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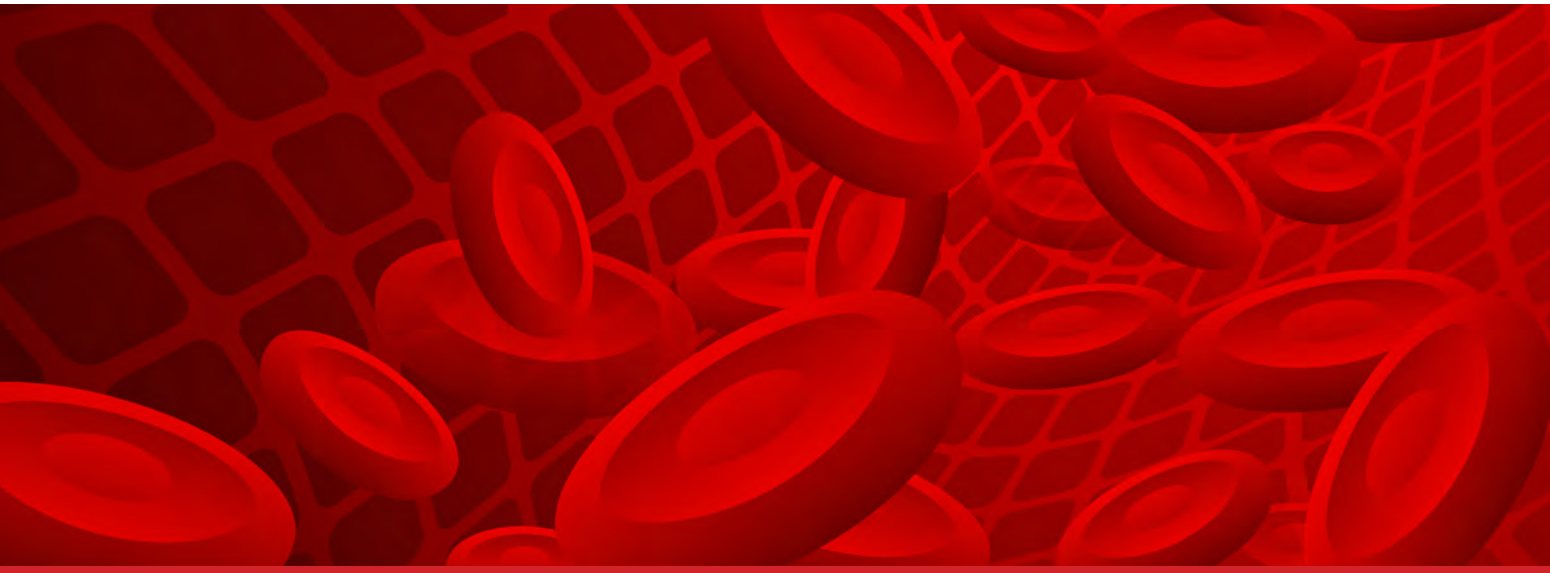

