiencies, as these can be easily remedied.

The order of laboratory tests in diagnosis of ACI is presented below.

Erythrocyte parameters

Complete blood count (CBC) is the first line test to diagnose anemia. It is the only test that should be used to precisely determine Hb concentration. Assessment of Hb concentration, both in capillary blood [27, 28] and non-invasively [28], is not accurate and should be avoided. Anemia of critical illness typically presents as normocytic and normochromic anemia, IDA as microcytic and hypochromic anemia, and megaloblastic as macrocytic and normochromic anemia, however analysis of erythrocyte indices is not conclusive. Low mean cell volume (MCV), mean cell hemoglobin (MCH), and mean cell hemoglobin concentration (MCHC) can be seen in thalassemias, however these conditions are quite rare and their prevalence varies by geographical region. MCV has been found to be within a reference range in up to 40% of patients with ID or mixed hematinic deficiency [29]. MCV is affected by pre-analytical factors such as sample temperature or storage time [30]. To conclude, in the absence of thalassemia, low MCV, MCH or MCHC suggest ID, whereas their normal values do not exclude ID. CBC should be the first test for screening and preliminary classification of anemia [26].

Reticulocytes

A decreased number of reticulocytes is present in ACI, IDA, megaloblastic anemia, and bone marrow aplasia/hypoplasia. An increased number is present in hemolysis, polycythemia, hemorrhage, and when hematopoietic agents are used.

Reticulocyte Hb content

The name of the test varies with the analyzer: reticulocyte Hb equivalent — Ret-He (Sysmex XE/XN), mean reticulocyte Hb content — MCHr (Abbott Sapphire), reticulocyte Hb equivalent — RHE (Mindray BC6800), and reticulocyte Hb content calculated — RHCc (ABX-Horiba Petra) [31]. Reticulocytes circulate in the peripheral blood for 1–2 days and then they

mature into erythrocytes. Determination of reticulocyte Hb shows if there is enough iron available for erythropoiesis at the time. Due to the short lifespan of reticulocytes, these parameters change within a few days and can be used to monitor iron availability and treatment progress. In patients with CKD, CHr can predict response to iron even when ferritin is increased as high as 800 µg/L [32]. Patients with sepsis or septic shock with serum ferritin even above 800 µg/L with low Ret-He, can positively respond to parenteral iron (unpublished data, clinicaltrials.gov identifier: NCT05217836). The Ret-He test was introduced in 2005. This test generally is rapid, convenient and cost-effective. It has been used to identify IDA in inflammatory conditions: rheumatoid arthritis [33], cancer [34], chronic disease [35], and gastroenterological disease [36]. CHr cannot distinguish IDA from thalassemia; however, in populations with a low prevalence of thalassemia, the Mentzer index may be used to identify thalassemia [37]. The Mentzer index is calculated by dividing MCV by RBC, with a value <13 suggesting thalassemia with a sensitivity of 98% [38]. Different cut-off values of reticulocyte Hb have been proposed for diagosis of IDA: 25 pg [39], 28 pg [40], 29 pg [32], and 30 pg [41, 36]. The current guidelines recommend a cut-off value of 29 pg in adults (excluding pregnancy) and children, until further data is available [42].

Iron studies (iron, transferrin, transferrin saturation, ferritin)

Serum iron determination is required for the calculation of transferrin saturation (TSAT) and, due to high diurnal variability, should not be measured in isolation. Transferrin concentration variability is lower than for iron. Nevertheless, transferrin synthesis is impaired in malnutrition and chronic disease, therefore specificity of transferrin in diagnosis of ID remains inadequate. TSAT is the ratio of serum iron to transferrin. ACI presents as low iron, transferrin and variable TSAT. IDA presents as low iron, increased transferrin, and low TSAT. The most useful differentiating parameter here is serum ferritin. Whereas a ferritin level <30 µg/L signifies typical IDA, ferritin 30–100 µg/L and TSAT <20% may suggest ID. Patients with ACI may present with normal or increased ferritin levels (>100 µg/L); the degree of elevation depends on the underlying condition. With ferritin >100 µg/L and TSAT >20%, we still cannot be sure if there is ID accompanying ACI [43]. Ferritin and transferrin are acute response proteins, and therefore they lose their diagnostic utility in the critically ill. Ferritin and transferrin saturation cannot be used for a precise diagnosis of absolute (ACI + IDA) or functional (ACI) ID in critically ill patients [44]. A wide range (20–85%) of patients with AI have absolute ID (AI + IDA) which may be caused by bleeding episodes related/unrelated to primary diagnosis and/or iatrogenic blood loss, mainly associated with laboratory sampling or extracorporeal procedures [45].

Hepcidin

As hepcidin is the master regulator of iron metabolism, its concentration may be useful to discriminate between IDA and AI. In AI, there is increased concentration of hepcidin, whereas in IDA its concentration is low. There is variation in hepcidin concentration depending on fasting status, circadian rhythm, and the time of the day [46]. Moreover, renal function influences hepcidin concentration, as hepcidin is also produced by the kidneys and clearance of hepcidin is through the kidneys [47]. There are different hepcidin assays available. Mass-spectrometry and radioimmunoassays are specific, but lack adequate sensitivity [48]. Enzyme-linked immunosorbent assays (ELISA) seem to overcome these problems and are more widely available. Although serum hepcidin may help differentiate AI from AI + IDA, for a precise diagnosis it should be combined with biochemical markers (ferritin) [49] or hematological indices (CHr) [33]. Hepcidin and Ret-He are used in a two-step diagnostic pathway in gastroenterology in- and outpatients. Based on hepcidin concentration, anemia has been classified as IDA (low hepcidin <6 ng/mL), IDA and/or AI (normal hepcidin 6–46 ng/mL), or AI (high hepcidin >46 ng/mL). Then, in the second mixed group, Ret-He was determined and further differentiation into IDA (Ret-He <30 pg) or AI (Ret-He >30 pg) was possible [36]. Hepcidin cannot be used for a preliminary differentiation between AI and AI + IDA in dialysis patients because its level is increased due to impaired renal excretion [50]. Moreover, hepcidin can be used to predict response to oral iron in patients with IDA [51, 52]. There have been no studies using hepcidin to identify ID in critically ill patients. This interesting topic deserves further investigation in a prospective clinical manner (clinicaltrials.gov identifier: NCT05217836).

Other tests used in anemia diagnostics are presented in Table II.

Management of anemia of critical illness

The best treatment for ACI would be resolution of the primary condition that led to ACI. Disease-specific treatments can correct anemia in certain conditions, e.g. anti-TNF agents in inflammatory bowel disease [54] or rheumatoid arthritis [55].

Parenteral iron

It is imperative to identify patients who are iron-deficient because these patients would benefit from iron supplementation. Indiscriminate use of iron supplementation should not be used because mild anemia and ID may be beneficial in patients with infectious diseases [56]. The contraindications for parenteral iron, according to the manufacturers, include: hypersensitivity, decompensated cirrhosis and/or hepatitis, and acute or chronic infection. This latter contraindication is questionable, as causative anemia treatment is recommended by numerous organizations (e.g. British Society of Gastroenterology, American Gastroenterological

Table II. Other laboratory tests in anemia diagnostics

Laboratory test	Definition	Usefulness	Limitations
Percentage of hypochromic erythrocytes (%HypoHe)	Percentage of erythrocytes with Hb content ≤17 pg (subpopulation of mature erythrocytes with insufficient iron content)	Used to identify absolute ID in patients with AI (AI + IDA) with a cut-off value of 1.8% [35]	Relates to iron status in last three months, does not reflect acute changes in iron availability
Percentage of microcytic erythrocytes (% MicroR)	Percentage of erythrocytes with MCV <60 fL (subpopulation of mature erythrocytes with insufficient iron content)	Can be used to identify IDA in patients with AI with a cut-off value of <25.0% [35]	This parameter does not reflect acute changes in iron availability
Zinc protoporphyrin (ZPP)	Lack of iron leads to incorporation of zinc into porphyrin during hemosynthesis	Not recommended for diagnosis of ID (IIB) [42]	Limitations due to measurement technique (hyperbilirubinemia; CKD); false increase with Hb <100 g/L
Soluble transferrin receptor (sTfR)	Elevated concentration in majority of IDA and AI + IDA, within reference range in pure AI, decreased sTfR provides reliable diagnosis of IDA	Not recommended to identify ID [42]	Increased concentration may be associated with hemolytic anemia, deficiency of vitamin B12 or folic acid, hematological malignancies; confounded by inflammation — several cytokines affect sTfR levels independently of iron status
Ferritin index	Calculated as sTfR/log ferritin	Some discrimination between AI (<1) and AI + IDA (>2) [53]	Overlap between values

Hb — hemoglobin; ID — iron deficiency; AI — anemia of inflammation; IDA — iron-deficiency anemia; MCV — mean cell volume; CKD — chronic kidney disease

Association, National Blood Authority Australia), and transfusion of allogeneic erythrocytes leads to increased morbidity and mortality, including sepsis and infection [57, 58]. Increased risk of infection with parenteral iron remains a theoretical threat unsupported by studies [59]. Parenteral iron has been shown to successfully correct ID in different populations of AI patients [60]. There have been calls to revise approval for parenteral iron and widen its indications [61]. The parenteral iron formulations available in Poland are set out in Table III. Different doses of these formulations have been used in critically ill patients: iron sucrose 100 mg three times per week [62], iron sucrose 1,000 mg (single dose) [63], ferric carboxymaltose 500 mg once every five days [64], and ferric carboxymaltose 1,500 mg (single dose) [63]. In the setting of infection, divided doses (e.g. 200 mg) as opposed to single total doses of intravenous iron, should be preferred.

Table III. Parenteral iron formulations available in Poland

Iron formulation	Pharmacological agent	Brand name (manufacturer)
Iron-carbohydrate	Ferric gluconate	No i.v. agent available
	Iron(III)-hydroxide sucrose complex	Venofer® (Vifor)
	Iron(III)-hydroxide dextran complex	CosmoFer® (Pharmacosmos)
		Ferrum Lek® (Sandoz)
Glycan-coated	Iron(III)-hydroxide carboxymaltose complex	Ferinject® (Vifor)
	Iron(III)-derisomaltose	Diafer® (Pharmacosmos)
		Monover® (Pharmacosmos)
	Ferumoxytol	No i.v. agent available

i.v. — intravenous

Agents affecting erythropoietin and proinflammatory cytokines

Higher mortality with erythropoiesis-stimulating agents (ESA) has been reported in cancer patients [65], in dialysis patients not responding to ESA [66], and in pre-dialysis patients [67]. The official approval for ESA in the European Union market is for preoperative autologous donation, pre-dialysis/dialysis end stage CKD, and chemotherapy-induced anemia. There are calls to revise the approval for ESA and widen its indications, as commonly reported complications may in fact be attributable to other factors [68]. Hypoxia-inducible factors stabilizers (prolyl hydroxylase inhibitors) (clinical trials) act through endogenous erythropoietin formation and iron delivery from enterocytes and macrophages, and may be a viable therapeutic option in AI [69].

Allogeneic red blood cell transfusion

Red blood cell (RBC) transfusion is an allogeneic tissue transplantation and should be viewed as a treatment of last resort in anemic critically ill patients. It is associated with multiple complications: sepsis, infection, multi-organ dysfunction, thromboembolic events, cardiac events, respiratory failure, acute kidney injury, and prolonged hospitalization [58]. RBC transfusion at a restrictive Hb threshold is safe and potentially reduces in-hospital mortality in critically ill adults compared to a liberal strategy (transfusion at Hb <7 g/dL vs. <9 g/dL) [70]. As transfusion of RBC at restrictive triggers still may not improve oxygen delivery in some patients, and may in fact be deleterious, so called 'physiological transfusion triggers' have started to be used in RBC transfusion decision making [71]. Even elderly patients may tolerate very low Hb concentrations [72].

Direct hepcidin inhibitors and agents preventing binding of hepcidin to ferroportin (clinical trials)

These agents may act through different mechanisms: inhibition of hepcidin production, neutralization of circulating hepcidin, protection of ferroportin from hepcidin inhibition, and inhibition of hepcidin-inducing signals (e.g. IL-6) [73].

Potential role of erythroferrone (pre-clinical investigation)

Erythroferrone (ERFE) inhibits liver hepcidin synthesis during stress erythropoiesis, ensuring sufficient iron supply for bone marrow erythroblasts, and therefore ERFE has been suggested to protect against AI [74]. Some experimental research has confirmed the inhibitory effect of ERFE on hepcidin [75], however the inhibitory effect of ERFE on hepcidin was not evident in a population of rheumatoid arthritis patients [76].

Contributory factors

It is wise to correct modifiable patient factors contributing to anemia. Vitamin deficiencies should be replenished: vitamin B12, folic acid, and vitamin D. However, we must remember that vitamin deficiencies are rare in patients hospitalized in the ICU: in one study only 2% of patients had a vitamin B12 deficiency and another 2% had a folic acid deficiency [77], while in another study 2.4% of surgical patients had a vitamin B12/folic acid deficiency [26]. If possible, pharmacological agents leading to anemia should be discontinued: nonsteroidal anti-inflammatory drugs, antiplatelet agents, heparins, angiotensin-converting enzyme inhibitors, proton pump inhibitors, neuroleptics, penicillin derivatives (e.g. piperacillin), cephalosporins (e.g. ceftriaxone), and trimethoprim-sulphametoxazole [78, 79].

Iatrogenic blood loss (e.g. phlebotomy, stress-related gastrointestinal bleeding) is an important factor in the ICU and should be minimized. Phlebotomy blood loss can be reduced by ordering fewer laboratory tests (only tests that potentially could change the clinical management of patients) [80], by using low-volume sampling tubes [81], by drawing the minimum amount of blood for a particular test, by applying in-line blood conservation devices allowing reinfusion of blood that would otherwise be wasted [82], by the more common use of point-of-care micro-analytic tests, and by non-invasive monitoring [83].

Conclusions

The high prevalence of anemia in critically ill patients should encourage clinicians to implement proactive measures to prevent, detect, diagnose and treat anemia. In fact, anemia is the most common hematologic disease in the ICU. Taking into account the availability of tests, their limitations, uncertainty, cost, and iatrogenic blood loss, a diagnosis of pure ACI or mixed ACI + IDA can be established using solely complete blood count with analysis of reticulocytes (a standard 2 mL EDTA test tube) which provides Hb concentration in erythrocyte and reticulocyte. Before reticulocyte Hb content can be used as an indicator of ID, thalassemia should be excluded either by checking the patient's history or by calculating the Mentzer index (MCV/RBC). The management of ACI should incorporate discontinuation of pharmacological agents causing anemia, reduction of iatrogenic blood loss, dividing doses of parenteral iron when reticulocyte Hb content is below the reference range, and combined therapy of divided doses of parenteral iron with ESA in approved indications. Reticulocyte Hb content, determined twice a week, is useful for monitoring treatment. Transfusion of RBC should remain a treatment of last resort.

Authors' contributions

PC — conceptualization; writing of paper. ŁK — revision, writing of paper.

Conflict of interest

The authors declare no 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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ORIGINAL RESEARCH ARTICLE

VIA MEDICA

Neutropenic enterocolitis and multidrug-resistant bacteria colonization in lymphoma patients undergoing autologous stem cell transplantation

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Abstract

Introduction: There is little iterature data regarding neutropenic enterocolitis (NE) development after autologous hematopoietic cell transplantation (auto-HCT) in non-Hodgkin lymphoma (NHL) patients. The aim of this study was to determine the incidence, risk factors, and clinical outcome of NE after auto-HCT in NHL patients with respect to the impact of multidrug-resistant Gram-negative bacteria (MDRG) and vancomycin-resistant enterococci colonization on the early outcome after auto-HCT.

Material and methods: This retrospective single-center analysis included a total of 65 NHL patients who underwent auto-HCT after BEAM (BCNU, etoposide, cytosine arabinoside, melphalan) conditioning (BEAM-auto-HCT).

Results: NE was diagnosed in nine (13.8%) patients, a median four days after auto-HCT. In 6/9 (66%) patients, septic shock following NE was diagnosed. In univariate analysis, MDRG colonization before BEAM-auto-HCT was the only factor significant for NE development [odds ratio (OR) 2.4 (1.14–5.0), $p = 0.027$], although this was not confirmed in multivariate analysis. Additionally, NE [OR 5.2 (1.9–13.9), $p = 0.001$] and MDRG colonization prior to transplant [OR 2.7 (1.0–7.0), $p = 0.041$] were independent factors for septic shock development.

Conclusions: Our findings suggest that NHL patients presenting with MDRG colonization before transplant should be kept under careful surveillance because of the high risk of the development of early severe infectious complications, including abdominal ones.

Key words: colonization, multidrug-resistant bacteria, neutropenic enterocolitis

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Introduction

Neutropenic enterocolitis (NE) is a life-threatening complication occurring in patients in the course of neoplastic and non-neoplastic diseases, mainly after chemotherapy [1, 2]. Retrospective data on NE incidence and mortality varies significantly from 0.8% up to 26% and 32–50% respectively. This reflects differences according to its definition, diagnostic criteria, and ultimately, treatment. Some historical data suggests that NE incidence is underestimated [1, 3]. The exact pathogenesis of NE is probably multifactorial, and is still incompletely understood. The main factors related to its development are mucosal injury and impaired immunity including neutropenia. Chemotherapeutic agents such as cytarabine, gemcitabine, vincristine, etoposide, doxorubicin and others can directly damage mucosa or predispose to

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intestinal distension and necrosis, and may cause impairment of intestinal motility. The initial mucosal injury leads to intestinal edema, vascular dilatation, mucosal disruption, and bacterial intramural invasion. Moreover, intestinal infiltration by malignant cells may also be responsible for the pathogenesis of NE. The pathological features of NE include patchy necrosis, hemorrhages, ulcers, edemas, perforations, infiltrating microorganisms and depletion of neutrophils. The spectrum of pathogens involved in NE development include mainly Gram-negative bacteria, but also Gram-positive bacteria, fungi and viruses [4, 5].

Literature data is scarce concerning NE incidence after auto-HCT. It has been suggested that there is a higher incidence of NE after autologous hematopoietic cell transplantation (auto-HCT) in patients with non-Hodgkin lymphoma (NHL) (18.8%) when compared to other hematological malignancies [1]. In recent years, a lot of data on the role of rectal colonization with multidrug-resistant bacteria has been published, but its significance in NHL patients who have undergone auto-HCT has not been specifically investigated.

The aim of our study was to estimate the incidence, risk factors and clinical outcome of NE in NHL patients after auto-HCT with BEAM (BCNU, etoposide, cytosine arabinoside, melphalan) conditioning (BEAM-auto-HCT), with an emphasis on the significance of multidrug-resistant bacteria (MDR) rectal colonization.

Material and methods

Our retrospective analysis included 65 adult patients with NHL who underwent BEAM-auto-HCT in one transplant center between July 2013 and December 2018. Exclusion criteria from analysis involved conditioning other than BEAM chemotherapy and a history of chronic bowel disease or abdominal surgery.

Complication profile and the outcome of procedure were analyzed from the first day of conditioning up to day 30 post-transplant.

The Bioethical Committee of Poznan University of Medical Sciences approved this study in accordance with the Declaration of Helsinki (KB no 934/20).

Transplant procedures

Standard evaluation of patients qualified for auto-HCT and disease-specific assessment was performed within 30 days before transplant. Peripheral blood stem cells were mobilized and collected after chemotherapy, followed by recombinant granulocyte colony-stimulating factor (G-CSF). Patients were uniformly conditioned with a BEAM regimen (dexamethasone 24 mg/m^2 on days –8 to –2, carmustine 300 mg/m^2 on day –8, etoposide 200 mg/m^2 on days –7 to –4, cytarabine 2 × 3,000 mg/m^2 on day –3, and melphalan 140 mg/m^2 on day –2). All patients received a low-germ diet and were housed in single air-filtered rooms on a dedicated transplantation unit, with intensified hygiene measures (masks, gloves, and gowns for staff; water and air control; limited visits). The BEAM-auto-HCTs were performed according to the local procedure with routinely inserted central venous catheters and anti-infective prophylaxis with fluconazole and acyclovir until neutrophil engraftment.

Definitions

Severe neutropenia was defined as absolute neutrophil count (ANC) <0.5 G/L.

Neutropenic fever was defined as a one-time oral temperature of greater than 38.3 °C (approximately 100.9 °F) or a sustained temperature of greater than 38 °C (100.4 °F) for ≥1 h in a patient with an ANC <0.5 G/L or an ANC expected to decrease to <0.5 G/L within 48 h [6].

Infections occurring during neutropenia were classified as: microbiologically documented (MDI) when the pathogenic microorganism was diagnosed; as clinically documented (CDI) with the presence of signs and symptoms of inflammation at anatomic sites and non-recovered pathogen; or as fever of unknown origin (FUO) in cases of fever without a localized source of infection or identified pathogen [7].

Bloodstream infection (BSI) was defined as a laboratory-confirmed positive blood culture. In the case of potential common skin commensals such as coagulase-negative *Staphylococci*, *Corynebacterium species* other than *Corynebacterium dyphteriae*, *Bacillus species* other than *Bacillus anthracis*, *Micrococcus*, *etc.*, it was deemed necessary to draw at least two consecutive positive blood cultures on different occasions [8]. Catheter-related blood stream infection (CR-BSI) was diagnosed according to the Infectious Diseases Society of America (IDSA) recommendations [9].

Multidrug-resistant Gram-negative bacteria (MDRG) were considered in those cases which were not susceptible to at least three of the following antimicrobial categories: antipseudomonal penicillins, cephalosporins, carbapenems, aminoglycosides and fluoroquinolones [10]. A diagnosis of invasive fungal infection was based on the European Organization for Research and Treatment of Cancer (EORTC)/Mycoses Study Group (MSG) criteria [11].