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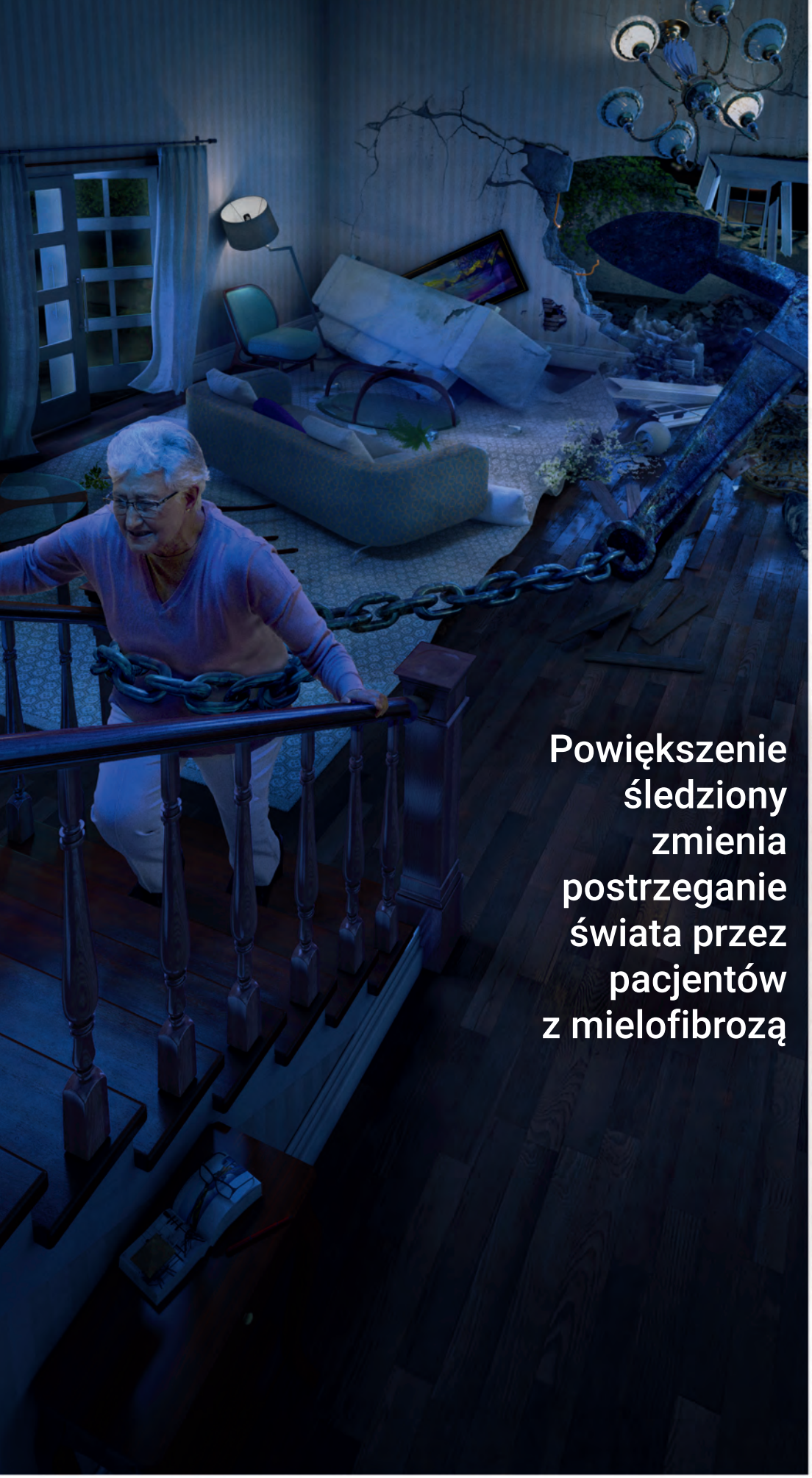
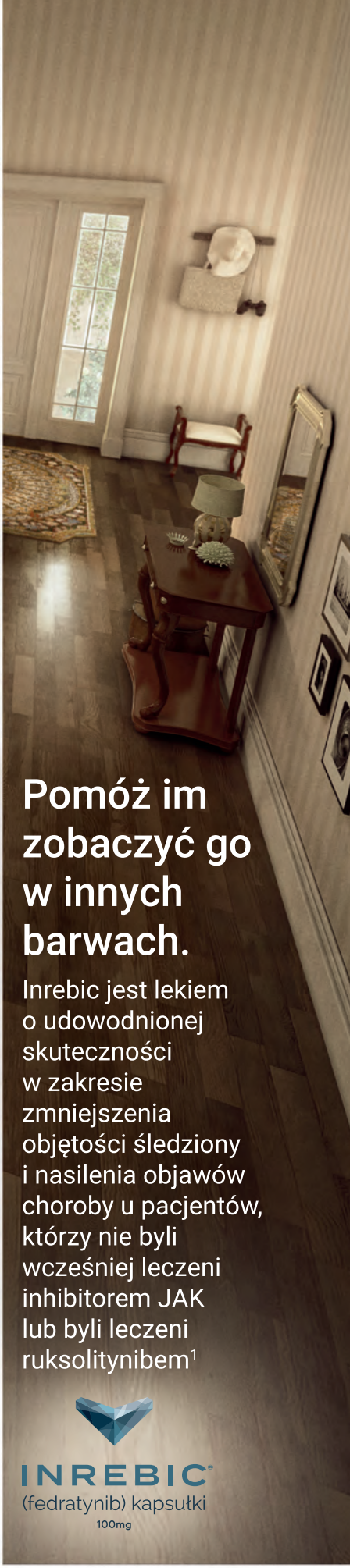


Powiększenie śledziony zmienia postrzeganie świata przez pacjentów z mielofibrozą



Pomóż im zobaczyć go w innych barwach.

Inrebic jest lekiem o udowodnionej skuteczności w zakresie zmniejszenia objętości śledziony i nasilenia objawów choroby u pacjentów, którzy nie byli wcześniej leczeni inhibitorem JAK lub byli leczeni ruksolitynibem[1]