Microbiological procedures

In the event of fever, blood cultures from the catheter and peripheral vein and cultures from the possibly infected sites were taken. The blood samples were injected into BacT/ /Alert FN and BacT/Alert FA culture media. Analyses were performed using a computerized system for monitoring blood cultures (BacT/Alert 3D BioMérieux, France). In the case of diarrhea, stool cultures and tests for Clostridioides difficile antigen and toxin were performed (TECHLABC.DIFF QUIK CHEK COMPLETE® test). Additionally, culture swabs with amies collection (Eurotubo Collection Swab, Delta Lab) were taken from the suspected sites and routinely

screened for vancomycin-resistant enterococci (VRE) and MDRG from the rectum before transplant and thereafter weekly until neutrophil recovery. Rectal swabs and stool samples were inoculated onto screening plates consisting of chromID® VRE Agar, chromID®CARBA SMART Agar (BioMérieux) and examined for growth after 24–48 h of incubation at a temperature of 37°C. Purple colonies on chromID VRE were presumptively identified as VRE. After Gram staining, positive cocci were then subcultured to sheep blood agar and incubated at 37°C in a normal atmosphere, and examined after 24 h. In addition to colony morphology and Gram staining, catalase reaction, and the Vitek GP (BioMérieux) test was used to identify the enterococci at species level. The susceptibility of *Enterococcus spp.* isolates to vancomycin was tested by use of the disk diffusion method. This method was performed according to the European Committee on Antimocrobial Susceptibility (EUCAST) standard. Colonies of Gram-negative rods grown on the selective chromogenic medium were presumptively identified as MDRG. The identification and drug sensitivity of the cultured microorganisms were conducted using the Vitek 2 Compact system (BioMérieux) with standard interpretation of susceptibility according to the EUCAST. To detect extended-spectrum-β-lactamase strains (ESBL), the phenotype method double-disk synergy test was used. A two-step algorithm to detect carbapenemases was performed: carbapenems hydrolysis using the Rapidec®Carba NP test (BioMérieux) followed by polymerase chain reaction (PCR) — the loop-mediated isothermal amplification (LAMP) method (AmplexDiagnostics GmbH, Germany) to detect the genes for carbapenemases: NDM, VIM, IMP, OXA-48 like, KPC, OXA-23, OXA-40, OXA-58. For some pathogens, sensitivity was estimated using the E-test. Susceptibility for colistin was performed with the use of the microdilution method (SenstTest Colistin Liofilchem). All patients were also screened with biweekly galactomannan testing during the neutropenia period.

Neutropenic enterocolitis

NE was suspected in febrile neutropenic patients with abdominal pain and/or diarrhea, vomiting, guarding or ileus. The diagnostics included abdominal ultrasound (US) and the extended microbiology as described above. Sonography was performed in all patients suspected for NE with the use of a GE Voluson 730 at the patient's bedside with a standard scanning technique of the abdomen within 24 h of the onset of symptoms. Plain abdominal radiography, abdominal computed tomography (CT) or surgical assessment were planned only in the event of a suspicion of surgical complications or an unclear US result. NE was diagnosed according to the Gorschluter criteria, including bowel wall thickening >4 mm on US or CT in patients with neutropenic fever and symptoms of abdominal infection [3]. *Clostridioides difficile* enterocolitis was not classified as NE.

Statistical analysis

Descriptive statistics were used to present the parameters of the analyzed group. The ShapiroWilk test was performed to assess normal distribution. To compare the general characteristics of patients with and without NE, the chi square test was used for categorical variables and the Mann-Whitney U test for continuous variables. Similar analysis was performed to determine the impact of NE and MDRG colonization before transplant on early clinical outcome and severe complication incidence.

Univariate analysis for each potential risk factor was performed using logistic regression. Factors for which the *p*-value was <0.10 in univariate analysis were submitted to a multivariate conditional logistic regression model. Backward stepwise regression procedures were used to develop the final multivariate model. The probabilities of survival were estimated by the Kaplan–Meier method, and univariate comparisons were performed using the log-rank test. A *p*-value <0.05 was considered as significant. Odds ratios (ORs) and 95% CIs (confidence intervals) were calculated on the basis of the final model. The statistical analyses were performed with STATISTICA 13 and STATISTICA Medical Package 2.0 (StatSoft, Inc., Tulsa, OK, USA).

Results

The patients' clinical characteristics are set out in Table I.

Hematological recovery occurred in 62 (95%) patients, with neutrophil reconstitution on median day 11 (range 6–18). Three patients died before engraftment due to septic shock caused by *Pseudomonas aeruginosa* VIM (Verona Integron-encoded metallo-β-lactamase) on median day 7. The median duration of severe neutropenia was nine (range 8–21) days. Febrile neutropenia was observed in 59 (90%) patients. The characteristics of the neutropenic infections are set out in Table II.

NE was diagnosed in nine (14%) patients with a median time of incidence of four (range 2–7) days after BEAM-auto-HCT. All NE patients had a fever with a median duration of five (range 3–14) days, diarrhea and abdominal pain that was predominantly localized in the right lower quadrant of the abdomen. US revealed bowel wall thicknesses in all cases ranging from 5 mm to 12 mm, and two patients presented with bowel walls >10 mm. Asymmetric thickening of the mucosal wall was mainly localized in the ileocecal region. In one patient, a hemorrhage from the lower part of the gastrointestinal tract (GI) occurred, but a colonoscopy performed after neutrophil recovery revealed no abnormalities. All patients were assessed by a surgeon although no surgical management was necessary in any of the cases of NE. The general characteristics of the NE patients, including detailed microbiological findings, are set out in Table III.

Table I. Patients' baseline characteristics

Characteristics	All patients, n = 65
Male gender	44 (68%)
Age, median	51 (19–67)
Histopathology	
ALCL ALK+	1
DLBCL	22
EATL	1
FL	10
MCL	19
MZL	5
PBL	1
PCNSL	1
PMBL	5
THL	1
No of prior lines of therapy	1–4
Indication for auto-HCT	
Consolidation	12
Refractory disease	32
Relapse of disease	21
Disease status before auto-HCT	
Complete remission	34
Partial remission	23
Stable disease	8
Source of stem cells	
PB	64
BM	1
VRE(+) colonization before auto-HCT	32
MDRG colonization before auto-HCT	34

ALCL — anaplastic large cell lymphoma; DLBCL — diffuse large B cell lymphoma; EATL — enteropathy associated T-cell lymphoma; FL — follicular lymphoma; MCL — mantle cell lymphoma; MZL — marginal zone lymphoma; PBL — plasmablastic lymphoma; PCNSL — primary central nervous system lymphoma; PMBL — primary mediastinal lymphoma; THL — triple hit lymphoma; auto-HCT— autologous hematopoietic cell transplantation; PB — peripheral blood; BM — bone marrow; VRE — vancomycin resistant enterococcus; MDRG — multidrug resistant Gram-negative bacteria

Table II. Neutropenic infections

Infection	All patients, n = 65
Fever	58 (89%)
FUO	7 (11%)
MDI	48 (74%)
CDI	3 (4.6%)
BSI	27 (41.5%)
Septic shock	7 (10.7%)
CRBSI	7 (10.7%)
Diarrhea	41 (63%)
NE	9 (13.8%)
Clostridioides difficile enterocolitis	1 (1.5%)
Pneumonia	7 (10.7%)
Urinary tract infection	5 (7.6%)
Aspergillosis	0
Influenza	0

FUO — fever of unknown origin; MDI — microbiologically documented infection; CDI — clinically documented infection; BSI — blood stream infection; CRBSI — catheter related blood stream infection; NE — neutropenic enterocolitis

In a total group of 65 pts, MDRG and VRE colonization was confirmed prior to the BEAM-auto-HCT in 20 (31%) and 22 (34%) patients respectively. All NE patients were colonized with MDRG before auto-HCT, and all produced extended spectrum beta-lactamase (ESBL) including nine patients with *Enterobacterales* colonization (two patients *Escherichia coli* and seven patients *Klebsiella pneumoniae*) and in one patient with ESBL-producing *Chryseobacterium indulogenes* as another pathogen. In our series, 7/9 NE patients were colonized with *Enterococci* including five cases of VRE forms (four *Enterococcus faecalis* and one *Enterococcus faecium*). Stool cultures revealed a wide spectrum of pathogens including those observed in rectal swabs and additional ones: ESBL-producing *Stenotrophomonas maltophilia*, VIM-producing *P. aeruginosa* and *Candida cruzei*. Classic enteric bacteria such as *Salmonella enterica, Shigella species, Yersinia species, Campylobacter species, Aeromonas species, Vibrio species, enterohemorrhagic Escherichia. coli* and viruses were not detected. Bloodstream infections were found in four patients with NE including two cases with MDRGs [ESBL-producing *K. pneumoniae* and VIM-producing *P. aeruginosa*] and two cases of *Enterococci* non-VRE.

All patients with NE were treated empirically with carbapenems and colistin. Vancomycin was given to six patients and linezolid to three. Moreover, three patients were treated additionally with amikacin, three with amphotericin, and two with tigecyline according to microbiological identification or the results of rectal swabs. All the patients received parenteral nutrition and G-CSF. Additionally, three patients received intravenous immunoglobulins. Septic shock occurred in 6/9 (66%) patients, and all cases were in the group with microbiologically documented NE. A fatal course of NE was observed in only one patient, who developed septic shock, paralytic ileus and bloody vomiting necessitating a nasogastric tube; the patient was referred to the intensive care unit (ICU) and ultimately died seven days after transplant. Patients with NE had a trend for shortened survival at day 30 after auto-HCT ($p = 0.078$).

Table III. Neutropenic enterocolitis patients' characteristics

Gender/age histopathology	No of prior therapy/ /status at autoHCT	NE- day after auto-HCT/ /thickness of wall	Neu reconstitution	VRE colonization prior to auto-HCT susceptibility	
M/55 MCL	4/CR	+4 d/7 mm	+10	*E. faecalis:* vancomycin, teicoplanin	
M/38 PMBL	4/PR	+5 d/6 mm	+18	*E. faecalis* VRE	
M/62 MCL	3/PR	+4 d/6 mm	+15	*E. faecalis* VRE	
F/58 DLBCL	3/SD	+7 d/5 mm	+12	*E. faecium* VRE	
M/43 PBL	1/CR	+3 d/5 mm	+11	*E. faecalis* VRE	
F/52 FL	3/CR	+2 d/8 mm	+13	No	
M/64 EATL	3/CR	+3 d/9 mm	+12	*E. faecalis* VRE	
M/51 MCL	1/CR	+5 d/5 mm	+13	*E. faecium*: gentamycin, vancomycin, teicoplanin	
M/61 MCL	2/PR	+7 d/11 mm	+11	No	

Ch. indulogenes — *Chryseobacterium indulogenes*; CR — complete remission; DLBCL — diffuse large B-cell lymphoma; EATL — enteropathy associated T-cell lymphoma; *E. faecium* — *Enterococcus faecium*; *E. faecalis* — *Enteroccus faecalis*; ESBL — extended spectrum β-lactamases; FL — follicular lymphoma; *K. pneumoniae* — *Klebsiella pneumoniae*; MCL — mantle cell lymphoma; ND — no data; PBL — plasmablastic lymphoma; *P. aeruginosa* — *Pseudomonas aeruginosa*; shd — susceptible for higher doses; PMBL — primary mediastinal B-cell lymphoma; PR — partial remission; VIM — Verona Integron-encoded metallo-β--lactamase; VRE — vancomycin resistant enterococci

Risk factor analysis

Risk factor analysis for NE incidence was performed with the following factors: gender, age, stage, indication for auto-HCT, number of prior lines of chemotherapy (≤2 vs. >2), diabetes mellitus, VRE or MDRG colonization before BEAM-auto-HCT, time of severe neutropenia, time to neutrophil recovery, and IgG levels before transplant.

Univariate analysis revealed that MDRG colonization before BEAM-auto-HCT was the only risk for NE development [OR 2.4; 95% CI 1.14–5.0, $p = 0.027$], although its independent significance was not confirmed in multivariate analysis.

Additional analyses revealed two factors significant for septic shock development: MDRG colonization before transplant [OR 3.2; 95% CI 1.47–6.975, $p = 0.0035$] and NE [OR 5.89; 95% CI 2.4–14.6, $p = 0.0001$]. Multivariate analysis confirmed the prognostic significances of NE [OR 5.2; 95% CI 1.9–13.9, $p = 0.001$] and MDRG colonization [OR 2.7; 95% CI 1.0–7.0, $p = 0.041$] for septic shock incidence.

Discussion

Our analysis is a continuation of the previous study on NE from our center, which was the first prospective study evaluating the incidence and risk factors of NE in a population of patients undergoing high dose therapy with subsequent

	MDRG colonization before auto-HCT susceptibility	Stool cultures susceptibility	BSI/pathogen	Septic shock	Alive/cause of death
	Ch. indulogenes ESBL(+): sulfametoxazole/trimetoprim, shd levofloxacin *K. pneumoniae* ESBL(+): imipenem, colistin, shd meropenem	*Ch. indulogenes* ESBL(+): sulfametoxazole/trimetoprim, shd levofloxacin *E. faecalis*: vancomycin, teicoplanin	No	No	Yes
	K. pneumoniae ESBL(+): *susceptible* — impenem, meropenem, colistin, shd amikacin	*K. pneumoniae* ESBL(+)	No	Yes	Yes
	K. pneumoniae ESBL(+): imipenem, meropenem, tigecilin, colistin shd amikacin	*K. pneumoniae* ESBL (+) *C. cruzei*	No	Yes	No PD (+ 11 months after auto-HSCT)
	K. pneumoniae ESBL(+): impenem, meropenem, colistin	S. *maltophilia* ESBL(+): levofloxacin, trimetoprim/ /sulfametoxazole	Yes *K. pneumoniae* ESBL(+)	No	Yes
	E. coli ESBL(+): imipenem, meropenem, etarpenem, amikacin, gentamycin, tobramycin	*P. aeruginosa* VIM: colistin *E. coli* ESBL(+) *Entrococcus faecalis* VRE	Yes *P. aeruginosa* VIM: colistin, shd, artreonam	Yes	No +7 d after auto-HSCT — NE, septic shock, bloody vomiting
	K pneumonia ESBL(+): imipenem, meropenem, amikacin, colistin, sulfametoksazol	ND	No	No	Yes
	K. pneumoniae ESBL(+): imipenem, colistin, shd meropenem	*K. pneumoniae* ESBL(+) *E. faecalis VRE*	No	Yes	Yes
	E. coli ESBL(+): piperacilin/tazo, meropenem, imipenem, amikacin, tigecilin, colistin	ND	Yes *E. faecium*: vancomycin, teicoplanin	Yes	Yes
	K. pneumoniae ESBL(+): imipenem, meropenem, amikacin	*K. pneumoniae* ESBL(+)	Yes *E. faecium*: vancomycin, teicoplanin	Yes	Yes

auto-HCT [1]. The research revealed a higher incidence of NE after auto-HCT in the group of NHLs patients compared to other malignancies. Based on this finding, we decided to investigate the incidence, risk factors and outcome for NE after auto-HCT in NHLs patients conditioned exclusively with BEAM therapy, with a special emphasis on the potential role of MDRG and VRE colonization.

In our study, NE was diagnosed in 14% of patients, which is comparable with previously reported rates in NHLs patients after transplant [1]. The reason for the last one may be related to the use of homogenous conditioning with the BEAM protocol which contains high-dose cytarabine and etoposide. Both agents have been known to induce GI mucosal damage, and the use of cytarabine has been associated with the development of NE in several studies [3, 12, 13]. Early development of NE after high dose chemotherapy seems to indicate the importance of the conditioning regimen in the development of NE, rather than the duration of neutropenia. Finally, lymphoma infiltration of the bowel wall cannot be definitively excluded, although patients undergoing auto-HCT are usually in at least partial remission [1]. The mortality rate in our study was significantly lower compared to the historical data mentioned above. This is probably due to early diagnosis and the appropriate intensive treatment and monitoring, although survival analysis on day 30 after transplant revealed that

patients with NE had a trend towards shortened survival (p = 0.078). Univariate analysis revealed MDRG colonization before BEAM-auto-HCT is the only risk for NE development, however, its significance was not confirmed in multivariate analysis. It is worth noting that all of the NE patients were colonized by ESBL-producing MDRG strains, mainly by ESBL-producing *K. pneumoniae,* 7/9 (77%), and furthermore that half of them were colonized with VRE. All the MDRGs were susceptible to colistin and imipenem, and some of them were sensitive to meropenem and amikacin given in high doses. This probably reflects the wide use of the listed antibiotics. When compared to our cohorts treated between 2006 and 2010, recent years have seen a noticeable increase of MDRG infections, and their resistance to fluoroquinolones is still being observed despite the discontinuation of the use of them in prophylaxis [1]. Literature data reports a dramatic increase in MDRs and pandrug-resistant bacteria (PDR) infections in neutropenic patients over the past decade. Gram-positive resistant bacteria include methicillin-resistant staphylococci and VRE. The most affected species in the group of resistant G-negative bacteria include

K. pneumoniae, E. coli, P. aeruginosa and Acinetobacter baumanii [14–20]. Among resistant *Enterobacterales,* the percentage of ESBL-producing *K. pneumoniae* strains exceeds 50% in several series, although this is lower for resistant *Escherichia coli*, varying from 11% to 69% in different countries [14, 15]. In HCT patients, the incidence of carbapenem-resistant (CR) *K. pneumoniae* infections showed a 6-fold increase in 2010–2013, reaching rates of 0.5% in autologous transplant and 2.9% in allogeneic transplant settings [16]. Of note, rectal colonization by CR *K. pneumoniae* was followed by BSIs in 45% of neutropenic patients [17].

Most of our NE patients, 6/9 (66%), experienced septic shock, but fortunately a fatal course was observed in only one case. Based on multivariate regression analysis, two factors were identified as significant for septic shock development such as MDRG colonization before transplant and NE. The most serious complications of MDR bacteria colonization, including BSI or septic shock, may be life-threatening and sometimes require ICU treatment. An Italian multicenter prospective study including 144 patients revealed the frequency of MDR colonization at admission to be 6.5%. MDR colonization increased the risks of both BSI and BSI by the same pathogen. The 3-month OS was significantly lower for patients colonized with MDR bacteria. CR-related BSI and a urinary catheter were independent predictors of death. The authors concluded that tailored empiric antibiotic treatment should be decided on the basis of colonization [20]. In our study, gut colonization at admission was more frequent, with rates of MDRGs and VRE colonization of 31% and 34% respectively. This difference may result from the fact that our patients were heavily pretreated and had experienced many previous hospitalizations. In cancer patients, mucosal barrier damage, usually most marked in the small intestine, is the result of underlying treatment. The mechanisms involved in this process include the release of pro-inflammatory cytokines and tissue enzymes resulting in apoptosis and tissue injury which allows for subsequent bacterial translocation and a subsequent increase in the incidence of bacteremia. It has been demonstrated that mucositis, rather than prolonged neutropenia, is responsible for a high rate of bacteremia in HCT recipients [21, 22]. There is some data suggesting the impact of MDR gut colonization on infectious complications incidence, especially BSI, and moreover an increased risk of acute graft-versus-host disease (GvHD) and higher mortality in patients after allogeneic hematopoietic cell transplantation (allo-HCT) [23–25]. Data is limited concerning MDR colonization on the clinical outcome after auto-HCT, originating from retrospective studies and patients with different hematological malignancies [26–28]. Interestingly, one of them reported increased early non-relapse mortality secondary to infectious complications in a lymphoma subgroup colonized with MDR [26]. None of studies mentioned above analyzed the relationship between MDR colonization and NE incidence. To the best of our knowledge, our study is the first to emphasize the key role of MDRG colonization in a homogenous group of NHL patients who have undergone BEAM-auto-HCT. Our study has its limitations, i.e. the retrospective character of the analysis, and the small group of patients.

Conclusions

In conclusion, our findings suggest that NHL patients presenting with MDRG colonization before transplant should be kept under careful surveillance because of the high risk of early severe infectious complications development, including abdominal ones.

Authors' contributions

MJ — concept, data collection and analysis, drafting article, statistics. JRM — data analysis and critical revision of article. AŁD, MM — critical revision of article. LG — critical revision and approval of article.

Conflict of interest

None.

Financial support

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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In seeking diagnostic tool for laboratory monitoring of FXII-targeting agents, could assessment of rotational thromboelastometry (ROTEM) in patients with factor XII deficiency be useful?

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Abstract

Introduction: Targeting factor XII (FXII) is a new concept for safe thrombosis prophylaxis. Global hemostasis tests offer promise in terms of the laboratory monitoring of FXII inhibition. The present study examines selected parameters of rotational thromboelastometry (ROTEM) in patients with FXII deficiency.

The objective of this study was to assess the impact of FXII deficiency on selected parameters of ROTEM, which can be significant in the laboratory monitoring of FXII inhibition.

Material and methods: The study included 20 patients with FXII deficiency ≤40% and 21 volunteers free of it. Clotting time (CT), clot formation time (CFT), alpha angle (α), maximum clot firmness (MCF), and maximum lysis (ML) were recorded in ROTEM.

Results: For the INTEM test, CT and CFT readings were markedly higher in FXII deficient patients than in controls. No marked differences in relation to MCF and ML were found.

Conclusion: The results of ROTEM show that FXII deficiency has a great impact on the initiation and amplification of coagulation. This was confirmed by a number of marked correlations between FXII activity and certain ROTEM parameters. ROTEM tests merit further investigation as treatment control strategies in the context of FXII inhibition.

Key words: factor XII deficiency, ROTEM, FXII as a target for thrombosis prevention, laboratory monitoring of FXII inhibition

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Introduction

Medical device-induced thrombosis poses a significant medical challenge. Annually, several million people worldwide undergo the implementation of medical devices such as a cardiopulmonary bypass, renal hemodialysis, extracorporeal membrane oxygenation (ECMO), left ventricular assist devices, and intravenous catheters. The standard prevention of thrombosis relies on using high doses of heparin, but such treatment is associated with an increased risk of bleeding complication. The optimal treatment should prevent thrombosis without such risk.

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Table I. Characteristics of study population

Parameter	FXII deficient patients (n = 20)	Controls (n = 21)	*p*
Median age in years (range)	49 (21–73)	46 (23–67)	NS
Sex (F/M)	13/7	19/2	
PLT [× 10^9/L]	254 (142–369)	229 (151–376)	NS
PT [s]	11.8 (10.1–14.8)	11.5 (10.2–13.1)	NS
APTT [s]	83 (37.8–500)*	25,4 (22.4–28.2)	**<0.001**
Fibrinogen [mg/dL]	288 (224–475)	266 (206–376)	ns
FXII activity [%]	18.5 (0–40)**	105 (54–142)	**<0.001**

*Patients with APTT value >500 s (n = 5) were reported as 500 s; **patients with FXII activity <1% (n = 8) were reported as 0; FXII — factor XII; NS — non significant; F — female; M — male; PLT — platelets; PT — prothrombin time; APTT — activated partial thromboplastin time

In recent years, there has been growing interest in the preventive role of inhibition of factor XII, with a very low risk of bleeding [1–3].

The role of factor XII (FXII) was underestimated for decades, since even severe deficiency did not cause bleeding complication. However, recent studies have shown that this factor plays a crucial role in initiating plasma contact system [4–6]. Exposure of blood to negatively charged artificial or biological surfaces induces conformational changes in the catalytic domain of FXII, thereby triggering a series of proteolytic reactions eventually resulting in thrombin generation, fibrin deposition and activation of proinflammatory kallikrein–kinin system [1]. Although FXIIa triggers fibrin formation through activation of the intrinsic coagulation pathway, it appears to have no critical significance in fibrin clot formation during normal hemostasis due to vessel injury. Inhibition of factor XII, by blocking device surface-induced blood coagulation without bleeding risk, seems to be the optimal treatment target [7–10]. A number of potential therapeutic FXII-targeting agents are in preclinical and clinical trials for the treatment of thrombotic and inflammatory condition [3].

Even though the suspected bleeding risk related to such anticoagulant therapy is minimal, it will require laboratory assessment of hemostasis. Commonly used coagulation tests [such as activated partial thromboplastin time (APTT), and prothrombin time (PT)] are not suitable for monitoring hemostasis after FXII activity knockdown, providing information only on the initiation of clot formation. These tests are not adequate to rate the balance of hemostasis; for example, they remain within normal ranges in patients with antithrombin, protein C or protein S deficiency, where higher amounts of thrombin are generated compared to healthy subjects [11]. In fact, since 95% of the generated thrombin is not estimated in this test, nor is the amount of thrombomodulin sufficient for protein C activation, i.e. the initiation of anticoagulant activity, APTT is only suitable for the evaluation of the drivers of the initial phase of intrinsic and common pathway coagulation [12, 13].

Given this background, a more comprehensive and sensitive test is needed. Global hemostasis tests e.g. rotational thromboelastometry (ROTEM) appears to be a better choice. The objective of this study was to assess the impact of FXII deficiency on selected parameters of ROTEM, which can be significant in the laboratory monitoring of FXII inhibition.

Material and methods

Twenty patients diagnosed with FXII deficiency ≤40% were enrolled in the study (Table I). The study protocol was approved by the local ethics committee. All participants gave informed consent. The exclusion criteria were as follows: known liver disorder (plasma alanine transaminase concentration >2 upper limit range), renal failure (creatinine concentration ≥2 mg/dL), thrombocytopenia (platelet count <100 × 10^9/l), and taking any drug that strongly influences platelet function or coagulation for 10 days prior to study entry. The control group consisted of 21 subjects without FXII deficiency, of comparable age and with no history of any bleeding or thrombosis.

PT, APTT, concentration of fibrinogen, and FXII activity were measured using an ACL Top 500 system (Werfen, Le Pré-Saint-Gervais, France).

Activated rotation whole blood thromboelastometry was conducted using a computerized ROTEM device (Rotation Thromboelastometry, Pentapharm GmbH, Munich, Germany, software version 1.5.3). Four ROTEM tests, i.e. INTEM, EXTEM, FIBTEM and APTEM, were performed according to the manufacturer's instructions. The coagulation time (CT), clot formation time (CFT), α-angle, maximum clot firmness (MCF), maximum lysis (ML), and clot lysis index at 30, 45 and 60 minutes (LI 30, LI 45, LI 60 respectively) were among the investigated parameters.

The ROTEM output (TEMogram) reflects the coagulation process by indicating clot initiation (CT), followed by its amplification (CFT and a angle) and then the propagation phase (MCF). The next parameters of the TEMogram (e.g. LI 30 and ML) describe clot stabilization and lysis,

Table II. ROTEM data. Data expressed as median, range

ROTEM test		CT [s]	*p*	CFT [s]	*p*	Alpha (°)	*p*	MCF [mm]	*p*
INTEM	FXII DEF	216.5 (44–1,204)	**0.04**	101.5 (37–212)	**0.003**	72 (53–82)	NS	63 (49–76)	NS
	Controls	173 (148–339)		62 (48–167)		78 (59–82)		62 (54–70)	
EXTEM	FXII DEF	51 (28–1,057)	**0.03**	127 (76–186)	**0.002**	69.5 (56–81)	NS	63.5 (53–73)	NS
	Controls	59 (45–80)		94 (49–134)		71 (65–81)		63 (54–71)	
FIBTEM	FXII DEF	59 (45–734)	**<0.001**	108 (90–553)	NS	70.5 (37–78)	NS	13.5 (4–63)	NS
	Controls	52 (44–65)		493.5 (73–2,082)		66 (46–80)		13 (9–30)	
APTEM	FXII DEF	57.5 (46–76)	NS	103.5 (55–179)	NS	70 (28–81)	NS	62 (9–75)	NS
	Controls	57.5 (46–69)		100 (61–130)		73.5 (65–78)		63.5 (56–70)	

CT — coagulation time; CFT — clot formation time, α-angle, MCF — maximum clot firmness in patients with FXII deficiency and in control group; FXII — factor XII; NS — non significant

these being parts of the subsequent fibrinolysis process. The INTEM test, based on activators such as ellagic acid and phospholipids, gives information comparable to APTT, while EXTEM (tissue factor activation) provides information similar to that of PT. In general, CT values are influenced by the activity of coagulation factors, while CFT results depend on the activity of coagulation factors, platelet count and function, fibrinogen concentration, fibrin polymerization and hematocrit level. MCF is additionally influenced by thrombin concentration and the activity of FXIII [14, 15].

ROTEM technology is used among others in cardiac surgery, trauma, obstetrics and liver transplantation, but it is also tested experimentally in hemophilia to assess the individual response to factor replacement therapy [16]. Full details of the ROTEM laboratory technique have been provided in previous publications [14, 17–21].

Statistical analysis

The Mann-Whitney U-test was used to assess the significance of differences between studied groups. Correlations between variables were assessed by the Spearman rank correlation coefficient (r). In all measurements, $p < 0.05$ was considered statistically significant. Analyses were performed using STATISTICA v. 13.1 software (StatSoft, Tulsa, OK, USA).

Results

The screening coagulation tests, platelet count and activity of FXII data are shown in Table I. In the FXII deficient patient group, the median FXII activity was 18.5%, ranging from FXII activity below 1% (eight patients) to 40%. APTT values were significantly higher in the FXII-deficient group than in controls (83 s vs. 25.4 s, $p \leq 0.001$). In five patients, APTT values exceeded 500 s but these were recorded as 500 s.

ROTEM

The ROTEM values are displayed in Tables II–III.

Parameters concerning initiation and speed at which solid clot forms (clotting time, clot formation time, α-angle)

CT readings were found to be markedly higher in FXII deficient patients than in the control group according to the INTEM and FIBTEM tests. An opposite significant relationship was identified in relation to CT readings by the EXTEM test. CFT values were markedly higher in FXII deficient patients than in controls according to the INTEM and EXTEM tests. No significant differences concerning alpha angle values were observed.

However, the INTEM test found the median alpha angle to be significantly smaller in the subgroup of patients with FXII <1% (n = 8) than in controls (66 vs. 78, $p < 0.001$). There were also marked differences in CFT readings (126.5 vs. 101.5, $p = 0.02$) and alpha angle readings (66 vs. 72, $p = 0.01$) between the FXII <1% subgroup (n = 8) and the whole FXII-deficient group (n = 20).

Marked negative correlations were found between FXII activity and INTEM CT (r = –0.46), INTEM CFT (r = –0.62), while a positive correlation was observed between FXII activity and INTEM alpha angle (r = 0.75).

Table III. ROTEM data. Data expressed as median, range

ROTEM test		ML (%)	*p*	LI 30 [%]	*p*	LI 45 [%]	*p*	LI 60 [%]	*p*
INTEM	FXII DEF	18 (2–25)	NS	100 (98–100)	**<0.001**	97 (93–100)	<0.001	93 (88–98)	**0.002**
	Controls	18 (14–23)		98 (94–100)		93 (88–98)		89 (84–96)	
EXTEM	FXII DEF	20 (14–33)	NS	100 (98–100)	**0.009**	97 (92–100)	0.002	93 (88–98)	**0.004**
	Controls	22 (15–29)		99 (96–100)		94 (89–98)		90 (84–95)	
FIBTEM	FXII DEF	0 (0–23)	NS	100 (94–100)	NS	100 (95–100)	NS	100 (90–100)	NS
	Controls	1 (0–11)		100 (96–100)		100 (92–100)		100 (90–100)	
APTEM	FXII DEF	19.5 (0–26)	NS	100 (98–100)	NS	97 (92–100)	**0.04**	93.5 (88–100)	**0.02**
	Controls	21 (15–29		100 (97–100)		95.5 (91–98)		91.5 (85–95)	

ML — maximum lysis; LI 30 — clot lysis index at 30 min.; LI 45 — clot lysis index at 45 min.; LI 60 — clot lysis index at 60 min. in patients with FXII deficiency and in control group; FXII — factor XII; NS — non significant

Parameters concerning clot firmness (maximum clot firmness)

No marked differences were found between the studied groups regarding MCF readings. Also, there were no significant correlations between FXII activity and MCF values demonstrated in any ROTEM test.

Parameters concerning clot lysis (ML, LI 30, LI 45, LI 60)

ML readings did not differ markedly between the analyzed groups for any studied ROTEM test; however, the INTEM and EXTEM tests found the LI 30, LI 45, LI 60 results to be markedly higher in FXII-deficient patients than controls (Table III). Marked negative correlations were observed between FXII activity and INTEM LI 30 ($r = -0.49$) and EXTEM LI 60 ($r = -0.48$).

Discussion

As expected, the FXII deficient group demonstrated significantly higher APTT values than healthy volunteers. Patients with FXII deficiency (n = 20) demonstrated elongated CT and CFT according to the INTEM test, and no marked differences in α-angle and MCF readings compared to healthy volunteers. However, the median value of the INTEM α-angle was significantly lower among patients with FXII <1% (n = 8) than controls. These results are similar to those observed by Govers-Riemslag et al. [22] in four patients with FXII <5%; they noted that the addition of purified FXII to blood samples resulted in the normalization of all ROTEM parameters.

These findings, taken together with marked negative correlations between FXII activity and INTEM CT, INTEM CFT and a positive correlation between FXII activity and INTEM α-angle, demonstrate that FXII plays a pivotal role in the initiation and amplification of coagulation processes, but not in the propagation phase.

There were no differences seen between FXII patients and controls in relation to ML in the present study. Similarly, the LI 30, LI 45, LI 60 results were markedly higher in FXII-deficient patients than in controls, according to the INTEM and EXTEM tests, which indicates more stable clots. Additionally, we observed marked negative correlations between FXII activity and INTEM LI 30 and EXTEM LI 60. In their ROTEM analysis, Govers-Riemslag et al. [22] found fibrinolysis to be extremely delayed in one patient, with less than 90% of thrombus being lysed within two hours of measurement. This finding may underscore the role of FXII in fibrinolysis initiation. Previous studies demonstrated that activated factor XII (FXIIa) binds to fibrin, leading to higher fibrin density and greater stiffness of fibrin clots [23]. FXIIa has been also found to directly convert plasminogen into plasmin, leading to fibrinolysis acceleration [24]. In FXII-deficient patients, diminished clot lysis / impaired fibrinolysis has been noted [25, 26].

The limitations of the present study are its relatively small number of patients/controls and the fact that it compares ROTEM tests between different subjects. Although the ROTEM tests are thought to describe the hemostatic potential of each person, they still lack standardization, and the results are highly individual, which is still poorly understood [27]. Due to the high heterogeneity of the

individual results, ROTEM may be more accurate as a laboratory diagnostic tool when each subject is his/her own control. Moreover, ROTEM is not normally used to assess fibrinolysis, although, if properly modified, it could be also useful for this purpose [28, 29].

Conclusions

In conclusion, the results of ROTEM show that FXII deficiency has a great impact on the initiation and amplification of coagulation, but not in the propagation phase. This relationship was further confirmed by a number of marked correlations between FXII activity and certain ROTEM parameters. FXII seems to be only a weak activator of plasminogen [30], however it cannot be excluded that such influence disturbs the balance of hemostasis. This aspect should be taken into consideration, especially now that first clinical trials with anti-XII agent have already started. ROTEM tests merit further investigation as treatment control strategies in the context of FXII inhibition, especially when each subject is his/her own control.

Authors' contributions

JT, PS — concept authorship. JT, KC — content supervision. JT, MR, PS — development of assumptions and methods. EK, MT-S, PS — conducting research. JT, PS, WN — analysis of results and formulation of conclusions.

Conflict of interests

None.

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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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Characteristics of COVID-19 in pediatric patients with hematological malignancies

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Abstract

Introduction: As more data is collected, hematologists will be able to gain more insight into the impact of coronavirus disease 2019 (COVID-19) on pediatric patients with hematological malignancies.

Material and methods: We analysed 21 cases of COVID-19 in pediatric patients with onco-hematological diseases treated in the Western Ukrainian Pediatric Medical Center from March 2020 through May 2021. The majority of patients (71.4%) were diagnosed with acute lymphoblastic leukemia. All patients from the analyzed cohort had an asymptomatic, mild or moderate course of coronavirus-19 infection. The most common symptoms of COVID-19 were fever, cough, gastrointestinal symptoms, and dermatitis. Severe severe acute respiratory syndrome coronavirus 2 increased the risk of liver toxicity and venous thrombosis.

Results and conclusion: Our analysis showed that pediatric patients with hematological malignancies need the same treatment approach for COVID-19 as for other infective complications.

Key words: COVID-19, hematological malignancies, immunosuppression, pediatric patients

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Introduction

Children seem to be less at risk than adults of developing a severe form of coronavirus disease 2019 (COVID-19), but the specific risk in pediatric patients with hematological malignancies is not yet understood [1]. While cases with COVID-19 and asymptomatic severe severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive tests have been documented in children with acute lymphoblastic leukemia (ALL), the general observation is that most patients clear their infections with few complications. However, there have been serious cases of COVID-19 associated with mortality [2, 3].

Mortality in COVID-19 patients has been linked to the presence of the so-called 'cytokine storm' induced by the virus. Excessive production of proinflammatory cytokines leads to widespread tissue damage, resulting in multiorgan failure and death [4]. The healthy host's immune response to the SARS-CoV-2 virus is hyperactive, resulting in an excessive inflammatory reaction. Many who die from COVID-19 suffer hyper-inflammation with features of 'cytokine storm' syndrome [5].

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In addition, a serious condition that appears to be linked to COVID-19 is multisystem inflammatory syndrome in children (MIS-C). In children who go on to develop MIS-C, some organs and tissues, such as the heart, lungs, blood vessels, kidneys, digestive system, brain, and skin, become severely inflamed. This appears to be an excessive immune response related to SARS-Cov-2 [6]. Some patients with COVID-19 benefit from immunosuppression [7, 8].

However, it is unclear whether the risk of COVID-19 may be higher or lower in pediatric patients with hematological malignancies due to treatment-induced immunosuppression. The major threat to children with oncohematological diseases when they acquire COVID-19 is the malignancy itself [9]. Chemotherapy may have to be delayed if the patient tests positive for SARS-CoV-2. Delays in treatment may lead to increased morbidity and mortality. The questions of when to treat, when to wait, and how long to wait remain unanswered. For patients in advanced stages of the disease, the real benefit of the treatment in the context of the risk of COVID-19 must be considered [10].

Ukraine is currently fighting the pandemic and has recorded nearly 5 million cases of COVID-19 and 113,000 deaths. As more data is collected, we will be able to gain more insight into the impact of COVID-19 on pediatric oncology and hematology.

The aim of our study was to find common health problems caused by SARS-CoV-2 in a group of patients with oncohematological diseases.

Material and methods

This was a retrospective study of medical records of pediatric patients with hematological malignancies who tested positive for SARS-CoV-2. Data regarding age, sex, clinical symptoms, and results of laboratory and instrumental investigations were collected. Statistics Version-8 was used for data analyses.

Results

We analyzed 21 cases of COVID-19 in pediatric patients with hematological malignancies treated in the Western Ukrainian Specialized Pediatric Medical Center from March 2020 through May 2021, with 24 months of follow up. 15 patients (71.4%) were diagnosed with ALL, four (19%) with acute myeloid leukemia (AML), one (4.7%) with non-Hodgkin diffuse lymphoblastic lymphoma (NHL), and one (4.7%) with Langerhans cell histiocytosis (LCH). The majority of patients were treated for ALL; 14 of them (93%) were in remission and one patient (6.6%) was diagnosed with leukemia during the treatment of COVID-19 infection. Four patients with ALL (26.6%) were included in the high-risk group and treated with a high-dose intensive program of chemotherapy. Seven patients (46.6%) from the intermediate risk group were on non-intensive chemotherapy, and four patients (26.6%) were on maintenance therapy.

Two patients with AML (50%) in their first remission were on maintenance chemotherapy. One girl (25%), in her first early isolated bone marrow relapse of AML, was treated with high-dose intensive chemotherapy, and one child (25%) was in the second long-lasting remission status after allogeneic hematopoietic stem cell transplantation. Patients with NHL and LCH were on a maintenance chemotherapy program.

The sex ratio in our patient cohort was 2:1 M:F: 14 boys (66%) and seven girls (33%). The median age of patients with a positive SARS-CoV-2 test was 7 years (range: 2–16). The A(II)Rh(+) blood group was the most common found in patients (33.3%). 81% of COVID-19 cases were diagnosed with reverse transcription polymerase chain reaction (RT-PCR) tests, and 19% via serological tests. SARS-CoV-2 positivity remained for a median of 19 days (range: 7–67).

12 SARS-CoV-2 positive patients (57%) were treated at home, while nine (43%) were hospitalized for a median 15 days (range: 7–30).The vast majority of patients (76%) had mild SARS-CoV-2 infections, 19% were asymptomatic, and one (4.7%) was diagnosed with moderate severity bilateral pneumonia. The most common symptoms of COVID-19 were fever (76%), rhinitis and cough (57%). In 19% of patients, COVID-19 manifested with gastrointestinal symptoms (abdominal pain, diarrhea), 14.3% had skin manifestations (urticarial, maculopapular rash), and 4.7% had anosmia.

It is difficult to interpret the results of laboratory investigations of the patients from the analyzed cohort because they were treated with chemotherapy of differing intensities and this had a severe impact on the laboratory results. The level of hemoglobin ranged from 61 g/L to 137g/L (median 104 g/L), the level of platelets from 33 × 10^9/L to 872 × 10^9/L (median 223 × 10^9/L), the level of leukocytes from 0.07 × 10^9/L to 6.7 × 10^9/L (median 3.2 × 10^9/L), the level of neutrophils from 0% to 88% (median 42%), the level of lymphocytes from 12% to 74% (median 41%), the level of monocytes from 2% to 50% (median 14%), and the level of erythrocyte sedimentation rate (ESR) from 4 to 16 mm/h (median 9 mm/h). C-reactive protein (CRP) ranged from 4 to 48 mg/L (median 19 mg/L).

Most biochemical tests were normal, only the level of transaminase was elevated in four patients (19%): alanine aminotransferase (ALT) 100–2,650 IU/L, aspartate aminotransferase (AST) 70–1,800 IU/L. We did not find significant changes in coagulation tests: fibrinogen ranged from 2.3 to 3.9 g/L (median 2.9 g/L); activated partial thromboplastin time (aPTT) from 24 s to 46 s (median 33.7 s); prothrombin time (PT) from 13 s to 17.4 s (median 15.2 s). However, two patients with ALL were diagnosed with venous thrombosis: one patient had catheter-associated thrombosis of vena jugularis sinistra and was treated with enoxaparin for

10 days. Another patient had thrombosis of a small branch of v.tibialis dextra and was treated with enoxaparin for one week and rivaroxaban for three weeks. In both patients, anticoagulants were effective. Chest X-rays, computed tomography (CT)-scans, and ultrasound investigations of lung tissue helped diagnose bilateral pneumonia in one patient.

17 patients (81%) from the cohort stopped chemotherapy between the time of COVID-19 diagnosis and the time of a negative PCR test for SARS-CoV-2. In these cases, chemotherapy was stopped for 5 to 30 days (median 14) before being resumed.

One patient (4.7%) with ALL on maintenance treatment had chemotherapy intensity reduced. Two years after allogeneic bone marrow transplantation (allo-BMT), a patient with AML was withdrawn from the chemotherapy program. One patient with a high-risk ALL had first-line chemotherapy alongside COVID-19, but soon after that became critical and died of sepsis caused by antibiotic-resistant *St. hemolyticus*. One patient with early relapse of AML postponed BMT for three months. She experienced a second relapse seven months after allo-BMT and died 12 months later from disease progression.

Patients with overt symptoms of COVID-19 were treated with: wide-spectrum antibiotics; antifungal drugs; granulocyte--colony stimulating factor (G-CSF), in the case of severe cytopenia; intravenous immunoglobulins; and blood product transfusions. At 24 months, overall survival was 85%, and event-free survival was 82%.

The level of IgG against coronavirus six months after the diagnosis of COVID-19 was tested in four patients; IgG against SARS-CoV-2 was detected in two of them.

Discussion

Our analysis of 21 cases of COVID-19 in pediatric patients with hematological malignancies showed that all patients had asymptomatic, mild, or moderate courses of coronavirus-19 infections. This accords with the data of other researchers [9, 11]. The course of COVID-19 in our patients did not depend on the status of the disease (onset of leukemia or remission status) nor to the type of cancer treatment (low-dose chemotherapy or high-dose intensive chemotherapy). This conclusion is supported in the literature [11].

The majority of our patients were male (66%) and 33.3% had the A(II)Rh(+) blood group. The higher percentage of male patients in our study is comparable to another reported study [10]. The most common symptoms of COVID-19 were fever, cough, gastrointestinal symptoms, and dermatitis. In patients with hematological malignancies tested for COVID-19, we did not find any common changes in blood count due to the myelosuppressive effect of the previous chemotherapy. In patients with oncohematological diseases complicated by COVID-19, it is necessary to be aware of liver toxicity and the risk of venous thrombosis. Thrombotic complications were also reported by Diorio et al. [12].

Most patients from the analyzed cohort had a delay with program chemotherapy of no more than two weeks. This is important for the successful treatment of hematological diseases. One of our patients with relapsed AML, who had a long delay in allo-BMT after COVID-19, experienced a second relapse and died from disease progression. Some researchers have suggested that cancer patients can tolerate chemotherapy, including the induction phase, alongside COVID-19 treatment or chemotherapy doses can be modified [11]. However, it is unclear whether dose modification will have an effect on leukemia cure rates. Our patient with ALL, who had first-line chemotherapy simultaneously with COVID-19, soon died of septicemia.

Several authors have stated that in pediatric cancer patients with severe and critical COVID-19, remdesivir and convalescent plasma might have a potential benefit [3, 6]. However, we did not see severe COVID-19 cases in our patients. Our analysis showed that patients with hematological malignancies need the same approach for COVID-19 treatment as for other infective complications.