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Postać farmaceutyczna: kapsułka twarda. **Wskazania do stosowania**: Produkt leczniczy Inrebic jest wskazany w leczeniu powiększenia śledziony związanego z chorobą lub objawów występujących u dorosłych pacjentów z pierwotnym włóknieniem szpiku (znanym także jako przewlekłe idiopatyczne włóknienie szpiku), włóknieniem szpiku poprzedzonym czerwienicą prawdziwą lub włóknieniem szpiku poprzedzonym nadpłytkowością samoistną u pacjentów, którzy nie byli wcześniej leczeni inhibitorem kinazy janusowej (ang. *Janus Associated Kinase*), JAK lub byli leczeni ruksolitynibem. **Dawkowanie i sposób podawania**: Leczenie produktem Inrebic powinno być rozpoczęte, a następnie monitorowane przez lekarzy doświadczonych w stosowaniu przeciwnowotworowych produktów leczniczych. Dawkowanie: Przed rozpoczęciem leczenia produktem Inrebic, u pacjentów leczonych dotychczas ruksolitynibem, należy stopniowo zmniejszyć dawkę ruksolitynibu, a następnie zakończyć podawanie ruksolitynibu, zgodnie z charakterystyką produktu leczniczego ruksolitynibu. Przed rozpoczęciem leczenia produktem Inrebic należy oznaczyć początkowe stężenie tiaminy (witamina B1), wykonać morfologię krwi, badania czynności wątroby, oznaczyć stężenie amylazy i lipazy, azot mocznika (ang. *blood urea nitrogen*, BUN) i stężenie kreatyniny we krwi. Następnie badania należy powtarzać okresowo podczas leczenia oraz w uzasadnionych klinicznie sytuacjach. Nie należy rozpoczynać leczenia produktem Inrebic u pacjentów z niewyrównanym niedoborem tiaminy. Nie zaleca się rozpoczynania leczenia produktem Inrebic u pacjentów, u których początkowa liczba płytek krwi jest mniejsza niż 50 x 10^9/L oraz bezwzględna liczba neutrofili (ang. *absolute neutrophil count*, ANC) jest mniejsza niż 1.0 x 10^9/l. Zaleca się profilaktyczne stosowanie leków przeciwwymiotnych zgodnie z lokalną praktyką przez pierwsze 8 tygodni leczenia i kontynuowanie ich stosowania zgodnie ze wskazaniami klinicznymi. Przyjmowanie produktu Inrebic z posiłkiem o wysokiej zawartości tłuszczu może zmniejszyć częstość występowania nudności i wymiotów. Zalecana dawka produktu Inrebic wynosi 400 mg raz na dobę. Leczenie może być kontynuowane tak długo, jak długo pacjenci odnoszą korzyści kliniczne. W przypadku wystąpienia objawów toksyczności hematologicznej lub niehematologicznej należy rozważyć zmianę dawkowania (Tabela 1). Leczenie produktem Inrebic należy zakończyć, jeśli pacjent nie toleruje dawki 200 mg na dobę. W przypadku pominięcia dawki, następna zaplanowana dawka powinna zostać przyjęta następnego dnia. Nie należy przyjmować dodatkowych kapsułek w celu uzupełnienia pominiętej dawki. *Zmiany dawkowania:* W Tabeli 1 przedstawiono schemat zmiany dawkowania w przypadku wystąpienia objawów toksyczności hematologicznej, niehematologicznej i w przypadku leczenia encefalopatii Wernickego. *Zwiększanie stężenia tiaminy*: Przed rozpoczęciem oraz w trakcie leczenia należy wyrównać niedobór tiaminy, jeżeli jej stężenie jest zbyt małe. Podczas leczenia należy okresowo oznaczać stężenie tiaminy (np. co miesiąc przez pierwsze 3 miesiące, a następnie co 3 miesiące) i zgodnie ze wskazaniami klinicznymi. *Zmiany dawkowania podczas jednoczesnego stosowania silnych inhibitorów CYP3A4*: Jeżeli nie można uniknąć jednoczesnego stosowania silnych inhibitorów CYP3A4, należy zmniejszyć dawkę produktu Inrebic do 200 mg. Należy uważnie monitorować bezpieczeństwo pacjentów (np. co najmniej raz w tygodniu). W przypadku przerwania jednoczesnego podawania silnego inhibitora CYP3A4, dawkę produktu Inrebic należy zwiększyć do 300 mg raz na dobę w ciągu pierwszych dwóch tygodni po przerwaniu leczenia inhibitorem CYP3A4, a następnie do 400 mg raz na dobę, w zależności od tolerancji. W razie potrzeby należy dokonać dodatkowych zmian dawkowania w oparciu o wyniki monitorowania bezpieczeństwa stosowania i skuteczności produktu Inrebic. *Ponowne zwiększanie dawki*: Jeżeli działanie niepożądane spowodowane przez produkt Inrebic, które było powodem zmniejszenia dawki, jest skuteczne kontrolowane i objawy toksyczności ustąpią na co najmniej 28 dni, dawka może zostać ponownie zwiększona o jeden poziom dawkowania na miesiąc, do osiągnięcia dawki początkowej. Ponowne zwiększanie dawki nie jest zalecane, jeżeli zmniejszenie dawki było spowodowane objawami toksyczności niehematologicznej stopnia 4., zwiększeniem aktywności aminotransferazy alaninowej (AlAT), aminotransferazy asparaginianowej (AspAT) lub stężenia bilirubiny całkowitej stopnia ≥ 3. albo nawrotem objawów toksyczności hematologicznej stopnia 4.

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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Celgene sp. z o.o.
Al. Armii Ludowej 26, 00-609 Warszawa
tel.: +48 22 260 64 00, fax: +48 22 260 64 64

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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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VIA MEDICA

EDITORIAL

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Looking to the CAR-T future: vaccination, outpatient therapy, artificial intelligence and expanding indications

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On 28 November 2019, the first CAR-T therapy was carried out in Poland [1–3]. Today, several Polish centers are using this technology, and several others are preparing to do so. CAR-T therapy for children and young adults with acute lymphoblastic leukemia has been reimbursed by the National Health Fund since 1 September 2021, and for adults with non-Hodgkin lymphoma since 1 May 2022.

Today, c.150–200 patients are being treated with CAR-T cells every month in Europe, while more than 1,100 clinical trials are running worldwide. This hottest topic in hematology of the last few years has been traced also in Acta Haematologica Polonica [4–7].

In this issue, a set of five articles on CAR-T technology is presented: Dytfeld et al. [8] on outpatient therapy, Gil et al. [9] on artificial intelligence, Romejko-Jarosińska [10] on mantle cell lymphoma, Styczyński et al. [11] on vaccinations, and Żyłka et al. [12] on primary mediastinal lymphoma.