One patient from the analyzed cohort was diagnosed with ALL soon after the onset of COVID-19. Exposure to viruses can be a leukemia-inducing event [13]. Can a coronavirus infection cause the development of leukemia? The answer may become evident in future with ongoing epidemiological surveillance and scientific investigations.

Conclusions

This study provides an analysis of COVID-19 in pediatric patients with hematological malignancies treated in the Western Ukrainian Specialized Pediatric Medical Center. Most patients infected with SARS-CoV-2 showed a favorable clinical outcome, with a 24-month overall survival rate of 85% and an event-free survival rate of 82%. The overwhelming majority of patients had an asymptomatic, mild, or moderate course of COVID-19. The course of the coronavirus infection in our patients did not depend on the status of the disease (the onset of leukemia or remission status) or the type of cancer treatment (low intensity program chemotherapy or high-dose intensive chemotherapy). 57% of patients did not require hospitalization for COVID-19 and were treated at home while quarantining.

SARS-CoV-2 in the analyzed cohort of patients with blood cancer increased the risk of liver toxicity and venous thrombosis.

Most patients with oncohematological diseases complicated by COVID-19 needed a delay in chemotherapy of no more than two weeks. Interruption of chemotherapy for a longer period can cause treatment failure.

Our patients with hematological malignancies need the same approach for COVID-19 treatment as for other infective complications.

Further investigations are necessary to determine if the coronavirus can induce leukemia.

Authors' contributions

TO, LG — study design and administrative support. VO, SO, BC, KO — important clinical data. TI, DO — developed first draft of manuscript. SM, BN — assisted in writing and editing manuscript. All authors contributed to data analysis and interpretation, data checking, critical revision, and final approval.

Conflict of interest

None.

Financial support

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; and Uniform Requirements for manuscripts submitted to biomedical journals.

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Assessment of two main therapeutic regimens of chronic lymphocytic leukemia in a major referral center in Syria

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Abstract

Introduction: Due to the high cost of targeted therapy, chemoimmunotherapy regimens remain the standard therapy for chronic lymphocytic leukemia in many developing countries. In this study, we compare the treatment outcomes of the two main chemoimmunotherapeutic regimens.

Material and methods: Data was obtained from the oncology department archives at Tishreen University Hospital between 2016 and 2020. We enrolled previously untreated, fit patients with chronic lymphocytic leukemia who were treated with one of two regimens: either a fludarabine, cyclophosphamide, and rituximab regimen, or a bendamustine and rituximab regimen.

Results: 78 patients were enrolled in the study. 56.8% of the fludarabine, cyclophosphamide, and rituximab group achieved complete response versus 73.5% of the bendamustine and rituximab group. Progression-free survival was slightly shorter for fludarabine, cyclophosphamide, and rituximab than for bendamustine and rituximab [median 15.1 months (95% confidence interval {CI} 12.4–17.8] vs. 17.7 months (95% CI 15.4–20.1)] without statistical significance. In elderly patients (>65 years) median progression-free survival (PFS) was significantly (p = 0.046) longer with the bendamustine and rituximab treatment [median 19.9 months (95% CI 17.2–22.5)] than with the fludarabine, cyclophosphamide, and rituximab [median 11.6 months (6–17.2)]. Regarding overall survival, no significant difference between the two groups was documented. Delay and deletion of cycles, neutropenia and anemia were more frequent with the fludarabine, cyclophosphamide, and rituximab group. Furthermore, we found that elevated lactate dehydrogenase, positive expression of ZAP-70, stage C, and splenomegaly are all indicators of poor prognosis in correlation with PFS.

Conclusions: Our study found that the bendamustine and rituximab regimen is safer than, and has comparable efficacy to, the standard therapy of fludarabine, cyclophosphamide, and rituximab for previously untreated, fit patients with chronic lymphocytic leukemia.

Key words: chronic lymphocytic leukemia, chemoimmunotherapy, bendamustine, fludarabine

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Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia in developed countries [1]. It is a monoclonal B cell malignant disorder characterized by progressive accumulation of inefficient lymphocytes in the blood, the bone marrow, the lymph nodes and the spleen [2, 3].

CLL and small lymphocytic lymphoma (SLL) are different manifestations of the same disease; in SLL, the disease is mainly nodal [4], while CLL is diagnosed when more than 5×10^9/L B-lymphocytes are present in the peripheral blood for at least three months [5], with a lymphocytic clonality confirmed by immunophenotyping [3].

CLL is mainly a disease of the elderly. The median age at diagnosis is 65–72 years [6, 7]. It is extremely heterogeneous in its clinical course [8].

CLL typically demonstrates a characteristic immunophenotype, expressing CD5, CD19, dim CD20, dim CD22, CD23, dim-to-negative CD79b and dim monoclonal surface immunoglobulin (Ig) [9].

Regarding therapy, combination chemoimmunotherapy (CIT) regimens such as FCR (fludarabine, cyclophosphamide, rituximab) and BR (bendamustine, rituximab) have been the frontline therapies for CLL [10] until recently, when targeted small molecular inhibitors were approved for all cases, preferably ones with del17 and defective p53 [11, 12]. The toxicity and cost differences between CIT and ibrutinib are significant. Moreover, due to financial demands, the availability of novel inhibitors is limited [13], especially in a resource-limited country like Syria.

Material and methods

Study design and participants

This was a retrospective, cohort study. Data was obtained from the oncology department archives at Tishreen University Hospital in Latakia, Syria between 2016 and 2020. We enrolled previously untreated, fit patients with chronic lymphocytic leukemia who required treatment according to the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria [14] and had an Eastern Cooperative Oncology Group (ECOG) status of 0–2. Staging was decided according to the Binet staging system. Patients had to have an advanced clinical stage (Binet C) or confirmed active disease requiring treatment [14]. The main exclusion criteria were impaired renal function, previous therapy for chronic lymphocytic leukemia (except steroids), Richter transformation, and active secondary malignancy requiring treatment. The patient's initial data at diagnosis was obtained from the department's archives, including demographic characteristics, laboratory parameters, radiological findings, staging and immunophenotyping results. Patients were treated with one of two regimens, either the FCR or the BR regimen, where six 28-day cycles of rituximab, fludarabine and cyclophosphamide were compared to six 28-day cycles of bendamustine and rituximab. Intravenous fludarabine (25 mg/m^2 per day) and cyclophosphamide (250 mg/m^2 per day) were administered on the first three days of each cycle, while bendamustine (90 mg/m^2 per day) was administered intravenously on the first two days of each cycle. Rituximab 375 mg/m^2 was given intravenously to both groups on day 1 of each cycle. There was no prophylactic use of antibiotics or growth factors. An assessment of initial response was done one month (give or take seven days) after the beginning of the last cycle of treatment. Response to treatment was classified according to the iwCLL response criteria [14]. All adverse events, including neutropenia, anemia, thrombocytopenia, delay or deletion of cycles and hospitalization, were reported. Afterwards, patients were followed for two years.

Outcomes

The primary objective of this study was to compare the efficacy and safety of bendamustine and rituximab to the standard treatment of fludarabine, cyclophosphamide, and rituximab with regard to a primary endpoint of progression-free survival (PFS), defined as the time from diagnosis until progression or death from any cause. Secondary endpoints were overall survival (OS; defined as the time from diagnosis until death from any cause), the proportion of patients who achieved an overall response (OR), defined as the proportion of patients having achieved a complete remission or partial remission as a response to study treatment. We also evaluated the prognostic value of some demographic, clinical, and laboratory variables with regard to PFS. The sample was divided into two groups. The first included patients who achieved PFS ≥24 months and the second included patients with PFS <24 months.

Statistical analysis

Statistical analysis methods included descriptive statistics such as quantitative variables expressed by measures of central tendency and measures of dispersion, and qualitative variables expressed as frequencies and percentages, while inferential statistics included other tests. For natural distribution of data, we used a Kolomogorov-Smirnov test. For the difference between two independent groups (the two treatment groups as well as the two prognostic groups) we used an Independent T student test in case the distribution was natural, and a Mann-Whitney U test in case it was unnatural, while for the relation between qualitative variables we used a Chi-square test. As for survival time analysis, we used Kaplan-Meier curves according to Breslow. The results were considered statistically significant when the *p*-value was less than 0.05. The IBM SPSS Statistics (Statistical Package for the Social Sciences for Windows; Version 20) program was relied upon to calculate the statistical parameters and analyze the results.

Table I. Comparison between demographic and clinical characteristics, laboratory results and radiological findings between groups at diagnosis

Variable		FCR (n = 44)	BR (n = 34)	*p* value
Sex	Male	30 (68.2%)	22 (64.7%)	0.747
	Female	14 (31.8%)	12 (35.3%)	
Age		59.3 ± 8.1	61.4 ± 10.9	0.344
	≤65	33 (75%)	22 (64.7%)	0.323
	>65	11 (25%)	12 (35.3%)	
Laboratory results	WBC	75.1 ± 69.3	58.4 ± 79.1	0.313
	LYM	58.6 ± 56.7	48.1 ± 66	0.454
	Hb	10.9 ± 2.3	11.5 ± 2.5	0.274
	PLT	150.5 ± 90.8	159.5 ± 80.9	0.653
	LDH	438.1 ± 193.3	405.5 ± 160.4	0.428
Splenomegaly		34 (77.3%)	20 (58.8%)	0.080
Binet staging	Stage B	20 (45.5%)	20 (58.8%)	0.241
	Stage C	24 (54.5%)	14 (41.2%)	
Overall response	CR	25 (56.8%)	25 (73.5%)	0.312
	PR	15 (34.1%)	7 (20.6%)	
	Progression	4 (9.1%)	2 (5.9%)	

WBC — white blood cells; LYM — lymphocytes; Hb — hemoglobin; PLT — platelets; LDH — lactate dehydrogenase; CR — complete response; PR — partial response

Results

Patients

One hundred and fifty cases of CLL were diagnosed in the oncology department between 2016 and 2020, 88 of whom were treated with either FCR or BR. The other most used first-line regimens were chlorambucil, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), and R-CVP (rituximab, cyclophosphamide, vincristine, prednisone), in that order. In addition, a large proportion of patients did not need any treatment at diagnosis. We excluded 10 patients from the study because they did not fulfill the inclusion criteria.

Eventually, 78 patients with CLL were enrolled in the study. Males were predominant with 52 (66%) patients. The ages of patients at diagnosis ranged between 39 and 81 years, median 60.2 ± 9.4. The FCR group included 44 patients, while the BR group had 34 patients. Fifty-five patients of the entire sample were ≤65 years, 33 patients in the FCR group and 22 in the BR group. Likewise, the proportion of patients older than 65 years was higher in the FCR group than in the BR group. All patients in both groups had ≥3 lymphadenopathy areas (the areas of involvement considered are: a) head and neck, including the Waldeyer ring; b) axillae; and c) groins, including superficial femoral) [3]. Only five patients in the entire sample had hepatomegaly, therefore these variables were not included in the study. Patients were distributed almost equally between stages B and C with 40 and 38, respectively. No patient in either group was in stage A. Laboratory results and demographic characteristics did not show any statistical value between the two groups. 56.8% of the FCR group achieved complete response vs. 73.5% of the BR group; four patients from the FCR group and two patients from the BR group had a progressive disease while being on treatment; and no cases of stable disease were documented (Table I, Figure 1).

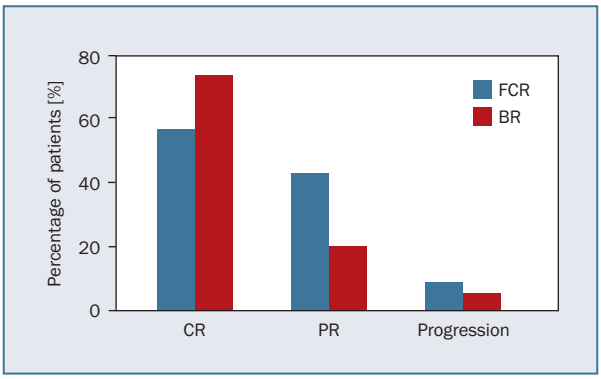

Figure 1. Bar chart demonstrates overall responses of patients between the two treatment groups; CR — complete response; PR — partial response; FCR — fludarabine, cyclophosphamide, rituximab; BR — bendamustine, rituximab

Response to treatment

Although the differences in complete responses among most prognostic subgroups were clinically higher in the BR group, none of it was significant with the exception of patients with expression of CD22 (Table II).

Table II. Overall response and complete response in FCR (fludarabine, cyclophosphamide, rituximab) and BR (bendamustine, rituximab) groups according to different variables

Variable	Response	FCR	BR	*p* value
Male (52)	CR	16 (53.3%)	17 (77.3%)	0.208
	OR	27 (90%)	21 (95.5%)	0.466
Female (26)	CR	9 (64.3%)	8 (66.7%)	0.976
	OR	13 (92.9%)	11 (91.7%)	0.910
Age ≤65 years (55)	CR	20 (60.6%)	17 (77.3%)	0.197
	OR	29 (87.9%)	20 (90.9%)	0.724
Age >65 years (23)	CR	5 (45.5%)	8 (66.7%)	0.305
	OR	11 (100%)	12 (100%)	1.0
Binet staging				
Stage B (40)	CR	12 (60%)	17 (85%)	0.077
	OR	18 (90%)	19 (95%)	0.548
Stage C (38)	CR	13 (54.2%)	8 (57.1%)	0.859
	OR	22 (91.7%)	13 (92.9%)	0.869
CD22 expression (n = 43)	CR	10 (47.6%)	17 (77.3%)	**0.044**
	OR	19 (90.5%)	21 (95.5%)	0.522
CD23 expression (n = 50)	CR	18 (53.9%)	12 (75%)	0.137
	OR	32 (94.1%)	15 (93.8%)	0.959
CD38 expression (n = 32)	CR	9 (50%)	10 (71.4%)	0.221
	OR	16 (88.9%)	14 (100%)	0.198
ZAP-70 expression (n = 23)	CR	5 (41.7%)	7 (63.6%)	0.292
	OR	11 (91.7%)	11 (100%)	0.328

CR — complete response; OR — overall response

Toxicity

The number receiving less than six treatment cycles was 21 (47.7%) with FCR and nine (26.5%) with BR ($p = 0.05$). Reasons for treatment discontinuation or delay in the FCR group were severe myelosuppression in 26 (66.7%) patients, early complete response in seven (17.9%) patients, death in two (5.1%) patients, renal failure in two (5.1%) patients, and two patients had a progressive disease. In the BR group, we found severe myelosuppression in 12 (75%) patients, early complete response in two (12.5%) patients, and two patients died.

Neutropenia, anemia, thrombocytopenia, and the incidence of severe infections were more frequent in the FCR group. Hospitalization rate and the use of granulocyte-colony stimulating factor (G-CSF) and erythropoietin were all significantly higher with FCR therapy than that with BR therapy until five months after the end of therapy (Table III).

Additionally, one patient in the FCR group developed a secondary lung tumor. No cases in our study died of external reasons other than treatment side effects or disease progression, nor did we lose contact with any patient. The main cause of death was severe myelosuppression followed by infections in both groups, with a higher incidence in the FCR group.

Survival

26 patients in the entire population died during the two-year period. The median OS and PFS was 19.5 ± 7.4 and 16.3 ± 8.4 months, respectively. Progression-free survival was slightly shorter for FCR compared to BR [median 15.1 months (95% confidence interval {CI} 12.4–17.8) vs. 17.7 months (95% CI 15.4–20.1)] without any statistical significance. In elderly patients (>65 years) median PFS was significantly ($p = 0.046$) longer with the BR treatment [median 19.9 months (95% CI 17.2–22.5)] than with the FCR [median 11.6 months (95% CI 6–17.2)]. PFS did not differ between the two treatment arms in the younger population (≤65 years) (Figure 2). Regarding OS, no significant difference between the two groups was documented (median 19 months for FCR vs. 20 months for BR) (Figure 3). Similarly, OS did not differ between the two age populations. However, OS was higher clinically with the BR therapy in the elderly (median 20.8 months vs. 15.6 months).

Table III. Comparison between adverse events in FCR (fludarabine, cyclophosphamide, rituximab) and BR (bendamustine, rituximab) groups

Adverse events	FCR (n = 44)	BR (n = 34)	*p* value
Deletion of cycles	21 (47.7%)	9 (26.5%)	**0.050**
Delay of cycles	32 (72.7%)	10 (29.4%)	**<0.001**
Hospitalization	12 (27.3%)	3 (8.8%)	**0.040**
Blood transfusion	7 (15.9%)	1 (2.9%)	0.061
Platelets transfusion	1 (2.3%)	0 (0%)	0.376
G-CSF use	16 (36.4%)	5 (14.7%)	**0.032**
Erythropoietin use	8 (18.2%)	1 (2.9%)	**0.037**

G-CSF — granulocyte-colony stimulating factor

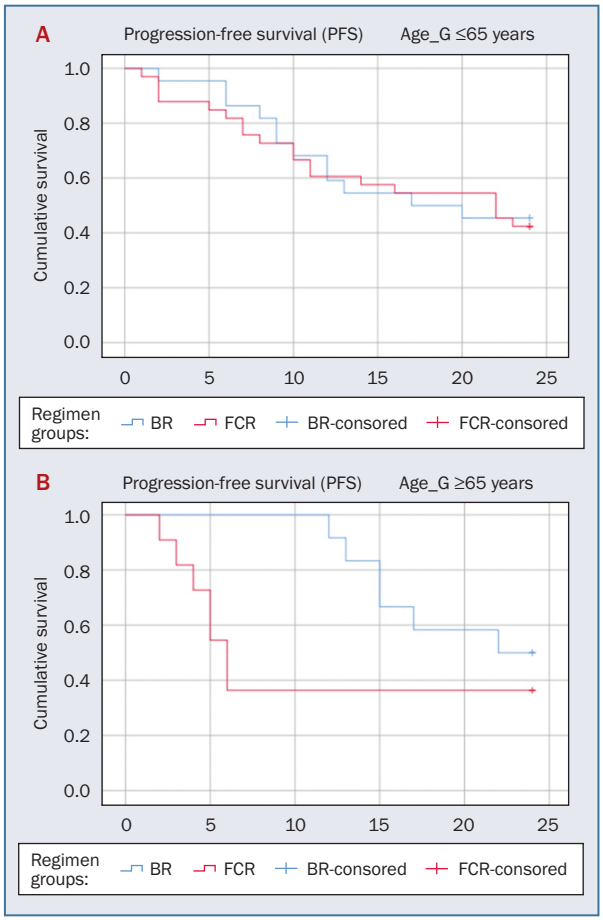

Figure 2. Kaplan-Meier curve demonstrates progression-free survival between the two treatment groups in patients ≤65 years (**A**), and in patients >65 years (**B**); BR — bendamustine, rituximab; FCR — fludarabine, cyclophosphamide, rituximab

Prognostic factors

We evaluated the demographic characteristics, laboratory parameters, radiological findings, staging and immunophenotyping results according to the two prognostic groups of PFS in the entire sample (Table IV). We found that LDH (p <0.001), ZAP-70 (p = 0.05), stage C (p = 0.003), and splenomegaly (p = 0.001) were all indicators of poor prognosis in correlation with PFS.

Discussion

In this study, we demonstrated the characteristics of a population of previously untreated fit patients in a major oncology center in Latakia, Syria. Then, we compared treatment outcomes in two groups, the FCR group and the BR group. The median age at diagnosis was 60.2 years. All patients were diagnosed with stages B and C because there are no routine tests in our country and visits to clinics are generally limited.

Our study found that a bendamustine and rituximab regimen could be considered non-inferior to the standard front-line therapy of fludarabine, cyclophosphamide, and rituximab for previously untreated, fit patients with chronic lymphocytic leukemia. On the contrary, the CLL10 trial [15], a major study conducted by the German CLL Study Group (GCLLSG), concluded that FCR had superior PFS compared to BR for young patients (median 55.2 months vs. 41.7 months, p = 0.0003). However, both studies agreed that BR is the safer choice in elderly patients (>65 years). The German study showed that there was no significant difference in PFS in elderly (>65 years) patients in the FCR group compared to the BR group, while our data showed that PFS was significantly longer with the BR treatment (median 19.9 months) than with the FCR (median 11.6 months) (p = 0.046). The difference in PFS between the German study and our study could be explained by the small size of the sample, poor management of CIT adverse effects, and the short follow-up period in our study. Furthermore, no difference in OS was observed between treatment groups in either study. However, this might change with a longer observation time, and it might also be affected by those patients who received second-line treatment regimens.

Similarly to the CLL10 trial, we found that elderly patients treated with bendamustine and rituximab had a longer PFS than younger patients treated with the same

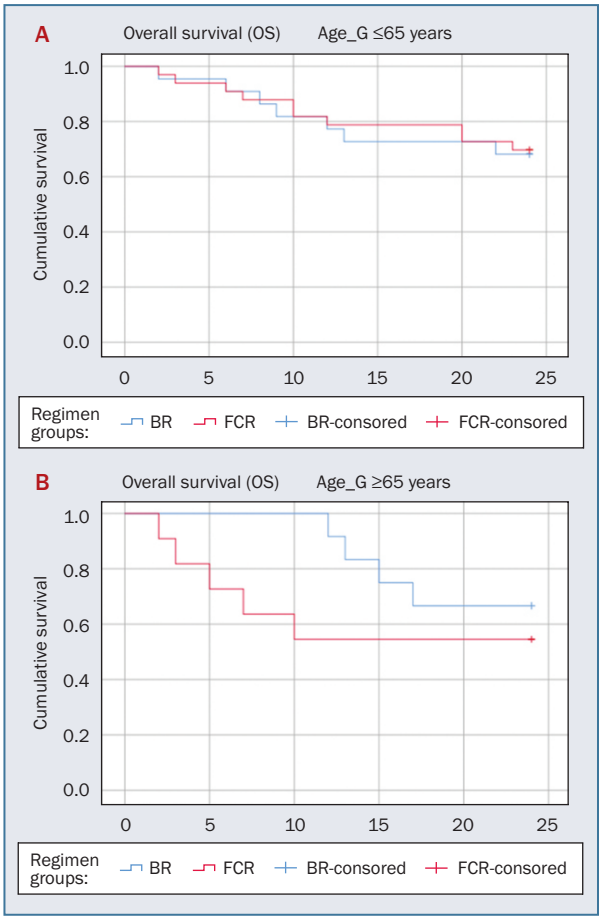

Figure 3. Kaplan-Meier curve demonstrates overall survival between the two treatment groups in patients ≤65 years (**A**), and in patients >65 years (**B**); BR — bendamustine, rituximab; FCR — fludarabine, cyclophosphamide, rituximab

regimen. However, no differences in pharmacokinetics of bendamustine in different age groups have been observed in previous studies [16].

Regarding response to treatment, we found that CD22 was associated with a higher complete response rate in the BR group. This has not appeared before in the literature. Therefore, it needs further investigation in the future.

FCR was associated with more toxic effects than was BR. Multiple studies have compared dose-reduced fludarabine, cyclophosphamide, and rituximab in elderly CLL patients. In these studies, PFS was shorter compared to a full-dose regimen. This could be due to early treatment cessation or lower efficacy [17–19].

A bendamustine and rituximab regimen has been reported to be efficient and well-tolerable as a front-line therapy for elderly CLL patients [20, 21]. Additionally, severe cytopenias have also been described before with FCR therapy [22], predisposing a higher infection rate. Our study detected only one case of a second malignancy after FCR because of the short follow-up. Yet retrospective studies have found that the lifetime risk of secondary malignancies after FCR therapy actually ranges between 4% and 10% [23].

Several factors should be considered with young, fit patients with CLL, such as molecular status, CIT eligibility, patient preference, quality of life, duration of treatment, sequencing, short-term and long-term safety implications, insurance availability, and transplant eligibility.

Results with targeted therapies, such as ibrutinib and venetoclax, are very superior to those achieved with CIT regimens [24, 25] in first-line untreated CLL patients especially with del17 and defective P53, while CIT is only preserved as first-line treatment for patients with mutated *IGHV* and without del17 [26]. Despite this, CIT is still widely used instead of target therapies in first-line treatment for untreated fit CLL patients in low-income countries such as Syria. The reasons for this fact include the huge increases in treatment costs, and the lack of transparency and free-market competition, especially in countries with significant healthcare budget constraints [13, 27, 28].

In addition, some patients in developed countries still prefer CIT rather than Bruton kinase (BTK) inhibitors like ibrutinib and acalabrutinib. This is because of the disturbing side effects of ibrutinib (mainly cardiovascular ones), the high cost of these drugs, and the need for long-term administration until progression or unacceptable toxicity [28].

Cytogenetics are the main limitation to our study. They are becoming an essential part of the treatment approach, but most patients in low-income countries such as Syria cannot afford them. Thus, we needed to investigate further clinical and laboratory parameters to assess the prognosis and survival of CLL patients.

Similarly to the CLL10 study, our study demonstrated that splenomegaly, the elevation of LDH, Binet C, and the positive expression of ZAP-70 were all correlated with a poor prognosis. This association has been well established in several previous studies [29–31]. However, those studies reported other important indicators like lymphocytosis and positive expression of CD38 and CD23, which are highly prognostic of a poor disease course, but could not be proved in our study. This could be explained by the small sample size and the heterogeneous nature of the tests, given that they were carried out in different laboratories.

Furthermore, when analyzing different variables between the two treatment groups, PFS did not differ between the two prognostic groups regarding age category. This could be justified by the selection of very fit elderly patients. Thus, we can conclude that therapy decisions should rely on an assessment of fitness, rather than on chronological age.

Conclusions

Our study found that a BR regimen had comparable efficacy to the standard front-line therapy of FCR for previously untreated, fit patients with CLL. BR is the safer choice in

Table VI. Evaluation of demographic characteristics, laboratory parameters, radiological findings, staging and immunophenotyping results according to the two prognostic groups of progression-free survival (PFS)

Variable		PFS ≥24 months (n = 34)	PFS <24 months (n = 44)	*p* value
Sex	Male	21 (61.8%)	31 (70.5%)	0.419
	Female	13 (38.2%)	13 (29.5%)	
Age		60.3 ± 8.7	60.1 ± 10.1	0.928
	≤65	24 (70.6%)	31 (70.5%)	0.990
	>65	10 (29.4%)	13 (29.5%)	
Laboratory results	WBC	58.2 ± 69.2	75.3 ± 73.6	0.302
	LYM	45.3 ± 55.6	60.7 ± 64.4	0.270
	Hb	11.7 ± 1.9	10.7 ± 2.7	0.074
	PLT	159.5 ± 67.8	150.5 ± 98.6	0.649
	LDH	343.4 ± 153.5	486.1 ± 174.4	**<0.001**
CDs expression	CD22	19 (73.1%)	24 (68.6%)	0.703
	CD23	21 (72.4%)	29 (78.4%)	0.575
	CD38	11 (39.3%)	21 (55.3%)	0.199
	ZAP-70	6 (21.4%)	17 (44.7%)	**0.050**
Binet staging	Stage B	24 (70.6%)	16 (36.4%)	**0.003**
	Stage C	10 (29.4%)	28 (63.6%)	
Radiological findings	Splenomegaly	17 (50%)	37 (84.1%)	**0.001**

WBC — white blood cells; LYM — lymphocytes; Hb — hemoglobin; PLT — platelets; LDH — lactate dehydrogenase

elderly patients (>65 years). While striving for better diagnostic and therapeutic availability and reduced costs, there is a need to use the limited available investigations and drugs at our disposal to better treat CLL patients.

Authors' contributions

LH — data collection and manuscript writing. FH, SA — supervising the work and making final adjustments.

Conflict of interest

None.

Financial support

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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Standardizing blood dose using body surface area and analyzing effect of blood storage on hemoglobin increment in pediatric patients

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Abstract

Introduction: Pediatric patients exhibit a wide variation in weight which results in diverse transfusion practices. This study aims to standardize red blood cell (RBC) doses according to body surface area (BSA) and to analyze the role of RBC storage in post-transfusion hemoglobin levels.

Material and methods: In this original prospective cohort study on hospitalized pediatric patients aged up to 14, we classified patients into transfusion-dependent (n = 31) and non-transfusion-dependent (n = 158). The non-transfusion-dependent group was further classified into ≤10 kg (n = 72) or >10 kg (n = 86) according to body weight (bw). We derived a regression equation between BSA and blood dose in non-transfusion-dependent subjects, and modified the equation by fixing blood dose to 15 mL/kg bw for only BSA based blood dose. We measured pre-transfusion and post-transfusion hemoglobin (Hb) levels, and ascertained effects of blood storage ≤15 days (n = 15) and >15 days (n = 16) on post-transfusion Hb.

Results: Pediatric patients ≤10 kg and >10 kg bw (n = 158); mean ± standard deviation of weight and BSA were 4.5 ± 3.1 kg; 22.9 ± 10.4 kg; 0.26 ± 0.14 m^2; 0.9 ± 0.28) m^2 respectively. The regression equation ≤10 kg and >10 kg bw when adjusted. Blood dose fixed at 15 mL/kg bw adjusted blood dose ≤10 kg; 15 mL/kg bw = −19.12 + 329.69x BSA m^2. The regression equation >10 kg bw: adjusted blood dose >10 kg bw; 15 mL/kg bw = −158.8 + 563.3x BSA (m^2). The adjusted blood dose with BSA did not exceed 20 mL/kg bw. No significant differences were observed in pre and post-transfusion Hb in transfusion-dependent (n = 31) versus non-transfusion-dependent patients (n = 158) due to the RBC storage duration.

Conclusions: RBC blood dose can be standardized by regression equation between standardized RBC dosage and BSA. Post-transfusion Hb is not dependent on days of RBC storage at the blood bank.

Key words: body surface area, regression equation, RBC storage changes, dose banding

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Introduction

Transfusion practices show variations due to the clinical presentation of patients and differing understanding of transfusion benchmarks among clinicians.

The pediatric age group is especially vulnerable to such variations due to a higher oxygen consumption and higher cardiac output to blood volume ratio than the adult population [1]. Premature infants also have higher fetal hemoglobin (HbF) than full-term infants with decreased erythropoietin production [1, 2]. Children differ from adults due to the wide variation in body size (up to 10-fold) for any given age group [3, 4]. Approaches towards standard blood dosing include blood transfusion according to body weight (kg), total blood volume, body surface area (BSA), body mass index (BMI), and dose banding appropriate to the body surface area. These are some of the measures for blood dosing regimen with predictable endpoints [5–8].

New-born children and infants have a higher variation of body weight than older children and adults in anthropometric indices e.g. a greater head circumference than chest circumference at birth and during the first year of life, a big trunk with relatively short legs, and older children displaying variations in weight for height due to undernutrition or wasting [5, 9]. A reference standard dosing regimen which estimates blood dose or RBC distribution volume as a mathematical function of body size for any age or weight category could result in predictive endpoints in transfusion [5, 10, 11]. A significant correlation between regression coefficients is one way to ensure such a relationship between the blood dose to be transfused and the body size, especially in pediatric patients.

A blood transfusion dose of 10 mL/kg body weight (bw) to 20 mL/kg within the pediatric population is acceptable under most guidelines [5, 7]. A standardization of RBC transfusion volume has been attempted, with several formulae based on physiological characteristics such as baseline hemoglobin (Hb), hematocrit of RBC unit, weight etc and their statistical relationships [5, 7, 10, 12]. A regression equation based relationship predicting the Hb (g/dL) levels and volume transfused (ml) according to body size has been attempted to estimate blood dosing [10, 11].

A potential cause of variation of post-transfusion hemogram is the 'age of stored RBC' effect on a patient's Hb on attaining a steady baseline value. Fresh RBCs are no longer considered superior compared to the older (stored) RBCs for transfusion for the overall outcome of hospital stay [13]. An evaluation of whether older units attain comparable baseline Hb concentration 24 hours after transfusion as 'new RBC units' could affect transfusion therapy upon patients [13, 14].

Our observational study had the following aims:

- to standardize RBC dose for transfusion using 'body surface area' (BSA) in pediatric patients, to calculate blood dose acceptable to guidelines of normal homeostasis;
- to compare the effect of RBC storage up to 15 days, and greater than 15 days, on hemoglobin increment (g/dL) 24 hours after blood transfusion in transfusion-dependent and non-transfusion-dependent patients.

Definitions

Pearson correlation coefficient typically measures a linear relationship between two continuous variables.

Linear regression is used to study the linear relationship between a dependent variable y and one or more independent variables x. The linear regression models describe the dependent variable by the equation y = a + + bx; where a (the intercept) and b (the slop) of the regression line are estimated from an underlying relationship between variables y and x (adapted from Schneider et al. Dtsch Arztebl. 2010).

Body surface area: an accurate measurement of body size, usually determined by using the weight and height of a person.

Material and methods

This prospective cohort study involved data of pediatric (age 0–14) subjects admitted at a tertiary level hospital from 1 January to 31 December 2019. We adhered to the STROBE statement for the present study as a research template [15].

Institutional ethical approval of this study was obtained (No: 543/IEC-AIIMSRPR/2018).

We conducted the study according to a planned protocol (flow diagram) set out in Figure 1. We obtained a pre-transfusion sample just before the transfusion, with a follow-up sample 24 hours after transfusion of a non-transfusion-dependent patient. The samples were then tested by routine hemogram in an automated cell counter (Sysmex S100). We conducted this prospective cohort study under the following sub-categories (Figure 1).

Model 1

Weight sub-groups [≤10 kg (n = 72) and >10 kg (n = 86)] in non-bleeding patients for a regression equation evaluating change of blood dose with unit change in BSA.

Model 2

Transfusion-dependent (n = 31) and non-transfusion-dependent patients (n = 152) for comparison of the effect of RBC storage (≤15 days and >15 days) on post-transfusion Hb (g/dL) increment.

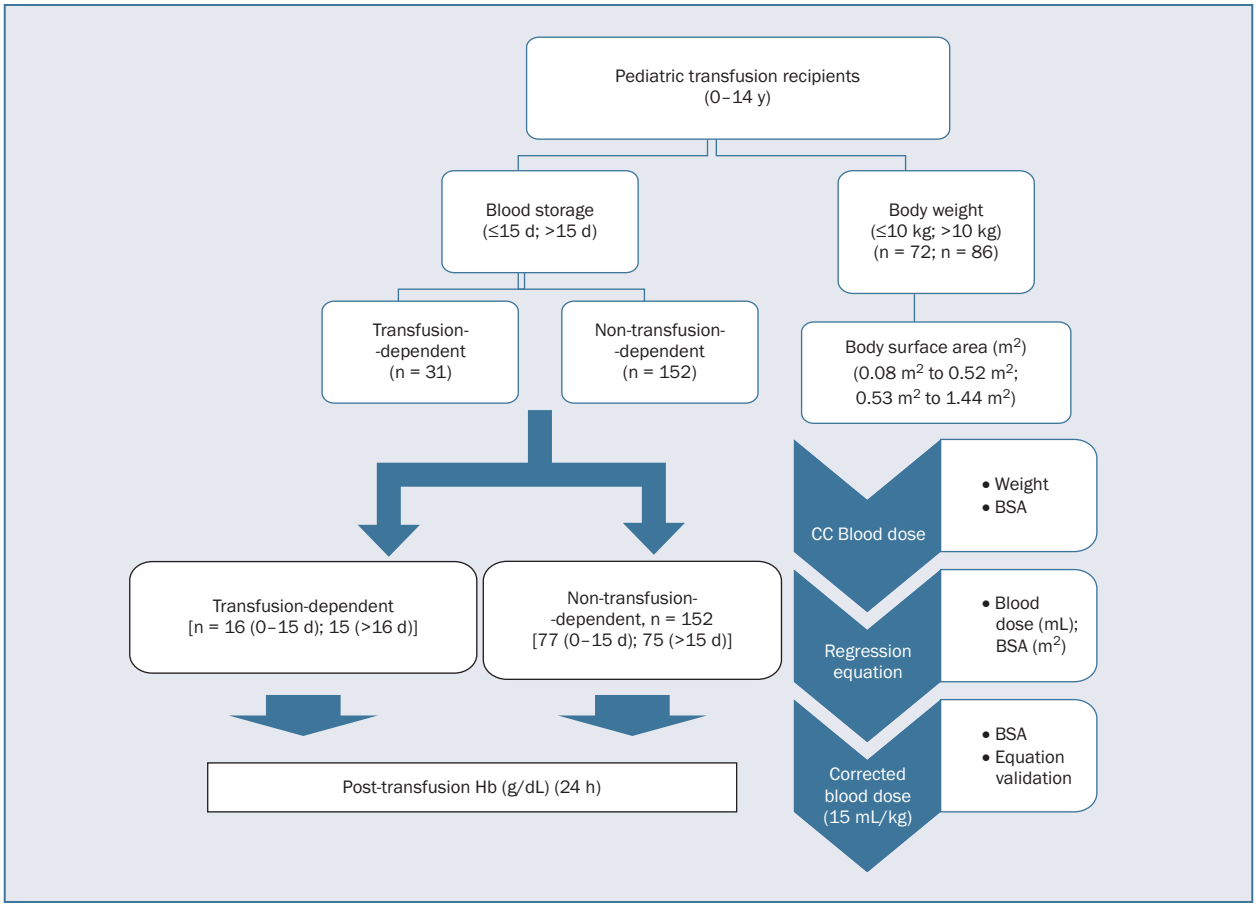

Figure 1. Study design of research

Inclusion criteria

Model 1

Pediatric patients aged 0–14 undergoing transfusion (red cells, whole blood).

Model 2}

Transfusion of whole blood/red blood cell units stored at the blood bank ≤15 days and >15 days to the following sub-group of patients: routine pediatric transfusion recipients considered as non-transfusion-dependent and transfusion-dependent patients [sickle cell disease (SCD); thalassemia major; blood dyscrasias etc. requiring repeated transfusions].

Exclusion criteria

Patients >14 years; surgical patients; emergency transfusions; actively bleeding patients under clinical evaluation; unrefrigerated blood categorized as fresh blood.

The outcome variables were as follows: blood dose calculated from BSA from the regression equation ($y = a + bx$) based upon blood dose and BSA as dependent and independent variables respectively.

An adjusted blood dose was acquired after fixing the blood dose to 15 mL/kg bw which yielded the final regression equation. We validated the adjusted blood dose from BSA by comparing the same with weight-based blood dose (15 mL/kg bw) for a standard blood dose according to BSA.

A statistical comparison of Hb increment after RBC transfusion in the transfusion dependent and non-transfusion dependent paediatric subjects (independent sample T test).

Potential confounders

Variation within regression equation depending on the sample size and patient characteristics. Transfusion variables such as underlying alloimmunization of the patient in the transfusion-dependent group. Ongoing hemolysis, undiagnosed blood loss, sampling errors, patient variables such as dehydration and fluid administration.

Statistical calculations

Model 1

Pre-transfusion and post-transfusion hemogram estimated in two weight categories [(≤10 kg (n = 72) and >10 kg (n = 86)]. The minimum sample size was derived using the correlation coefficient of blood dose to the BSA alpha probability p (<0.05); power (0.8) [16].

Table I. Comparison of statistical parameters. Less than or equal to 10 kg versus greater than 10 kg weight category

Parameter	Less than or equal to 10 kg body weight (n = 72)	Greater than 10 kg body weight (n = 86)
Range weight (kg) and BSA area (m^2)	Weight (0.8 kg to 10.40 kg) BSA (0.08 m^2 to 0.52 m^2)	Weight (11 kg to 50 kg) BSA (0.53 m^2 to 1.44 m^2)
Mean ±SD weight and BSA	Weight 4.5 ±3.1 kg BSA 0.26 ±0.15 m^2	Weight 22.9 ±10.4 kg BSA 0.9 ±0.28 m^2
Mean ±SD pre-transfusion Hb	Pre-transfusion Hb 7.0 ±1.7 g/dL	Pre-transfusion Hb 6.3 ±1.5 g/dL
Blood dose	Blood dose 86.0 ±74.6 mL respectively	Blood dose 243.0 ±86.1 mL
Pearson correlation coefficient (CC) blood dose with weight (kg) and BSA (m^2)	Weight 0.64 BSA 0.68 ($p \leq 0.01$)	Weight 0.47 BSA 0.50 ($p < 0.05$)
Regression coefficient (r^2) blood dose with weight (kg) and BSA (m^2)	0.41 for BSA ($p < 0.05$)	0.25 BSA (m^2) as predictor variable respectively ($p \leq 0.05$)

BSA — body surface area; SD — standard deviation; Hb — hemoglobin

A Pearson correlation coefficient (CC) performed separately for each weight category (≤10 kg and >10 kg) to estimate CC of blood dose (mL) with weight (kg) and BSA (m^2) (Table I).

We performed a linear regression analysis (r^2) for variation in blood dose (mL) administered to patients with a unit change BSA (m^2) in our patient data. Blood dose (y) = b + ax [where y = blood dose (mL), b = constant equal to value of y when x = 0, a is the coefficient of x i.e. the slope of regression line of how much y changes with a unit change in x where x = BSA). To compute a regression equation between blood dose and the BSA, we used 'blood dose' as a 'dependent variable', with BSA (m^2) as an 'independent variable'.

A validation of this modified regression equation was performed on a standard weight/BSA chart.

Two modalities validated the adjusted equation:

- a comparison of 'calculated blood dose' from BSA of a patient (subjects) included in the present study with blood dose calculated as 15 mL/kg bw and 20 mL/kg bw respectively for each weight category (≤10 kg and >10 kg)
- a comparison of weight-based 'calculated blood dose with the corresponding BSA of patient' from data acquired from chemotherapy standardization group 2008 [17].

Model 2

We compared the effect of RBC storage (≤15 days vs. >15 days) on pre-transfusion and post-transfusion Hb g/dL of both multi-transfused (transfusion-dependent) and routinely transfused (non-transfusion-dependent) patients. Two sample T-test on 24 hours Hb levels for the duration of RBC storage (≤15 days vs. >15 days).

A 'independent T testing' of pre-transfusion and post-transfusion Hb (≤15 days, >15 days RBC storage) for both transfusion-dependent and non-transfusion-dependent patients.

A comparison of increment for transfusion-dependent and non-transfusion-dependent patients for the effect of blood storage (RBC storage ≤15 days and >15 days) on the post-transfusion Hb levels (in g/dL) 24 hours after RBC transfusion (independent T test).

We estimated the following parameters for the patients:

- hemogram [(Hb (g/dL); Hct (%)] performed by cell counter (Sysmex, S-100);
- body surface area (monsteller formula) [18].

We estimated missing data for weight/height using an IAP reference chart for the 5+ age-group (gender specific) and Fenton chart for pre-term neonates [4, 19, 20].

Patients lost to follow-up were not included in the present study.

We performed all statistical calculations on SPSS Statistics (version 26.0); independent T-test of the blood dose (derived) and blood dose (15 mL/kg bw; 20 mL/kg bw) on Minitab (trial version) [21]. The calculations for each weight category (≤10 kg and >10 kg) and 'days of storage' on post-transfusion Hb were performed on Minitab (trial version) and Prism 9 for macOS [21, 22].