More indications will need reimbursement; expanding indications in ALL are needed, and multiple myeloma patients are being offered new hope. Although patients with T-cell ALL, AML and solid tumors can today only dream about such therapy, it is only a question of time before this becomes reality.

Authors' contributions

JS — sole author.

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; Uniform requirements for manuscripts submitted to biomedical journals.

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VIA MEDICA

REVIEW ARTICLE

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Chronic myeloid leukemia: where do we stand, where can we go?

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Abstract

The introduction of BCR-ABL tyrosine kinase inhibitors to the treatment of chronic myeloid leukemia (CML) has significantly changed the long term therapy results.

After an initial 12 months of therapy with tyrosine kinase inhibitor (TKI), a 3-log reduction of the BCR-ABL copies number on an international scale is possible in 22–46% of patients, depending on the TKI used. In TKI-responsive patients, long-term TKI treatment results are even better, with the BCR-ABL transcript level decreasing over time, even to the point of becoming undetectable. Therefore, an operational cure can be diagnosed in CML patients with an optimal response to 1st-line TKI treatment, a therapy duration of longer than 5–8 years, and BCR-ABL transcript level below MR4.0–MR4.5 for a period of more than two years. The latter has been the basis of multiple concepts of permanent or periodic discontinuation of TKI treatment [treatment-free remission (TFR)]. Initial TKI discontinuation clinical trials resulted in satisfactory results, with a disease recurrence rate of c.40–60% after 2–3 years. The mechanism of disease recurrence was then studied, with detailed characterization of the CML stem cells (CML SCs) immunophenotype and the mechanisms of survival and self-renewal under TKI selective pressure. A better understanding of the biology of CML allowed the formulation of new therapy concepts of CML SCs eradication, and new criteria for successful TFR qualification.

Key words: chronic myeloid leukemia, tyrosine kinase inhibitors, chronic myeloid leukemia stem cells, immune system escape, treatment-free remission, new treatment concepts

Acta Haematologica Polonica 2022; 53, 3: 153–165

Introduction

The introduction of imatinib (IM) to the treatment of chronic myeloid leukemia (CML) significantly changed the long term therapy results, with 5-year overall survival (OS) of 91.7% and progression-free survival (PFS) of 94.7% [1]. Recently, the second (2G-TKI, nilotinib, dasatinib) and third generation (3G-TKI, ponatinib) of BCR-ABL tyrosine kinase inhibitors (TKIs) have become widely used in CML patients intolerant/resistant to first line treatment with TKIs [2, 3]. Moreover, the fourth-generation allosteric BCR-ABL1 tyrosine kinase inhibitor [4G-TKI, asciminib (ABL001)] has been approved by the US FDA in CML patients resistant to first-, second- and third-generation TKIs. Its high efficacy has been proven, both in clinical trials [4] and in real-life conditions [5]. The detailed characteristics of currently used TKIs in CML patients are set out in Table I [4–31].

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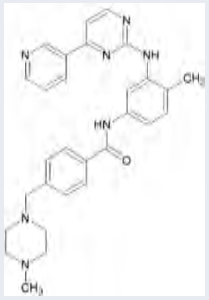
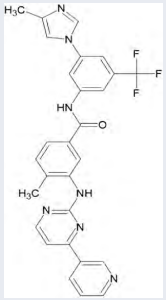
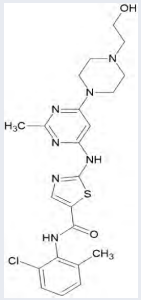
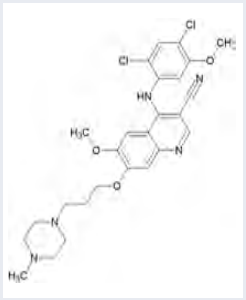
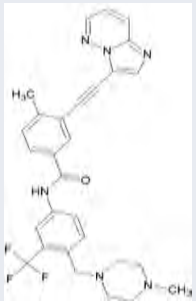
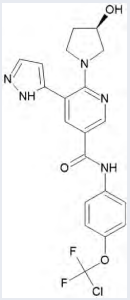
Table I. Characteristics of currently used tyrosine kinase inhibitors (TKIs) in chronic myeloid leukemia patients