Results

We reviewed the parameters evaluated under Model 1 (≤10 kg (n = 72) and >10 kg (n = 86) category (Table I)

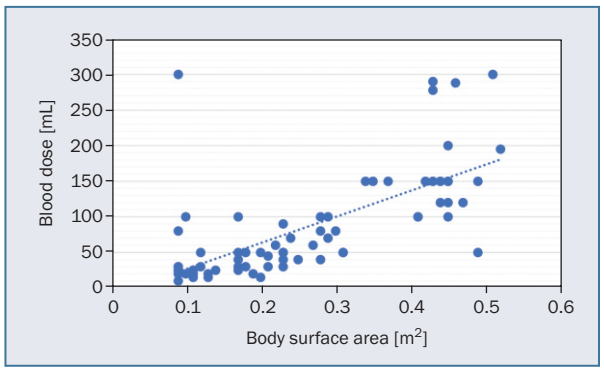

Figure 2. Blood dose to body surface area (BSA) (m^2) unadjusted patient data ≤10 kg body weight

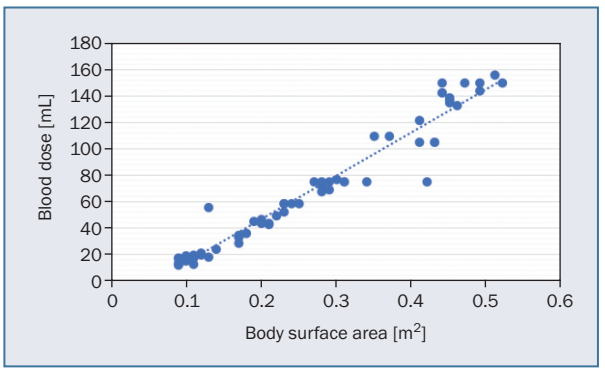

Figure 3. Blood dose to body surface area (BSA) (m^2) adjusted to 15 mL/kg for ≤10 kg body weight

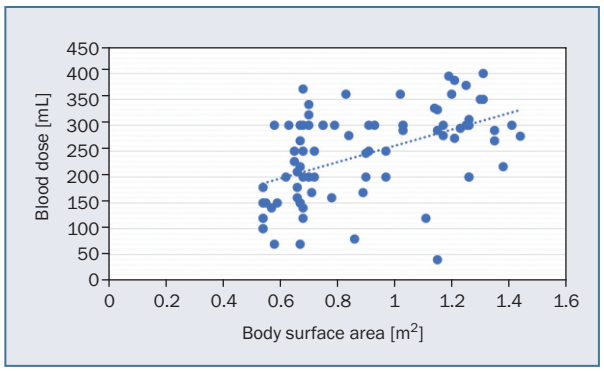

Figure 4. Blood dose to body surface area (BSA) (m^2) unadjusted patient data >10 kg body weight

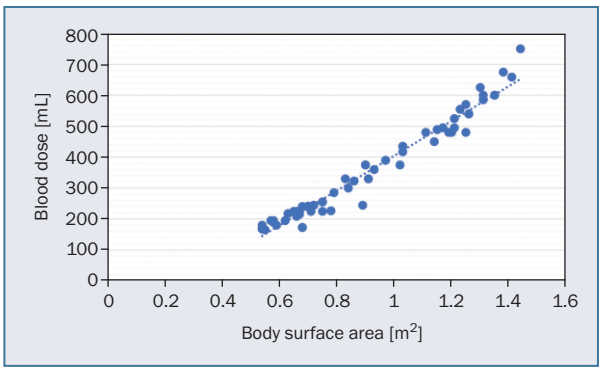

Figure 5. Blood dose to body surface area (BSA) (m^2) adjusted to 15 mL/kg for >10 kg body weight

collected over a 12 month period. CC of blood dose was performed with the weight of the subjects and corresponding BSA under both weight subgroups (Table I).

Both transfusion groups had a low to moderate, but significant, correlation coefficient (CC) of transfused blood dose with weight as well as BSA (p <0.05) (Table I, Supplementary Table 1 — see the supplementary file in the on-line version of the article).

BSA of range (0.08–0.52 m^2) for weight ≤10 kg (n = = 72) and (0.53–1.44 m^2) for >10 kg (n = 86) had regression coefficient r^2 = 0.46 and r^2 = 0.26 (p <0.05) (Table I).

The regression equation of blood dose and BSA based upon 'patient data' for weight category of ≤ 10 kg [BSA range (0.08–0.52 m^2)] and >10 kg (0.53–1.44 m^2) was as follows:

- weight sub-groups (≤10 kg bw) blood dose (mL) = = −10.3 + 366.9x BSA (m^2);
- weight sub-groups (>10 kg bw) blood dose (mL) = = 102.3 + 157.9x BSA (m^2).

We then adjusted blood dose to 15 mL/kg/bw for each weight category (≤10 kg and >10 kg) and derived blood dose, which formed the 'adjusted regression equation' with BSA. A scatter plot depicting the relationship of independent and dependent variables can be seen in Figures 2–5:

- adjusted blood dose (≤10 kg); (15 mL/kg bw) = −19.12 + 366.9x BSA (m^2);
- adjusted blood dose (>10 kg bw) (15 mL/kg bw) = = −158.8 + 563.3x BSA (m^2).

We then validated equation from data which compared patient weight (kg) and corresponding BSA (m^2). We then validated this equation from an existing data of 'Chemotherapy standardization group' which compared patient weight (kg) and corresponding BSA (m^2) [17].

The mean blood dose [(≤10 kg; n = 72) and (>10 kg bw; n = 86)] with standard 15 mL/kg bw was 67.4 ±46.5 mL and 342.2 ±157.7 mL respectively comparable to the blood dose (SD) calculated with derived regression equation using the BSA 67.42 ±45.46 m^2 and 342 ±155.1 m^2 (Table II).

This equation was further validated by using data from the data of a chemotherapy standardization group (Supplementary Tables 2A, 2B — see the supplementary file in the on-line version of the article) (≤10 kg and >10 kg) [19].

The blood dosages calculated with 15 ml/kg bw were not statistically different from dosage calculated by the regression equation for BSA (0.08–0.52 m^2) and (0.53– –1.44 m^2) Independent sample T-test (p = 0.91 and 0.53) (Supplementary Tables 3A, 3B — see the supplementary file in the on-line version of the article).

Table II. Comparison of blood dose from weight with body surface area (BSA)

		Blood dose (15 mL/kg bw) (≤10 kg)	Blood dose (20 mL/kg bw) (≤10 kg)	Calculated blood dose (≤10 kg)	Blood dose (15 mL/kg) (>10 kg)	Blood dose (20 mL/kg bw) (>10 kg)	Calculated blood dose (>10 kg)
N	Valid cases	72	72	72	86	86	86
M±ean ±SD		67.4 ±46.5	90.1 ±63.1	67.4 ±45.4	342.2 ±157.7	456.0 ±210	342.0 ±155.1
Minimum; maximum values		12.0; 156.0	16.0; 208.0	10.5; 152.3	165.0; 750.0	220.0; 1000.0	145.2; 750.0

SD — standard deviation

Blood doses calculated with bw (20 mL/kg) for ≤10 kg and >10 kg were significantly different compared to 'calculated dose' from the regression equation with mean [standard deviation (SD) higher in volume (mL) compared to the regression equation for BSA (0.08–0.52 m^2) and (0.53–1.44 m^2)] (independent test; p = 0.05 and 0.006) (Supplementary Tables 2A, 3B — *see* the supplementary file in the on-line version of the article).

Model 2: a comparison of blood storage period (≤15 days and >15 days) in 'transfusion dependent group'(n = 31); we did not observe a significantly different value of pre-transfusion Hb 5.7 ±2.1 g/dL and 5.5 ±1.7 g/dwith (p = 0.75); post-transfusion Hb 8.4 ±2.1 g/dL and 9.1 ±2.2 g/dL (p = = 0.29) and Hb increment 2.7 ±1.5 and 2.3 ±1.4 (p = 0.51) (2 sample T test) (Table III).

Non-transfusion-dependent group (n = 158) did not have significant difference: pre-transfusion Hb 6.6 ±1.5 g/ /dL and 6.6 ±1.7 g/dL (p = 0.94); post-transfusion Hb 9.2 ±1.9 g/dL and 9.0 ±2.2 g/dL (p = 0.68) and Hb increment 2.5 ±1.4 and 2.4 ±2.0 respectively. (Two-tailed independent T test (p >0.61) (Table III).

Transfusion-dependent and non-transfusion-dependent patients had significant differences in the pre-transfusion Hb (≤15 days and >15 days) (p = 0.016) with no statistical difference in post-transfusion Hb (p = 0.08). The Hb increments when compared for transfusion dependent and non-transfusion dependent were non-significantly different (p = 0.89; Table III).

Table III. Effect of red blood cell (RBC) storage on transfusion subgroup

Parameter	Less than or equal to 15 days RBC storage	Greater than 15 days RBC storage
Mean ±SD storage duration [days] RBC*	9.2 ± 3.6 (n = 79)	26.4 ± 6.4 (n = 79)
Mean ±SD pre-transfusion Hb [g/dl]*	6.6 ± 1.5	6.6 ± 1. 7
Mean ±SD post-transfusion Hb [g/dl]*	9.2 ± 1.9	9.0 ± 2.2
Mean ±SD Hb increment [g/dl]*	2.5 ± 1.4	2.4 ± 2.0
Mean ±SD storage duration [days] RBC#	8.8 ± 3.4 (n = 16)	26.4 ± 6.3 (n = 15)
Mean ±SD pre-transfusion Hb [g/dl]#	5.7 ± 2.1	5.5 ± 1.7
Mean ±SD post-transfusion Hb [g/dl]#	8.4 ± 2.0	9.1 ± 2.2
Mean ±SD Hb increment [g/dl]#	2.7 ± 1.5	2.4 ± 1.4

*Dependent (n = 158); #transfusion-dependent (TD) (n = 31); SD — standard deviation; Hb — hemoglobin

Discussion

Pediatric patients where the blood transfusion is in small aliquots targeting Hb show variation depending on physical parameters such as age, BSA, and blood dosage [2, 10, 23]. An objective of transfusion recommendations corresponding to BSA is to achieve the desired clinical response among patients with minimal allogeneic transfusions and transfusion associated side-effects [23–25].

The reasons for choosing non-bleeding, non-transfusion-dependent subjects to estimate blood dose equation were as follows: 1) blood is mostly administered to pediatric patients as per body weight, and not in units as in adults; and 2) non-bleeding patients are less likely to have post-transfusion Hb increment impacted by ongoing blood loss or hemodilution because of volume replacement.

The storage duration of RBC also does not adversely affect survival during the hospital stay [27, 28]. We assessed pre-transfusion Hb and 24 hours post-transfusion Hb as a function of 'days of storage' *ex vivo* and subsequent RBC survival. Post-transfusion Hb was chosen to assess days of storage effect because Hb assessment is generally performed to ascertain steady state response following RBC transfusions [13, 28].

A classification of underweight or overweight pediatric population requires age and sex-based standardization with a reference population under evaluation. BSA band based blood dosing or weight to BSA conversion, especially

in infants and children, needs further validation by clinical trials to establish safety in this context [5, 8, 10]. BSA based dosing has been documented to show discrepancies in adults and very young children [23, 29, 30]. In the present study, with adjusted equation based on 'BSA', a more streamlined correlation of blood dose and BSA with higher regression co-efficient was observed for both weight categories (≤10 kg and >10 kg) (Supplementary Table 1 — see the supplementary file in the on-line version of the article). (Figures 2–5).

This equation may show some variation within different representative populations, which however is unlikely to affect significantly the accuracy of calculating blood dose according to the BSA of the patient.

The regression equation calculated with 15 mL/kg bw reference values, and the calculated blood dose from the corresponding BSA did not exceed 20 mL/kg body weight (Supplementary Tables 2A, 2B — see the supplementary file the in the on-line version of the article).

Blood transfusion among patients with cardiac failure and children with malnourishment when transfused according to the BSA (m^2) and Hb (g/dL) threshold is likely to prevent over-transfusions and related adverse side-effects.

The blood transfusion-related to BSA can be standardized according to bands of BSA receiving a similar dosing regimen [8]. This measure could prevent erratic transfusion to a patient, especially pre-term and newborns, since there is considerable heterogeneity in the blood volume and BSA formula in this age group [3, 23]. A regression equation that accommodates such borderline cases with clinical trial-based validation of BSA based dosing from a large representative population size should be the next step for BSA based blood transfusion dosing.

A comparison of fresh versus old RBC (≤15 days and >15 days) for post-transfusion hemogram values among the pediatric population is another step towards attainment of a predictable post-transfusion Hb (g/dL) as an endpoint parameter. A single RBC unit for transfusion of newborns decreases potential donor exposure and chances of infection transmission and immune transfusion reactions.

We evaluated transfusion-dependent and non-transfusion-dependent populations separately to evaluate the effect of RBC storage-based lesions and test the similarity of post-transfusion hemogram after RBC transfusion among diverse test subjects. The blood transfusion in the present study attained similar endpoints (post-transfusion Hb and Hb increment) irrespective of patient type or RBC storage duration. The importance of more such studies to evaluate 'a steady-state hemogram' or other standardized parameters such as 'tissue oxygenation' should be a baseline to assess effect of storage duration upon the efficacy of RBC transfusion [31, 32].

This study had a small number of test subjects with limited standardization related to critical confounding variables such as known alloimmunization status, especially in transfusion-dependent patients; a high or low responder to transfusion demarcation might have been more evident in a larger sample size [10]. Post-transfusion hemogram parameters might have modified the effect of storage due to underlying clinical diagnosis. Missing data of weight and height obtained from the growth chart could have overlooked the physiological variations due to malnutrition or growth retardation, though it is unlikely to be significant. Previous recommendations of transfusing a patient from BSA advise caution in infants under six months and up to 12 months with a combination of weight and BSA for calculating the infusion dose [23].

This present study attempts to standardize endpoints of transfusion among the pediatric population; however, our study's findings should be replicated further in a clinical trial setting before incorporating them into routine patient use.

Conclusions

Blood dose according to the BSA is an appropriate substitute for weight-only based dosing for blood transfusion. However, clinicians utilizing any transfusion regimen with BSA must validate the equation in a clinical trial setting. The duration of blood storage does not affect the post-transfusion Hb in transfusion-dependent or non-transfusion-dependent patients.

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Conflict of interest

This work was accepted as an abstract for oral presentation at the annual conference of the ISBT 2020 and was published as an abstract of the conference Supplement.

Data and material available upon request.

Authors' contributions

SS — concept, research and ethical approval, first author, corresponding author, statistical calculations, interpretation and conclusions; SJ — scientific suggestions for manuscript, co-investigator in study, patient coordination; MP — patient coordination and data collection; AS — calculations, sample size, effect of blood storage duration on post-transfusion Hb (g/dL) levels; AG — availability of departmental resources, mentoring

Ethical approval

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Ruxolitinib-associated squamous cell carcinoma

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A 62-year-old Caucasian female with Fitzpatrick III phototype presented to our Dermatology consult due to an ulcerated nodule on the dorsum of her right hand which had been steadily growing over the last year. The patient had been under primary treatment with ruxolitinib 20 mg bid for four years due to primary myelofibrosis with unbalanced t(1;19) translocation, without V617F *JAK2* mutation. No other relevant medical conditions were reported, and the patient was not under any other concomitant medication. She denied significant exposure to ultraviolet radiation during her lifetime, either on a daily basis or during holidays. On physical exam, we observed a nodule with a 3 cm diameter, with central keratinization and ulceration, on the dorsum of the right hand (Figure 1A). The patient bore no stigmata of significant actinic damage either locally or on the remaining tegument. No premalignant lesions were detected. We conducted a punch biopsy that revealed a squamous cell carcinoma with moderate differentiation, but rather infiltrative, reaching the dermohypodermal junction (Figure 1B). Ruxolitinib was withdrawn, and the lesion was surgically removed.

Ruxolitinib is a Janus kinase (JAK) inhibitor which selectively targets JAK1 and JAK2. This drug is approved for treatment of high-risk myelofibrosis, polycythemia vera refractory or with intolerance to hydroxyurea and steroid-refractory acute graft-versus-host disease. Despite these indications, ruxolitinib, along with other JAK inhibitors, has been suggested to be useful in multiple dermatological conditions such as alopecia areata [1, 2], vitiligo [3], psoriasis [4] and atopic dermatitis [5] and rheumatological diseases such as rheumatoid arthritis or psoriatic arthritis. Long-term follow-up of patients enrolled in phase III trials for ruxolitinib has identified an increased risk for developing aggressive non-melanoma skin cancer (NMSC) [6], but other studies have failed to do so.

The case we report is highly suggestive to be related to ruxolitinib treatment, because this patient reported no significant exposure to ultraviolet radiation, had no signs of actinic damage, and had never been under other immunosuppressive treatments linked with NMSC risk. Recently, risk for NMSC under ruxolitinib has been shown to be particularly high in patients without *JAK2* mutation, as in this case [7].

The JAK-STAT pathway is an intracellular signaling pathway which is implicated in signal transduction for a wide range of extra-cellular stimuli, and its inhibition has gathered interest as a potent anti-inflammatory strategy for a number of hematological, rheumatological and dermatological conditions. The pro-oncogenic potential of ruxolitinib has been proposed to immune dysregulation with cytotoxic response dampening, thus facilitating neoplastic proliferation, but the mechanisms are far from clear [8, 9].

While this risk has been identified for ruxolitinib, tofacitinib, a specific JAK1 inhibitor, seems not to carry such an increased risk for NMSC [10]. Baricitinib, another JAK2 and JAK3 inhibitor, has been approved for the treatment of rheumatoid arthritis and atopic dermatitis. While sharing a common mechanism with ruxolitinib, to date no reports of increased risk for NMSC have emerged, but long-term data for this drug is still relatively scarce.

While JAK inhibitors are being proposed for the treatment of multiple conditions, caution is needed regarding the potential adverse effects. The analysis of pharmacovigilance data on long-term use of these drugs is warranted, and *in vitro* studies should be conducted to clarify the mechanisms underlying the apparent predisposition to NMSC in patients under some JAK inhibitors. Patients under these treatments should undergo regular skin inspection to detect potential malignant neoplasms early on.

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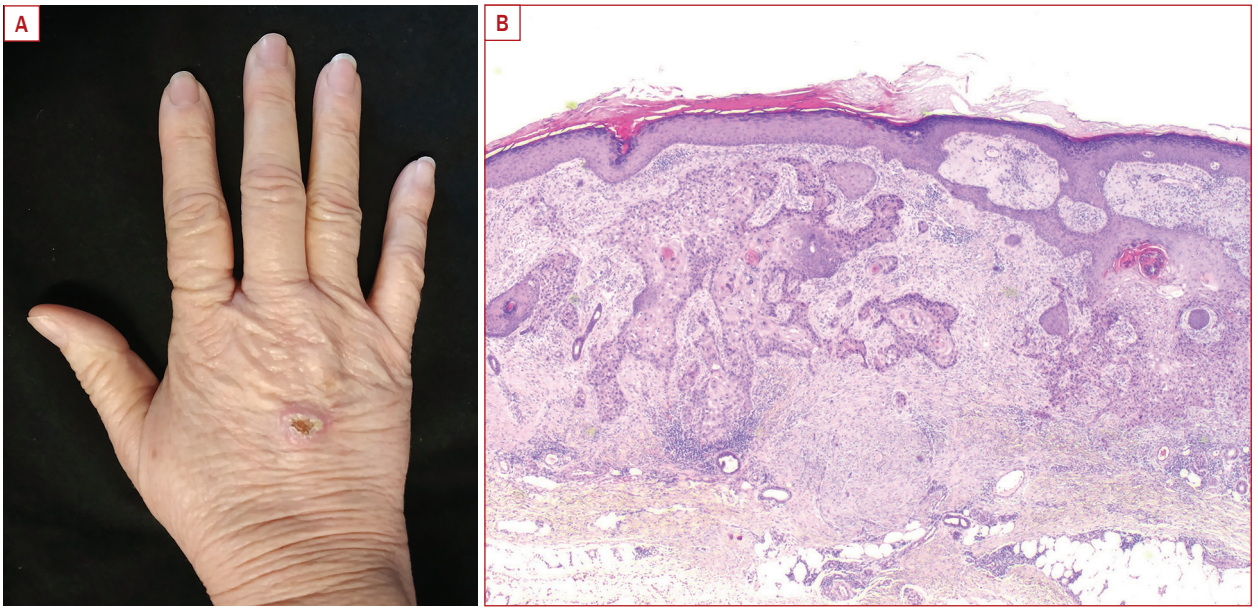

Figure 1A. Clinical picture of lesion; **B.** Histopathology of lesion [hematoxylin and eosin (H&E) stain, 25× magnification]

Hematologists, rheumatologists and other physicians prescribing these drugs should become acquainted with the clinical image of NMSC and conduct regular full body checks, even in patients without evident sun damage. Referral to a dermatologist should be considered as a preventive measure.

Authors' contributions

All authors contributed equally to the manuscript.

Conflict of interests

None.

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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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Double transformation of relapsing juvenile myelomonocytic leukemia to refractory acute myeloid leukemia

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Introduction

Juvenile myelomonocytic leukemia (JMML) is a clonal, hematopoietic disorder of childhood of which the clinical manifestation is leukocytosis, thrombocytopenia and overproduction of monocytes. It is the only pediatric entity classified by the World Health Organization (WHO) as a myelodysplastic syndrome/myeloproliferative neoplasm overlap syndrome [1, 2]. The incidence of JMML is 1.2 cases per 1,000,000 children and the disease is most often diagnosed at the age of two [3].

The WHO diagnostic criteria for JMML are [1, 3]:

I. Clinical and hematological features (all of these are mandatory if JMML is to be diagnosed):
   - absence of Philadelphia chromosome (*BCR/ABL* rearrangement);
   - peripheral blood monocyte count ≥1 × 10^9/L;
   - peripheral blood and bone marrow blast count <20%;
   - splenomegaly.

II. Gene features (the presence of just one of these is sufficient):
   - somatic mutations in *PTPN11* or *KRAS* or *NRAS* (germline mutations need to be excluded);
   - clinical diagnosis of neurofibromatosis-1 (NF-1) or *NF1* mutation;
   - germline *CBL* mutation and loss of heterozygosity of *CBL*.

III. For patients without a gene feature, in addition to the clinical and hematological features listed under criterion I, the following criteria must be met:
   - monosomy 7 or any other chromosomal abnormality, or at least two of the following criteria:
   - myeloid or erythroid precursors on peripheral blood smear;
   - fetal hemoglobin (HbF) increased for age;
   - granulocyte macrophage colony-stimulating factor (GM-CSF) hypersensitivity in colony assay;
   - white blood cells >10 × 10^9/L;
   - hyperphosphorylation of STAT5.

The characteristic feature of JMML is hyperactivation of the RAS pathway, induced by five main mutations which can occur either as somatic (*PTPN11* in 38%; *NRAS* in 18%; *KRAS* in 14%) or as germline (*NF1* in 5–10%; *CBL* in 12–18%) lesions in hematopoietic cells [1, 4, 5]. *RAS* mutations can provoke uncontrolled proliferation of cancer cells [6]. There have also been evident 'all-negative' (sometimes called 'quintuple-negative') JMML cases with the absence of the main genes mutations and lack of NF-1 clinical manifestation [1, 2, 4, 5, 7].

In c.49% of cases, the RAS pathway mutation is followed by secondary molecular alteration, which include mutations in the components of polycomb repressive complex 2, *SETBP1, JAK3*, spliceosome-related genes (*ZRSR2*) and monosomy 7 [1].