TKI/drug properties	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib	Asciminib
Chemical structure						
International Union of Pure and Applied Chemistry (IUAPC) name	4-[(4-methylpiperazin-1--yl)methyl]-N-[4-methyl-3--[(4-pyridin-3-ylpyrimi-din-2-yl)amino]phenyl] benzamide	4-methyl-N-[3-(4--methyl-imidazol-1-yl)--5-(trifluoromethyl)phenyl]--3-[(4-pyridin-3-ylpyrimidin--2-yl)amino]benzamide	N-(2-chloro-6-methylphenyl)--2-[[6-[4-(2-hydroxyethyl)-piperazin-1-yl]-2-methyl--pyrimidin-4-yl]amino]-1,3--thiazole-5-carboxamide	4-(2,4-dichloro-5--methoxyanilino)-6--methoxy-7-[3-(4-methyl--piperazin-1-yl)propoxy]-quinoline-3-carbonitrile	3-(2-imidazo[1,2-b]-pyridazin-3-ylethynyl)-4--methyl-N-[4-[(4-methyl--piperazin-1-yl)methyl]-3--(trifluoromethyl)phenyl]-benzamide	N-[4-[chloro(difluoro)-methoxy]phenyl]-6--[(3R)-3-hydroxypyrroli-din-1-yl]-5-(1H-pyrazol-5--yl)pyridine-3-carboxa-mide
Molecular formula	C29H31N7O	C28H22F3N7O	C22H26ClN7O2S	C26H29Cl2N5O3	C29H27F3N6O	C20H18ClF2N5O3
Spectrum of inhibitory activity	ABL1 ARG BCR-ABL KIT PDGFR DDR1 NQO2	ABL1 ARG BCR-ABL KIT PDGFR DDR1 NQO2	ABL1, ARG, BCR-ABL, KIT, PDGFR, SRC,YES,FYN, LYN, HCK, LCK, FGR, BLK, FRK, CSK,BTK, TEC, BMX, TXK, DDR1, DDR2, ACK, ACTR2B, ACVR2, BRAF, EGFR/ERBB1-5, EPHA8,EPHB1-2, EPHB4, EPHB6, ERBB2, ERBB4,FAK, GAK, GCK, HH498/TNNI3K, ILK, LIMK1-2, MAP2K5, MAP3K1-4, MAP4K1, MAP4K5/KHS1, MAPK11/ /p38 beta, MAPK14/p38 alpha, MYT1,NLK, PTK6/ /Brk, QIK, QSK, RAF1, RET, RIPK2, SLK, STK36/ULK, SYK, TAO3, TESK2, TYK2, ZAK [6]	BCR-ABL1, ABL1, SRC, LYN, HCK	*ABL1*, *KIT, PDGFR, SRC* family, *VEGFR, EGFR, HER2, FLT3, FGFR*, and *JAK2* [7]	BCR-ABL1 [8]

→

Table I (cont.). Characteristics of currently used tyrosine kinase inhibitors (TKIs) in chronic myeloid leukemia patients

TKI/drug properties	Imatinib	Nilotinib		Dasatinib	Bosutinib	Ponatinib	Asciminib
BCR-ABL tyrosine kinase inhibitory mode of action	Works by binding close to the ATP binding site, locking it in a closed or self--inhibited conformation, therefore inhibiting the enzyme activity of the protein semicompetitively [9, 10] CGP57148B, a 2-phenylaminopyrimidine derivative, has been shown to selectively inhibit the tyrosine kinase of ABL and BCR-ABL. We report here that this compound selectively suppresses the growth of colony- forming unit-granulocyte/ /macrophage (CFU-GM	Binds to and stabilizes inactive conformation of kinase domain of Abl protein [11]		Binds to ATP-binding site, but extends in opposite direction from imatinib. Binds inactive and active conformation of ABL kinase domain, requires fewer contact points with ABL, and has a greater affinity to ABL kinase domain compared to IM [12, 13]	ATP-competitive inhibitor of Src and Abl tyrosine kinases [14]	Acts as a multikinase inhibitor. Introduction of a triple bond ethynyl linker allowed spanning of bulky T315I isoleucine residue side chain in ATP-binding site, and overcame resistance to prior generation TKIs [15, 16]	Acts as an allosteric inhibitor and engages a vacant pocket at site of kinase domain normally occupied by myristoylated N-terminal of ABL1 — a motif that serves as an allosteric negative regulatory element lost on fusion of ABL1 to BCR BCR, myristoylated N-terminal is lost and ABL1 kinase is activated. By allosterically binding, to myristoyl site, asciminib mimics myristate and restores inhibition of BCR-ABL1 kinase activity [4]
BCR-ABL tyrosine kinase binding conformation	Inactive	Inactive		Active	Both	Inactive	Specifically targeting ABL myristoyl pocket
Half life time ($T_{1/2}$)	~20 hours	~17 hours		3–5 hours	32.4–41.2 hours enabling daily dose [17]	24 hours	5.5 hours (40 mg/d) 9 hours (200 mg bid)
Resistant BCR-ABL KD mutants** [8, 15, 18–23]	**Y253** **E255** **T315** M244 L248 G250	Q252 F317 M351 M355 F359 H396	**T315** L248 Y253 E255 F359	**T315** V299 F317	**T315** **V299** L248 G250 E255 F317	E250* Y253* E255* F311	**A337** **W464** **P465** **V468** **I502**

→

Table I (cont.). Characteristics of currently used tyrosine kinase inhibitors (TKIs) in chronic myeloid leukemia patients

TKI/drug properties	Imatinib	Nilotinib	Dazatinib	Bosutinib	Ponatinib	Asciminib
Oral dose per day	CP 400 mg/d AP 600 mg/d BP 800 mg/d	CP 2 × 300 mg (2nd-line) 2 × 400 mg (1st-line)	CP 100 mg/d AP/BP 140 mg/d	CP 500 mg/d	CP 15–45 mg/d	CP 80 mg/d or 40 mg bid
Main off-target effect	Hematologic: • anemia • neutropenia • thrombocytopenia Non-hematologic: • edema (periorbital and peripheral) • muscle cramps • musculoskeletal pain • diarrhea [24]	Hematologic: • thrombocytopenia • granulocytopenia • anemia Non-hematologic: • pruritus • asthenia Cardiovascular: • cardiovascular • ischemic adverse events [25, 26]	Hematologic: • thrombocytopenia • anemia • neutropenia Non-hematologic: • endocrine disorders (gynecomastia, irregular menses, hypoglycemia, hyperglycemia, increased triglyceride and cholesterol levels) • fluid retention • nausea, vomiting, diarrhea Cardiovascular: • pericardial effusion • pulmonary artery hypertension [27, 28]	Hematologic: • thrombocytopenia • neutropenia Non-hematologic: • rash • nausea • diarrhea • vomiting • elevated serum aminotransferases [29]	Hematologic: • anemia • thrombocytopenia • neutropenia Non-hematologic: • rash • elevated serum lipase • pancreatitis Cardiovascular: • hypertension • chest pain [30]	Hematologic: • thrombocytopenia and/or neutropenia Non-hematologic: • hepatic impairment • asymptomatic amylase and/or lipase elevations Cardiovascular: • hypertension • pericardial effusion [4, 5, 31]