A transformation from JMML to acute myeloid leukemi (AML) occurs in one third of cases [1]. Subsequently, there

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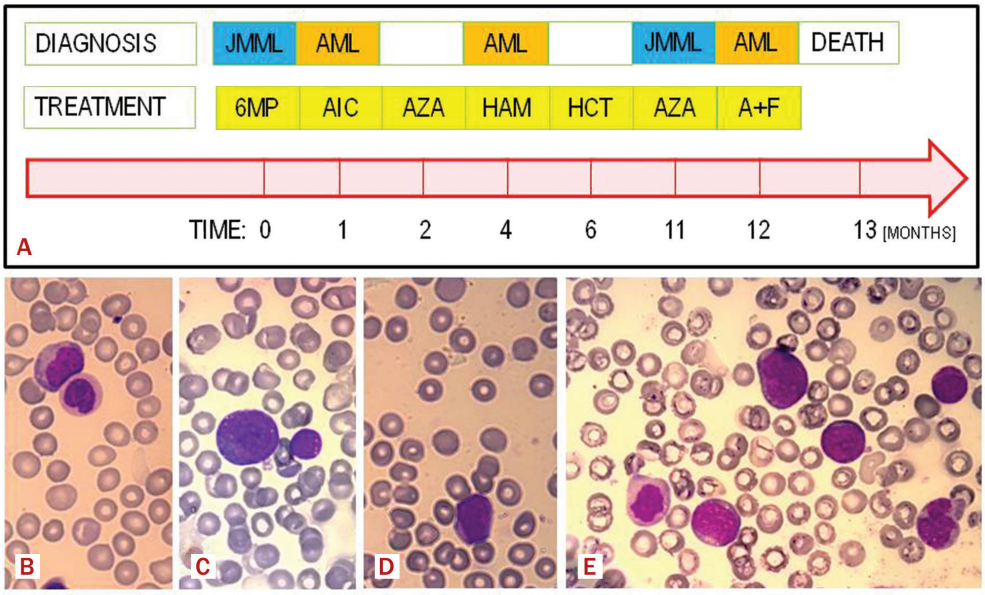

Figure 1A. Timeline of clinical course [juvenile myelomonocytic leukemia (JMML), acute myeloid leukemia (AML), mercaptopurine (6MP), cycles of AML-BFM-2004 protocol (AIC/HAM); allogeneic hematopoietic cell transplantation (HCT); azacytidine (AZA), cytarabine + fludarabine (A + F)]; **B.** Monocyte and granulocyte (BM, bone marrow) hematological smears (×1,000); **C.** Monocyte (PB, peripheral blood) hematological smears (×1,000); **D.** Myeloblast, hematological smears (×1,000); **E.** Three myeloblasts, two monocytes and lymphocyte

are documented factors associated with a higher transformation risk. *RRAS*-mutation, the presence of two or more RAS-activating mutations, and a secondary molecular alteration (*EZH2, ASXL1, SETBP1, JAK3, ZRSR2*, monosomy 7) characterizes cases with an increased risk of progression to AML [1, 3].

Case description

A 6-year-old boy was diagnosed with JMML (Figure 1A). Clinically, the patient developed a significant hepatosplenomegaly. Primary tests revealed: increased percentage of monocytes, increased level of HbF (18.6%), blasts in peripheral blood smear (below 20%), and 10–14% blasts in myelogram (Figure 1B–E). Genetic tests revealed the presence of heterozygotic mutation of *PTPN11* gene. The patient was qualified to allogeneic hematopoietic cell transplantation (allo-HCT), and cytoreductive mercaptopurine treatment was initiated immediately. During the therapy, his clinical condition worsened, with features of secondary hemophagocytic syndrome. Then JMML transformation to AML-M6 [blasts: peripheral blood (PB) 30%, bone morrow (BM) 35%] occurred, confirmed in the reference center. The boy received a first cycle (AIC) of AML-BFM-2004 protocol, with blasts clearance. Due to poor tolerance of chemotherapy, he was switched to azacitidine treatment, but after two cycles, myeloblasts were found in the bone marrow. Another cycle-(HAM) of AML-BFM-2004 protocol was administered, and then the patient underwent allo-HCT from a matched unrelated donor preceded by European Working Group of Myelodysplastic Syndrome (EWOG-MDS) conditioning BuCyMel + rATG. Hematological and molecular remission and full donor chimerism was achieved, but hepatosplenomegaly persisted. The boy received another cycle of azacytidine. After the first cycle, six months after HCT, mixed donor chimerism and molecular JMML relapse were confirmed, with *PTPN11* mutation in 36% of granulocytes and the presence of myeloblasts in BM. Two cycles of cytoreductive chemotherapy with cytarabine/fludarabine were applied, which were followed by prolonged myelosuppression and numerous infectious complications. The patient died a few days later in leukemic bone marrow progression with symptoms of pneumonia and multiorgan failure.

Our case report demonstrates a complicated clinical course of relapsing JMML, with conversion to AML both in initial and relapsed JMML. The explanation for incomplete clinical remission was probably splenomegaly not returning to normal size despite chemotherapy and conditioning before allo-HCT. Furthermore, this case proves that transformation can occur at any moment throughout the course of the disease — before or after allo-HSCT. Relapsing and aggressive course of JMML requires regular bone marrow biopsies with frequent evaluation of myeloblasts level in order to adjust treatment depending on the current diagnosis (JMML or AML). Frequent evaluation of myeloblasts quantity is essential for all patients with JMML in order to administer AML chemotherapy as soon as possible. Stratifying the transformation risk may help in finding the most suitable therapy plan for patients with an aggressive course of disease. Nevertheless, dealing with relapsing

JMML remains a considerable challenge, and the prognosis is poor. Further investigation into both the clinical and the molecular risk factors of AML progression is needed in order to adjust JMML therapy to make it more effective in the most aggressive cases.

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Authors' contributions
KC, TS — design of study. RD, MRP, KC, MK, BKR — provision of clinical data. All authors — analysis of clinical data. TS, JS — literature search and analysis of data. TS, JS — writing of manuscript: TS, JS. Critical revision and final approval: all authors

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None.

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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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VIA MEDICA

Single insult origin of Paget-Schroetter syndrome in adolescent successfully treated with balloon angioplasty and AngioJet thrombectomy system

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Case presentation

A 15-year-old girl presented to the emergency department complaining of a painful arm. The initial symptoms of a strange feeling in the right arm had occurred 1–2 months before hospitalization. Her legal guardian noticed significant swelling of the right extremity on the day prior to presentation. The consultant orthopedic surgeon had excluded musculoskeletal origin of the pain. Color Doppler ultrasound (CDUS) revealed massive thrombosis of the right brachial, axillary, and most of the subclavian, veins. No family history of deep venous thrombosis (DVT) and no risk factors of developing DVT were found. However, during the hospitalization it turned out that there was a history of major right upper extremity trauma three years prior to admission. Initially, anticoagulation treatment was started: nadroparin 0.6 ml subcutaneous (s.c.) twice daily. No improvement was observed for five days. After that time, a clinico-radiological meeting was conducted and the decision regarding catheter-directed thrombolysis (CDT) implementation was made. Under local anesthesia, a microcatheter was placed through peripheral 4F venous access. Initial infusion rate of alteplase of 0.3 mg/kg/h was reduced to 0.05 mg/kg/h after six hours. Over the next three days, consecutive venographies were performed. There was no possibility to access more proximal parts of the vein due to hard resistance resulting in partial recanalization of the axillary vein with poor clinical improvement. The CDT treatment was ceased. Computed tomography venography confirmed occlusion of the subclavian vein with typical pattern of multiple collateral vessels. A diagnosis of Paget-Schroetter syndrome (PSS) was made. Based on performed studies and clinico-radiological consensus, a decision was made on venous recanalization and thrombectomy with the use of the AngioJet system (Boston Scientific, USA).

The procedure was performed on hospital day 12 under general anesthesia. Additional right femoral venous access was made to guide during the crossing of the occluded subclavian vein. Initial percutaneous transluminal angioplasty (PTA) of the occluded segment was made with the use of a 3 mm balloon to allow the AngioJet system to cross the occlusion. In the next step, the brachial, axillary and subclavian veins were infused with 15 mg of alteplase using the AngioJet system equipped with a Solent Omni catheter, followed by mechanical thrombectomy using the same catheter.

In the last stage, PTA of the axillary and subclavian veins was performed with the use of increasing diameter balloons. Final venography confirmed recanalization of the treated segments with no outflow obstruction. There were no intra- or post-procedural complications. 19 days after admission to the hospital, the patient was discharged home with no symptoms and with restored flow in the treated veins, proved on CDUS. A further CDUS at three-month follow up confirmed patency of the treated veins.

Discussion

Deep venous thrombosis (DVT) in children is rare [1] with an estimated incidence of 10–14 per 10,000 pediatric

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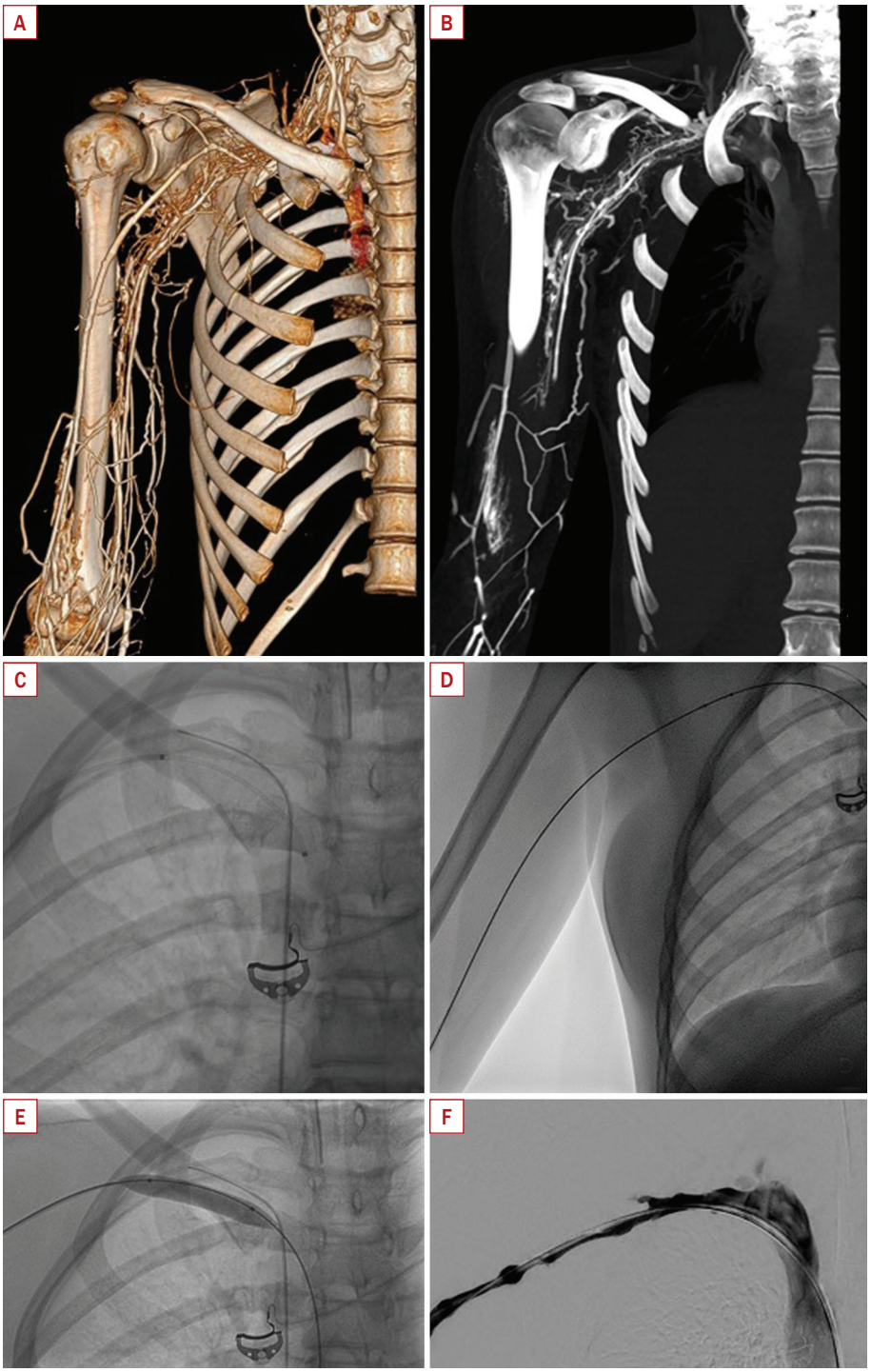

Figure 1. Computed tomography venography and interventional procedure. Three-dimensional (3D) volume rendered **(A)** and maximum intensity projection (MIP; **B)** coronal reconstruction computed tomography venography depicting occlusion of subclavian vein with typical pattern of multiple collateral vessels; **C.** Crossing of occluded subclavian vein; **D.** AngioJet system in use, markers of Solent Omni catheter visible in subclavian vein; **E.** Balloon angioplasty of subclavian vein; **F.** Digital subtraction venography presenting final result of procedure; guidewires still in place

admissions annually [2]the incidence, associated morbidity, and mortality are unknown. A Canadian registry of DVT and PE in children (ages 1 month to 18 years. There are two peaks of incidence in this population: neonates/ /infants and adolescents [3]. Although most incidences of DVT in the pediatric population are associated with central venous catheterization [3, 4], there are many other risk factors, including trauma which may lead to PSS. PSS

accounts for at least 10–20% of upper extremity DVTs, and is predominantly seen in teenagers and young adults [5].

In our patient, there was a history of prior trauma while skiing, with no data supporting chronic injury, favoring a single insult origin of PSS. Thoracic outlet decompression is considered to play a key role in the management of this syndrome. However, Lee et al. showed that only 25% of patients in whom recurrent or persistent symptoms after CTD were observed underwent surgery after a mean follow up of 13 months [6]. We found this approach to be the most suitable for our patient.

Once PSS is diagnosed, anticoagulation or CDT should be started. However, in our case, there was no response to this treatment and more invasive endovascular treatment had to be considered. Since there is a potential risk of a pulmonary embolism during recanalization of occluded veins, the decision was made to use the AngioJet system. This is a thrombectomy device with active aspiration acting by injecting heparinized saline at high-velocity, creating a strong vacuum effect using the Bernoulli effect. Another feature of this system is the power pulse mode which facilitates direct thrombus injection with thrombolytic, which was used in our patient.

Conclusions

The AngioJet system used in our pediatric patient was safe and effective. Although rare, physicians dealing with children should be aware of DVT and PSS and their potential short- and long-term complications. Once patients with DVT fail to respond to anticoagulation or thrombolysis, interventional treatment should be considered.

Authors' contributions

All authors have approved the final article.

Conflict of interest

None.