*Increase in IC50 for ponatinib as a sole anomaly typically not leading to clinical resistance, which is observed in cases of a compound mutation including *T315I*; **strong resistance is indicated in bold; CP — chronic phase; AP — acceleration phase; BP — blastic phase; bid (bid in die) — twice daily

Current results of CML treatment

Data originating from clinical trials and from real life studies has confirmed the high efficacy of TKIs in CML patients in the chronic phase in terms of the 3-log reduction of BCR-ABL1 copies number (major molecular remission, MMR) with a well standardized real-time PCR technique in the blood after 12 months of treatment. MMR response rates differed depending on the type and dose of TKI used, and amounted to 22–36.9% for IM 400 mg once a day, 44% for nilotinib 300 mg twice a day, 43% for nilotinib 400 mg twice a day, 46% for dasatinib 100mg once a day, and 47.2% for bosutinib 500 mg once a day [1, 32–34].

The long-term TKI treatment results show that in the TKI-responsive patients the BCR-ABL transcript level continuously decreases over time, to the point of becoming undetectable. The overall cumulative incidence of the confirmed MR4.5, and stable MR4.5 (4.5log reduction in BCR-ABL1 copies number in international scale, IS) after eight years of IM therapy is 51.7% and 36.5%, respectively [35]. Real life data is in agreement with the computer simulation results, showing treatment time to MR4.5 to be 10.7 and 9.1 years in IM-treated patients participating in the IRIS trial (training set) and the CML IV trial (validation set), respectively [36]. This data forms the basis of the concept of an operational cure and the permanent or temporary discontinuation of TKI treatment [treatment-free remission (TFR)] [37].

Data concerning the frequency of deep molecular responses (DMR, defined as the reduction of the transcript level below MR4 or MR4.5) on TKI treatment has been accumulated subsequently. Its analysis allowed the formulation of minimal criteria which should be fulfilled for a TFR attempt in CML patients, including a low or intermediate Sokal score, a typical BCR-ABL1 transcript type at diagnosis, a chronic phase of CML in the past history, an optimal response to 1st-line TKI treatment, a TKI therapy duration of longer than eight years, a DMR at the time of qualification, and a duration of DMR monitored in a standardized laboratory of longer than two years. Initial study results showed that only 10–12% of patients on IM appeared to be eligible for the discontinuation of a TKI [37, 38]. Subsequent data has shown that only a minority of CML patients reaching the sustained DMR on TKI therapy were candidates for the discontinuation of treatment without the risk of a molecular disease recurrence. Until now, many possible solutions have been proposed for optimizing the process of CML patient qualification for a TFR attempt. Initially, only those patients with an MR5.0 or an undetectable BCR-ABL transcript were qualified for the TFR studies (STIM pilot, STIM1, STRIM2, ASTIM and TWISTER) [39–42]. In all the aforementioned trials, a molecular CML recurrence was defined as BCR-ABL1 positivity in two consecutive assessments, or the loss of a MMR (or ≥1 log increase of the transcript level in STIM1 and STIM 2 trails). The TFR rate after the median follow-up of 12 months was 61% (STIM2), 50% after 18 months (STIM pilot), 61% after 31 months (A-STIM), 47% after 42 months (TWISTER), and 38% after 77 months (STIM2). The EURO-SKI trial results confirmed that there was no difference in the TFR rates between patients with >MR4.5 and MR4 [43, 44]. Afterwards, patients with a stable MR4.0 were also enrolled in TFR clinical trials. Unfortunately, to date there is no consensus regarding the criteria which should be used for the qualification of CML patients for an TFR attempt to minimize the probability of MMR loss. According to the different criteria for TFR proposed by Hughes et al., Rea et al., Hochhaus et al., and Radich et al., the probability of CML patient recruitment for TFR varies from 9.5% to 55% [45–49]. Molecular recurrence-free survival after TKI cessation, according to the eligibility criteria proposed by Hughes et al., Rea et al., Radich et al., and Hochhaus et al., varies from 35% to 60% after a follow-up of 45–100 months [45–49]. Therefore, considerable efforts have been made to further optimize the criteria for TFR attempt qualification. The incorporation of genomic data into future model(s) of unfavorable risk assessment will likely change the currently used algorithms for TFR qualification [50–53].

Nowadays, the NCCN and ELN guidelines recommend the re-initiation of TKI therapy at the time of molecular recurrence, defined as a loss of MMR after the first TFR attempt [48, 54].