Financial support

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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▼ 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, 0,4-2×10^8 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 2×10^6 żywotnych limfocytów CAR-T anty-CD19/kg masy ciała (zakres od 1×10^6 do 2×10^6 limfocytów/kg) z maksymalną liczbą limfocytów CAR-T anty-CD19 wynoszącą 2×10^8. Substancje pomocnicze o znanym działaniu: 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 nieprzezroczystej dyspersja barwy od białej do czerwonej. **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. Produkt Yescarta jest wskazany w leczeniu nawrotowego lub opornego na leczenie chłoniaka grudkowego (ang. *follicular lymphoma*, FL) u dorosłych pacjentów, którzy uprzednio otrzymali co najmniej trzy 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 co najmniej 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 podania każdej poprzedniej dawki. W wyjątkowej sytuacji braku dostępności tocilizumabu uwzględnionego w wykazie produktów leczniczych zagrożonych brakiem dostępności Europejskiej Agencji Leków przed rozpoczęciem infuzji muszą być dostępne odpowiednie, alternatywne leki do leczenia CRS zamiast tocilizumabu. Dawkowanie: Yescarta to produkt przeznaczony wyłącznie do stosowania autologicznego (patrz punkt 4.4). Pojedyncza dawka produktu Yescarta zawiera 2×10^6 żywotnych limfocytów CAR-T na kilogram masy ciała (lub maksymalnie 2×10^8 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 zalecanych dniach, tj. 5., 4. i 3. dniu przed infuzją produktu Yescarta należy koniecznie 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:* Pacjenci muszą być monitorowani 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 lub podmiotowych CRS i (lub) zdarzeń neurologicznych. Po pierwszych 10 dniach od infuzji o monitorowaniu pacjenta zdecyduje lekarz. Pacjenci muszą być poinformowani o konieczności pozostania w pobliżu kwalifikowanej placówki klinicznej przez co najmniej 4 tygodnie po infuzji. Szczególne grupy pacjentów: *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 konieczne dostosowywanie dawki u pacjentów w wieku 65 lat i starszych. Skuteczność leczenia była zgodna ze skutecznością leczenia w całej leczonej populacji pacjentów. Sposób podawania: 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 musi 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 skontaktować się z firmą 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. Delikatne ręczne mieszanie powinno doprowadzić do rozproszenia małych grudek materiału komórkowego. Produktu Yescarta nie wolno myć, wirować ani powtórnie odtwarzać zawiesiny na nowym nośniku przed infuzją. Rozmrażanie trwa około 3 do 5 minut. Po rozmrożeniu produkt Yescarta zachowuje trwałość w temperaturze pokojowej (od 20°C do 25°C) do 3 godzin. Jednakże infuzję produktu Yescarta trzeba rozpocząć w ciągu 30 minut od zakończenia rozmrażania. *Podawanie:* Wyłącznie do stosowania autologicznego. Tocilizumab oraz sprzęt ratunkowy muszą być dostępne przed infuzją i podczas monitorowania. W wyjątkowej sytuacji braku dostępności tocilizumabu uwzględnionego 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 przepłukać 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 infuzji całej zawartości worka przepłukać zestaw do infuzji roztworem chlorku sodu (0,154 mmol sodu/ml) z tą samą szybkością 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:** Identyfikowalność: 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 koniecznie przechowywać przez okres 30 lat po upłynięciu terminu ważności produktu. Ogólne: 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. Pacjenci muszą być monitorowani 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 trzeba rozważyć monitorowanie parametrów życiowych i czynności narządów. Powody odroczenia leczenia: Ze względu na zagrożenia związane z leczeniem produktem Yescarta podanie infuzji należy koniecznie wstrzymać, jeśli u pacjenta występuje którykolwiek z następujących stanów: utrzymujące się ciężkie działania niepożądane (w szczególności działania dotyczące płuc, serca lub niedociśnienie tętnicze), w tym związane z wcześniejszymi chemioterapiami; czynne, niekontrolowane zakażenie; czynna choroba przeszczep przeciwko gospodarzowi (ang. *graft-versus-host disease*, GVHD). Badania serologiczne: Przed pobraniem komórek do wytworzenia produktu Yescarta należy koniecznie wykonać badania przesiewowe na obecność HBV, HCV i HIV (patrz punkt 4.2). Oddawanie krwi, narządów, tkanek i komórek: Pacjenci leczeni produktem Yescarta nie mogą być dawcami krwi, narządów, tkanek ani komórek do przeszczepienia. Choroba współistniejąca: 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. Pierwotny chłoniak ośrodkowego układu nerwowego (OUN): 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. Zespół uwalniania cytokin: 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 w badaniu ZUMA-1 oraz od 1 do 11 dni w badaniu ZUMA-5 (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 poprzedniej dawki. W wyjątkowej sytuacji braku dostępności tocilizumabu uwzględnionego 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 tętnicze, brak odpowiedzi po podaniu płynów lub niedotlenienie wymagające podania dodatkowego tlenu), należy koniecznie 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 wolno 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 koniecznie 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: Nasilenie zespołu uwalniania cytokin (CRS) i algorytmy postępowania.** Nasilenie CRS[a]: Stopień 1.: 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. Stopień 2.: Objawy wymagają umiarkowanej interwencji, po której ustępują. Zapotrzebowanie na tlen wynoszące mniej niż 40% FiO_2 lub niedociśnienie tętnicze reagujące 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. Stopień 3.: Objawy wymagają poważnej interwencji, po której ustępują. Zapotrzebowanie na tlen przekraczające lub równe 40% FiO_2 lub niedociśnienie tętnicze wymagające 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). Stopień 4.: 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.* Neurologiczne działania niepożądane: U pacjentów leczonych produktem Yescarta bardzo często obserwowano ciężkie neurologiczne działania niepożądane, znane również jako zespół neurotoksyczności związany z komórkami efektorowymi układu odpornościowego (ang. *immune effector cell-associated neurotoxicity syndrome*, ICANS), 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 koniecznie monitorować pod kątem objawów przedmiotowych i podmiotowych neurologicznych działań niepożądanych (Tabela 2). Pacjenci muszą być monitorowani w kwalifikowanej placówce opieki zdrowotnej co najmniej codziennie przez pierwsze 10 dni pod kątem objawów przedmiotowych i podmiotowych toksyczności neurologicznej/ICANS. 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/ICANS. W zależności od stopnia nasilenia danego działania niepożądanego trzeba rozważyć monitorowanie parametrów życiowych i wydolności narządów. Pacjentów, u których wystąpi toksyczność neurologiczna stopnia 2. lub wyższego/ICANS, należy koniecznie 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: Nasilenie neurologicznych działań niepożądanych/ICANS i algorytmy postępowania.** Stopień 2.: 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. Stopień 3.: 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. Stopień 4.: 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*).* Zakażenia i gorączka neutropeniczna: Podczas stosowania produktu Yescarta bardzo często obserwowano ciężkie zakażenia (patrz punkt 4.8). Pacjenci muszą być monitorowani 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. Reaktywacja HBV: 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 trzeba przeprowadzić badanie przesiewowe w kierunku HBV, HCV i HIV. Przedłużająca się cytopenia: 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. Hipogammaglobulinemia: 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. Reakcje nadwrażliwości: 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. Wtórne nowotwory złośliwe: 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. Zespół rozpadu guza (ang. *tumour lysis syndrome*, TLS): 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 koniecznie monitorować pod kątem przedmiotowych i podmiotowych objawów TLS, a objawy należy leczyć zgodnie ze standardowymi wytycznymi. Wcześniejsze leczenie terapią anty-CD19: 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. Substancje pomocnicze: Ten produkt leczniczy zawiera 300 mg sodu na worek infuzyjny, co odpowiada 15% zalecanej przez WHO maksymalnej 2 g dobowej dawki sodu dla osoby dorosłej. 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: Podsumowanie profilu bezpieczeństwa: Dane dotyczące bezpieczeństwa opisane w tym punkcie pochodzą od ogółem 227 dorosłych pacjentów leczonych produktem Yescarta w dwóch głównych wieloośrodkowych badaniach klinicznych (ZUMA-1 oraz ZUMA-5, w których leczono 108 pacjentów z DLBCL lub PMBCL oraz 119 pacjentów z FL). *Chłoniak rozlany z dużych komórek B oraz pierwotny chłoniak śródpiersia z dużych komórek B:* 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. Opisane dane pochodzą z analizy 54-miesięcznego okresu obserwacji, gdzie mediana rzeczywistego okresu obserwacji wyniosła 23,5 miesiąca (zakres od 0,3 do 67,8 miesiąca). Do najbardziej poważnych i najczęstszych działań niepożądanych należały CRS (93%), encefalopatia (60%) oraz zakażenia (40%). Ciężkie działania niepożądane wystąpiły u 51% pacjentów. Do najczęstszych działań niepożądanych należały: encefalopatia (22%), zakażenia nieswoistymi patogenami (15%), zakażenia bakteryjne (6%), zakażenia wirusowe (6%), gorączka neutropeniczna (5%) i gorączka (5%). Najczęściej występujące (≥ 5%) niehematologiczne działania niepożądane stopnia 3. lub wyższego obejmowały encefalopatię (31%), zakażenia nieswoistymi patogenami (19%), CRS (11%), zakażenie bakteryjne (9%), zakażenie wirusowe (6%), stan majaczeniowy (6%), hipotensję (6%), zwiększenie aktywności transaminaz (6%) i nadciśnienie (6%). *Chłoniak grudkowy:* Dane dotyczące bezpieczeństwa opisane w tym punkcie odzwierciedlają skutki narażenia na produkt Yescarta w badaniu fazy II ZUMA-5, w którym 119 pacjentów z nawrotowym/opornym FL otrzymało limfocyty CAR-T w zalecanej dawce zależnej od masy ciała. Opisane dane pochodzą z analizy 24-miesięcznego okresu obserwacji, gdzie mediana rzeczywistego okresu obserwacji wyniosła 25,9 miesiąca (zakres od 0,3 do 44,3 miesiąca). Do najpoważniejszych i najczęstszych działań niepożądanych należały CRS (77%), zakażenia (59%) oraz encefalopatia (47%). Ciężkie działania niepożądane wystąpiły u 45% pacjentów. Do najczęstszych działań niepożądanych należały: encefalopatia (16%), zakażenia nieswoistymi patogenami (12%), CRS (12%), zakażenia bakteryjne (5%), gorączka (4%), zakażenia wirusowe (4%) oraz zakrzepica (3%). Najczęściej występujące (≥ 5%) niehematologiczne działania niepożądane stopnia 3. lub wyższego obejmowały encefalopatię (14%), zakażenia nieswoistymi patogenami (11%) oraz CRS (6%). Tabelaryczna lista działań niepożądanych: Działania niepożądane opisane w tym punkcie zaobserwowano u pacjentów narażonych na działanie produktu Yescarta w badaniach klinicznych ZUMA-1 (n = 108) oraz ZUMA-5 (n = 119), a także w raportach po wprowadzeniu produktu do obrotu. 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). 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: gorączka neutropeniczna[#], neutropenia[#], limfopenia[#], leukopenia[#], niedokrwistość[#], małopłytkowość[#]. Często: koagulopatia[a]. *Zaburzenia układu immunologicznego:* Bardzo często: zespół uwalniania cytokin, hipogammaglobulinemia[n]. Często: nadwrażliwość. Niezbyt często: limfohistiocytoza hemofagocytarna. *Zaburzenia metabolizmu i odżywiania:* Bardzo często: hiponatremia[#], hipofosfatemia[#], hiperurykemia[#], zmniejszone łaknienie[o], zmniejszenie masy ciała. Często: hipokaliemia[#], hipokalcemia[#], hipoalbuminemia[#], odwodnienie[p]. *Zaburzenia psychiczne:* Bardzo często: majaczenia[y], bezsenność. Często: zaburzenia afektywne[z]. *Zaburzenia układu nerwowego:* Bardzo często: encefalopatia[s], drżenie[u], ból głowy[t], zawroty głowy[v]. Często: drgawki, hemipareza, ataksja[x], neuropatia obwodowa[w]. Niezbyt często: porażenie czterokończynowe, obrzęk rdzenia kręgowego, zapalenie rdzenia kręgowego, dyskalkulia, mioklonie. *Zaburzenia serca:* Bardzo często: tachykardia[b], arytmia[c]. Często: zatrzymanie akcji serca, niewydolność serca[d]. *Zaburzenia naczyniowe:* Bardzo często: niedociśnienie tętnicze[hh], nadciśnienie tętnicze. Często: zakrzepica[ii]. *Zaburzenia układu oddechowego, klatki piersiowej i śródpiersia:* Bardzo często: duszność[cc], kaszel[bb]. Często: hipoksja[dd], wysięk opłucnowy, zapalenie błony śluzowej nosa[ee]. Niezbyt często: niewydolność oddechowa[ff]. *Zaburzenia żołądka i jelit:* Bardzo często: wymioty, biegunka[f], zaparcia, ból brzucha[g], nudności. Często: dysfagia*, suchość w jamie ustnej[h]. *Zaburzenia skóry i tkanki podskórnej:* Bardzo często: wysypka[gg]. *Zaburzenia układu mięśniowo-szkieletowego i tkanki łącznej:* Bardzo często: zaburzenia ruchowe[r], ból mięśniowo-szkieletowy[q]. Niezbyt często: rabdomioliza. *Zaburzenia nerek i dróg moczowych:* Często: zaburzenia czynności nerek[aa]. *Zaburzenia ogólne i stany w miejscu podania:* Bardzo często: gorączka[j], obrzęk[k], zmęczenie[i], dreszcze. Często: ból. Niezbyt często: niewydolność wielonarządowa. *Zaburzenia oka:* Często: zaburzenia widzenia[e]. *Badania diagnostyczne:* Bardzo często: zwiększona aktywność transaminaz[#l]. Często: hiperbilirubinemia[#m]. * Dysfagię zgłaszano w ramach toksycznego działania na układ nerwowy i encefalopatii. # Częstość występowania na podstawie parametru laboratoryjnego w stopniu 3. lub wyższym. a. Koagulopatia obejmuje: koagulopatię, zmniejszenie stężenia fibrynogenu we krwi, rozsiane wykrzepianie wewnątrznaczyniowe, zwiększenie międzynarodowego wskaźnika znormalizowanego, wydłużony czas protrombinowy. b. Tachykardia obejmuje: tachykardię, tachykardię zatokową. c. Arytmia obejmuje: arytmię, migotanie przedsionków, trzepotanie przedsionków, blok przedsionkowo-komorowy, blok przedsionkowo-komorowy 1. stopnia, bradykardię, blok prawej odnogi pęczka Hisa, wydłużony odstęp QT w EKG, odwrócenie załamka T w EKG, dodatkowe skurcze, nieregularne tętno, bradykardię zatokową, dodatkowe pobudzenia nadkomorowe, częstoskurcz nadkomorowy, arytmię komorową, dodatkowe pobudzenia komorowe, tachykardię komorową. d. Niewydolność serca obejmuje: niewydolność serca, ostrą niewydolność lewokomorową, zmniejszoną frakcję wyrzutową, kardiomiopatię takotsubo. e. Zaburzenia widzenia obejmują: nieostre widzenie, zmniejszoną ostrość wzroku. f. Biegunka obejmuje: biegunkę, zapalenie okrężnicy, zapalenie jelit. g. Ból brzucha obejmuje: ból brzucha, dyskomfort w okolicy brzucha, ból w dolnej części brzucha, ból w górnej części brzucha, tkliwość brzucha, niestrawność, dyskomfort w nadbrzuszu. h. Suchość w jamie ustnej obejmuje: suchość w jamie ustnej, suche wargi. i. Zmęczenie obejmuje: zmęczenie, astenię, zmniejszoną aktywność, złe samopoczucie. j. Gorączka obejmuje: hipertermię, gorączkę. k. Obrzęk obejmuje: obrzęk, obrzęk spojówek, obrzęk twarzy, obrzęk uogólniony, obrzęk miejscowy, obrzęk narządów płciowych, obrzęk obwodowy, obrzęk okołooczodołowy, obrzmienie obwodowe, obrzęk moszny, obrzmienie, obrzmienie twarzy. l. Zwiększona aktywność transaminaz obejmuje: zwiększoną aktywność transaminaz, zwiększoną aktywność enzymów wątrobowych, zwiększoną aktywność aminotransferazy alaninowej, zwiększoną aktywność aminotransferazy asparaginianowej. m. Hiperbilirubinemia obejmuje: hiperbilirubinemię, zwiększone stężenie bilirubiny. n. Zmniejszone stężenie immunoglobulin obejmuje: hipogammaglobulinemię, zmniejszone stężenie immunoglobulin G we krwi. o. Zmniejszone łaknienie obejmuje: zmniejszone łaknienie, hipofagię. p. Odwodnienie obejmuje: odwodnienie, hipowolemię. q. Ból mięśniowo-szkieletowy obejmuje: ból stawów, ból pleców, ból kości, ból w boku, ból w okolicy pachwin, ból mięśniowo-szkieletowy w klatce piersiowej, mialgię, ból szyi, chorobę zwyrodnieniową stawów, ból w kończynie. r. Zaburzenia ruchowe obejmują: zaburzenia ruchowe, sztywność mięśni, skurcze mięśni, spastyczność mięśni, nadwyrężenie mięśni, osłabienie mięśni. s. Encefalopatia obejmuje: encefalopatię, agrafię, niepamięć, afazję, afonię, apraksję, zaburzenia poznawcze, splątanie, zmniejszony poziom świadomości, zaburzenia uwagi, dyzartrię, dysgrafię, dyskinezę, hipersomnię, zespół neurotoksyczności związany z komórkami efektorowymi układu odpornościowego, ospałość, leukoencefalopatię, utratę świadomości, upośledzenie pamięci, zmiany statusu psychicznego, neurotoksyczność, senność, zaburzenia mowy, stupor. t. Ból głowy obejmuje: ból głowy, dyskomfort w okolicy głowy. u. Drżenie obejmuje: drżenie, potrząsanie głową. v. Zawroty głowy obejmują: zawroty głowy, stan przedomdleniowy, omdlenie. w. Neuropatia obwodowa obejmuje: neuropatię obwodową, alodynię, radikulopatię szyjną, przeczulicę, niedoczulicę, parestezje, parosmię, neuropatię obwodową ruchową, neuropatię obwodową czuciową. x. Ataksja obejmuje: ataksję, zaburzenia równowagi, zaburzenia chodzenia, zaburzenia przedsionkowe. y. Majaczenia obejmują: majaczenia, pobudzenie, urojenia, dezorientację, omamy, niepokój psychoruchowy. z. Zaburzenia afektywne obejmują: zachowanie impulsywne, manię, zmianę nastroju, atak paniki. aa. Zaburzenia czynności nerek obejmują: ostre uszkodzenie nerek, zwiększone stężenie kreatyniny we krwi, niewydolność nerek. bb. Kaszel obejmuje: kaszel, mokry kaszel, zespół kaszlowy górnych dróg oddechowych. cc. Duszność obejmuje: duszność, duszność wysiłkową. dd. Hipoksja obejmuje: hipoksję, zmniejszoną saturację tlenem. ee. Zapalenie błony śluzowej nosa obejmuje: alergiczny nieżyt nosa, wysięk z nosa. ff. Niewydolność oddechowa obejmuje: niewydolność oddechową, ostrą niewydolność oddechową. gg. Wysypka obejmuje: wysypkę, pęcherzowe zapalenie skóry, rumień, świąd, wysypkę rumieniową, wysypkę plamistą, wysypkę plamisto-grudkową, wysypkę krostkową, zespół Stevensa-Johnsona, pokrzywkę. hh. Niedociśnienie tętnicze obejmuje: niedociśnienie tętnicze, zespół przesiąkania włośniczek, niedociśnienie rozkurczowe, hipoperfuzję, niedociśnienie ortostatyczne. ii. Zakrzepica obejmuje: zakrzepicę, zakrzepicę żył głębokich, okluzję wyrobu, zator, zakrzepicę żył szyjnych, zator obwodowy, niedokrwienie obwodowe, zator płucny, zakrzepicę żyły śledzionowej, zakrzepicę żył podobojczykowych, zakrzepicę w wyrobie, niedrożność naczyń. Opis wybranych działań niepożądanych z badań ZUMA-1 oraz ZUMA-5: *Zespół uwalniania cytokin:* CRS wystąpił u 93% pacjentów w badaniu ZUMA-1 oraz u 77% pacjentów w badaniu ZUMA-5. U jedenastu procent (11%) pacjentów w badaniu ZUMA-1 oraz u 6% pacjentów w badaniu ZUMA-5 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) u pacjentów w badaniu ZUMA-1 oraz 4 dni (zakres od 1 do 11 dni) u pacjentów w badaniu ZUMA-5, a mediana czasu trwania 7,5 dnia (zakres od 2 do 29 dni, z wyjątkiem jednego przypadku dłuższej obserwacji trwającej 58 dni) u pacjentów w badaniu ZUMA-1 oraz 6 dni (zakres od 1 do 27 dni) u pacjentów w badaniu ZUMA-5. U dziewięćdziesięciu ośmiu procent pacjentów (98%) w badaniu ZUMA-1 oraz 99% pacjentów w badaniu ZUMA-5 doszło do ustąpienia CRS. Najczęściej występujące objawy przedmiotowe i podmiotowe związane z CRS obejmowały gorączkę (90%), niedociśnienie tętnicze (42%), niedotlenienie (23%), dreszcze (23%), tachykardię (17%) i tachykardię zatokową (17%). Ciężkie działania niepożądane, które mogą być związane z CRS, obejmowały: gorączkę (5%), hipoksję (3%), niedociśnienie tętnicze (1%), ostre uszkodzenie nerek (1%), migotanie przedsionków (1%), trzepotanie przedsionków (1%) oraz zmniejszenie frakcji wyrzutowej (1%). Wskazówki dotyczące monitorowania i leczenia – patrz punkt 4.4. *Neurologiczne działania niepożądane:* Neurologiczne działania niepożądane wystąpiły u 66% pacjentów w badaniu ZUMA-1 oraz u 57% pacjentów w badaniu ZUMA-5. U trzydziestu jeden procent (31%) pacjentów w badaniu ZUMA-1 oraz u 16% pacjentów w badaniu ZUMA-5 wystąpiły działania niepożądane stopnia 3. lub wyższego (ciężkie lub zagrażające życiu). Toksyczne działania neurologiczne wystąpiły w ciągu pierwszych 7 dni od infuzji u 93% pacjentów w badaniu ZUMA-1 oraz u 65% pacjentów w badaniu ZUMA-5. Mediana czasu do wystąpienia działań niepożądanych wynosiła 5 dni (zakres od 1 do 17 dni) u pacjentów w badaniu ZUMA-1 oraz 7 dni (zakres od 1 do 177 dni) u pacjentów w badaniu ZUMA-5. Mediana czasu trwania wynosiła 13 dni w badaniu ZUMA-1 oraz 14 dni w badaniu ZUMA-5, przy czym objawy ustąpiły w ciągu 3 tygodni po infuzji u odpowiednio 61% i 60% pacjentów. Najczęstszymi objawami przedmiotowymi i podmiotowymi związanymi z neurologicznymi działaniami niepożądanymi były: drżenie (30%), encefalopatia (28%), splątanie (25%), afazja (15%) i senność (12%). Ciężkie neurologiczne działania niepożądane zgłaszane u pacjentów, którym podano produkt Yescarta, obejmowały: encefalopatię (12%), splątanie (5%), afazję (3%), pobudzenie (2%), senność (2%) oraz majaczenia (1%). 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 zgłaszano wystąpienie obrzęku rdzenia kręgowego oraz ICANS, w kontekście neurotoksyczności. Wskazówki dotyczące monitorowania i leczenia – patrz punkt 4.4. *Gorączka neutropeniczna i zakażenia:* Gorączkę neutropeniczną zaobserwowano u 16% pacjentów po infuzji produktu Yescarta. Zakażenia wystąpiły u 50% pacjentów. Zakażenia stopnia 3. lub wyższego (ciężkie, zagrażające życiu lub prowadzące do zgonu) wystąpiły u 22% pacjentów. Zakażenia nieswoistymi patogenami oraz zakażenia bakteryjne i wirusowe stopnia 3. lub wyższego wystąpiły u, odpowiednio, 15%, 7% i 5% pacjentów. Najczęstszym miejscem zakażenia były drogi oddechowe. Wskazówki dotyczące monitorowania i leczenia – patrz punkt 4.4. *Przedłużająca się cytopenia:* Neutropenia, niedokrwistość i małopłytkowość stopnia 3. lub wyższego wystąpiły u, odpowiednio, 60%, 32% i 29% 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%, 16% i 8% pacjentów. W badaniu ZUMA-1 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:* Hipogammaglobulinemię zgłoszono u 16% pacjentów leczonych produktem Yescarta. Łącznie 36 (33%) ze 108 pacjentów w badaniu ZUMA-1 otrzymywało dożylne leczenie immunoglobulinami w momencie przeprowadzania analizy po 54 miesiącach, a 32 (27%) ze 119 pacjentów w badaniu ZUMA-5 otrzymywało dożylne leczenie immunoglobulinami w momencie przeprowadzania analizy po 24 miesiącach. Wskazówki dotyczące leczenia – patrz punkt 4.4. Immunogenność: Immunogenność produktu Yescarta oceniano za pomocą testu immunoenzymatycznego (ELISA) wykrywającego przeciwciała wiążące FMC63, z których wywodzą się przeciwciała anty-CD19 CAR. U trzech ze 106 pacjentów w badaniu ZUMA-1 przed leczeniem produktem Yescarta wstępne badanie przeciwciał anty-FMC63 z użyciem testu ELISA dało wynik dodatni. W badaniu ZUMA-5 u 13 ze 116 pacjentów przed leczeniem produktem Yescarta wstępne badanie przeciwciał z użyciem testu ELISA dało wynik dodatni, a 2 pacjentów z wynikiem ujemnym przed rozpoczęciem leczenia miało wynik dodatni po zakończeniu leczenia. Wyniki potwierdzających testów komórkowych wykazały, że wszyscy pacjenci leczeni produktem Yescarta oraz mający dodatni wynik testu ELISA mieli wynik ujemny w zakresie przeciwciał po wykonaniu badania potwierdzającego przed, w trakcie i po zakończeniu leczenia. Wpływ tych przeciwciał na skuteczność lub bezpieczeństwo stosowania nie był dostrzegalny. Specjalne grupy pacjentów: 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. Zgłaszanie podejrzewanych działań niepożądanych: Po dopuszczeniu produktu leczniczego do obrotu istotne jest zgłaszanie podejrzewanych działań niepożądanych. Umożliwia to nieprzerwane monitorowanie stosunku korzyści do ryzyka stosowania produktu leczniczego. Osoby należące do fachowego personelu medycznego powinny zgłaszać wszelkie podejrzewane działania niepożądane za pośrednictwem: *Departament 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. **NUMER POZWOLENIA NA DOPUSZCZENIE DO OBROTU:** EU/1/18/1299/001. **WYDANE PRZEZ:** Komisję Wspólnot Europejskich. **OGÓLNA KATEGORIA DOSTĘPNOŚCI:** Rpz. **DATA WYDANIA PIERWSZEGO POZWOLENIA NA DOPUSZCZENIE DO OBROTU I DATA PRZEDŁUŻENIA POZWOLENIA:** Data wydania pierwszego pozwolenia na dopuszczenie do obrotu: 23 sierpnia 2018. **DATA ZATWIERDZENIA LUB CZĘŚCIOWEJ ZMIANY TEKSTU CHARAKTERYSTYKI PRODUKTU LECZNICZEGO:** 06/2022. Szczegółowe informacje o tym produkcie leczniczym są dostępne na stronie internetowej Europejskiej Agencji Leków http://www.ema.europa.eu.

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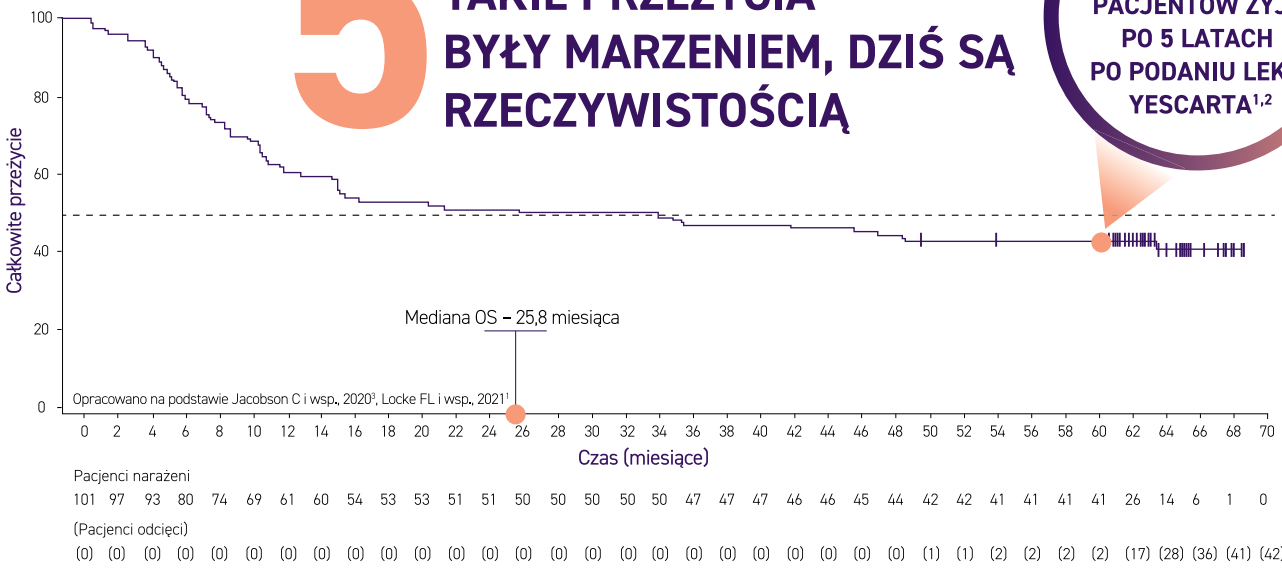
YESCARTA®▼
(aksykabtagen cyloleucel)

Zdjęcia nie przedstawiają rzeczywistego pacjenta

5 LAT TEMU TAKIE PRZEŻYCIA BYŁY MARZENIEM, DZIŚ SĄ RZECZYWISTOŚCIĄ

43%*
PACJENTÓW ŻYJE PO 5 LATACH PO PODANIU LEKU YESCARTA[1,2]



Produkt Yescarta jest wskazany w leczeniu nawrotowego lub opornego na leczenie chłoniaka rozlanego z dużych komórek B (DLBCL) i pierwotnego chłoniaka śródpiersia z dużych komórek B (PMBCL) u dorosłych pacjentów, którzy uprzednio otrzymali co najmniej dwie linie leczenia systemowego**.

* Wartości szacunkowe wg Kaplana-Meiera dla 5-letniego wskaźnika OS wyniosły 42,6%. ** Pełna lista wskazań dostępna w załączonej Skróconej Informacji o Leku

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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