The 2G-TKI discontinuation studies results are limited. They include 327 patients with 1st-line TKI failure (IM, interferon/IM), and 190 patients treated upfront with nilotinib. Unfortunately, different criteria were applied in different studies for the TFR attempt qualification before the 2G-TKI discontinuation (MR4–MR4.5), and different definitions of molecular disease relapse (loss of MMR to loss of MR4.5) were applied. For these reasons, the interpretation of TFR rates at 24 months (ranging from 44 to 62.8 months) is difficult [50, 55–59].

According to recent data, the re-initiation of TKI therapy results in secondary molecular remission in a significant proportion of CML patients. Therefore, the idea of a second TFR attempt has been tested. In 2017, Legros et al. presented data concerning 70 patients successfully treated with IM who attempted a first TFR (IM = 60, nilotinib = 5, dasatinib = 5) and, after disease relapse, underwent a second TFR attempt. The TFR probability at 6, 12, 24, and 36 months after the second attempt to discontinue TKI was established at 66%, 48%, 42%, and 35%, respectively [60]. However, it should be mentioned that a second TFR is not yet considered standard practice.

It was previously documented that the majority of patients in DMR still harbor leukemic cells [61] capable of initiating disease relapse upon the withdrawal of TKI treatment [41]. The presence of CML leukemic stem cells in IM-treated patients in DMR with undetectable levels of mRNA was

confirmed in 32.8% of samples by Pagani et al. with the help of a genomic DNA Q-PCR assay [62]. The mechanism of the persistence of CML SCs in TKI-responsive CML patients in DMR is not fully understood. Recently, it was postulated that CML SCs are protected from MHC class I-dependent CD8+ cytotoxic T lymphocytes (CTLs) elimination in the bone marrow by regulatory T cells (Tregs) expressing tumor factor 4 receptor (Tnfrsf4). This hypothesis is based on the observation that Tregs are preferentially localized in the CML bone marrow close to CD8+ CTLs, and that TNFRSF4 mRNA levels correlate with the expression of Treg-restricted transcription factor FOXP3 [63]. Moreover, it has been shown that human CML stem cells are insensitive to IM, despite the inhibition of BCR-ABL activity [64]. This observation forms the basis of a hypothesis that primitive CML cells are not oncogene-addicted [65, 66].

CML, TKI treatment and immune system function

It has been postulated that TKI-induced changes in immune system functioning may affect the risk of a CML relapse after TKI discontinuation (Table II) in a different way. In CML patients in the chronic phase, suppression of the immune system is present at the time of diagnosis. This is mainly caused by the promotion of the expansion of myeloid-derived suppressor cells (MDSC) and regulatory T cells (Treg) by cytokines/chemokines released by proliferating CML progenitor cells. MDSC originate from malignant *BCR-ABL1* clone mediate immunosuppressive activity via a number of mechanisms, including the increased production of reactive oxygen, nitrogen species, arginase-1 (molecule inhibiting T cells), and TGF-β1 [67].

Moreover, MDSC can recruit Treg and inhibit cytotoxic T cells [68]. The immune escape of malignant cells is also promoted due to increased expression of the programmed death-1 (PD-1) inhibitory molecule on the CD4+/CD8+ T cells [69] and PD-L1 upregulation on CML cells [70, 71]. Quantitative and functional defects of the innate effector natural killer (NK) cells and the cytotoxic T-lymphocyte responses to leukemia-associated antigens (CTL-LAA) broaden the spectrum of immune system defects in CML patients at the time of diagnosis [69].

The significance of the immune system for a successful TFR was confirmed by the Immunostim study, which documented an association between elevated peripheral blood natural killer (NK) cells and a positive clinical outcome following IM discontinuation [85]. Other immunomodulatory effects of TKI administration leading to immune system re-activation and restoration of effector-mediated immune surveillance were recently documented. TKI treatment resulted in the restoration of NK cell receptor repertoire and an enhanced NK cell function, a decrease of immune suppressors (MDSC, Treg and T lymphocytes PD-1+), the restoration of LLA-CTL responses including PD-1 downregulation to normal levels, and an increase in DC number and antigen presenting cell function [67]. The restoration of immune system function in CML patients on TKI seems to be optimal

Table II. Off-target effect of BCR-ABL tyrosine kinase inhibitor's administration on immune system in patients with chronic myeloid leukemia

Off target effect on immune system	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib
Hypogammaglobulinemia (via inhibition of Burton kinase) [72–74]	+				
Decrease in memory-B-cell count (via inhibition of Burton kinase) [72, 75]	+				+
B-cell immune responses impairment [74, 76]	+	+	+		
Treg and effector T cells function impairment (via inhibition of Src kinase) [77–79]	+	–	+	+	
Decreased cytotoxicity and reactivity of NK cells [79]	+	–	+		
Abrogation NK cells cytokine production [79]			+		
Decreased proliferation and function of CD8+ T lymphocytes [80]		+			
LGLs expansion [81, 82]	–	–	+		
Increased proliferation of cytotoxic (CD3+CD8+) T cells and/or NK cells (CD3–CD16+/56+) [83]			+		
Decrease of NK cells count [75]	+			+	+
Decrease of MDSCs level [84]	?	?	?	?	?

NK — natural killer cells; Treg — regulatory T lymphocytes; LGLs — large granular lymphocytes; MDSCs — myeloid-derived suppressor cells

after reaching MR4.5 (BCR-ABL1 ≤0.0032%), a time when the increased effector NK cell number and function and T cell immune responses, and reduced numbers of PD-1+ CD4+/CD8+ T cells and monocytic MDSC are maximal [69].

Another question concerns the role of immune surveillance by natural killer and T cells in maintaining a successful TFR and disease activity control [66]. In 2017, Jacomet et al. postulated that the deficiency of iNKT/InnateCD8+ T cells axis is present in CML patients [86]. Their hypothesis was confirmed by the observation of CML patients in TFR ≥2 years carried out by Cayssials et al. documenting the increase of functionally active innate CD8(+) T-cells [NK-like KIR/NKG2A(+)] and their number [87]. The presence of specific CTLs directed against CXorf48 (cancer testis antigen) expressed in LSC is also correlated with the relapse rate in CML patients who discontinued imatinib after maintaining complete molecular remission for more than two years [88]. The success of the TFR attempt likely depends on the 'quite normal' efficiency of the immune system. This is possible only if MR4.5 response to TKI treatment is reached, and when NK cells number and effector T-cell cytolytic function is increased, and when PD-1 expression on the T-cell and numbers of monocytic MDSCs is reduced [69].

Chronic myeloid leukemia stem cells

CML SCs are not fully defined yet in terms of immune and functional characteristics [89]. CML SCs likely share an immunophenotypic profile with normal hematopoietic stem cells (HSCs) and reside in the CD34+/CD38–/Lyn– cell fraction [90]. Also, CD25 and CD44 are expressed in both CML SCs and healthy HSCs [91, 92]. On the other hand, interleukin-1-receptor accessory protein (IL-1RAP) and CD26 [dipeptidyl peptidase-4 (DPP4)] are aberrantly expressed on the CML SCs' surface, but not in normal CD34+ cells [93–95]. CML SCs can self-renew and generate large numbers of leukemic progenitor cells (CD34+CD38+) with the capacity to differentiate or enter a dormant state. In 2012, BCR-ABL1-independent CML SCs was postulated by Hamilton et al. [96]. They documented that the process of survival and self-renewal of CML LSCs was associated with activation of the cellular signalling process, including cell-intrinsic and cell-extrinsic survival pathways.

The first group includes abnormal signaling via the Janus kinase–signal transducer and activator of transcription 3/5 (JAK–STAT3/5), WNT/β-catenin, sonic Hedgehog (Hh) or PIK3/AKT pathways, abnormal function of protein phosphatase-2 (PP2A), promyelocytic leukemia (PML) protein, dual specificity tyrosine phosphorylation regulated kinase 2 (DYRK2), repression of autophagy process, deregulated expression of microRNAs (i.e. the upregulation of miR-29a--3p, miR660-5p, has-mir183), disturbed epigenetic regulation of genes expression by enhancer of Zeste Homolog 2 [a member of the polycomb repressive complex 2 (PRC2)], deregulation of fatty acid cellular metabolism due to arachidonate 5-lipoxygenase (ALOX5)-associated abnormalities of arachidonic acid conversion to leukotrienes required for malignant cells self-renewal, and BCR-ABL1-related autocrine production of cytokines resulting in growth factors-independent STAT5 activation [i.e. interleukin (IL) 3, granulocyte colony-stimulating factor (G-CSF)]. Other key regulators influencing the apoptosis, self-renewal, cell fate and senescence process of CML SCs include abnormal transforming growth factor-β (TGF-β)/Forkhead box O (FOXO) interaction and Musashi 2 (Msi2)/Numb of NOTCH signaling [97–105].

Bone marrow microenvironment and CML SCs

CML SCs reside in the same bone marrow microenvironment (BMM) as normal stem cells. The cross-talk between CML SCs and BMM is mediated by soluble factors like cytokines [IL-3, IL-1α/β, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-6, and interferon gamma (IFN-γ), myostatin propeptide (MSTNpp), sCD14, IL-21 and IL-13v, and CCL-28], chemokines [i.e. C-X-C motif chemokine ligand 12 (CXCL12)] secreted by mesenchymal stromal cells, and osteoblastic cells), growth factors via autocrine and/or paracrine mechanisms, and cell-to-cell (mesenchymal stromal cells, osteoblastic cells endothelial cells, neurons) direct interactions via surface adhesive molecules (i.e. β_1-integrin). The aforementioned interaction may have resulted in an enhanced proliferation, quiescence, and drug resistance of CML SCs [106–109]. Lastly, the role of miR-126 secreted by the endothelial cells in the process of CML SC quiescence and self-renewal control has been postulated [110]. Similarly, the role of miR-300, expressing dual anti-proliferative and PP2A-acivating properties, in the process of CML SCs quiescence and persistence has recently also been confirmed [111].

Due to the high diversity of CML SCs (subclonal character, different metabolic characteristics, and molecular and immunophenotypic fingerprints) and high inter- and intra-patient heterogeneity, the possibility of a common, unified strategy for CML SC eradication has been neglected. What is more, CML SCs eradication is now irrelevant due to the significant improvement of TKI long term treatment results and encouraging results of TFR attempts [112].

The current concept of chronic myeloid leukemia treatment with tyrosine kinase inhibitors based on the reduction of measurable residual disease and the recovery of immune system function is set out in Figure 1.

New therapeutic approaches concerning CML treatment

A better understanding of the biology of CML has allowed the formulation of a number of new therapy concepts for

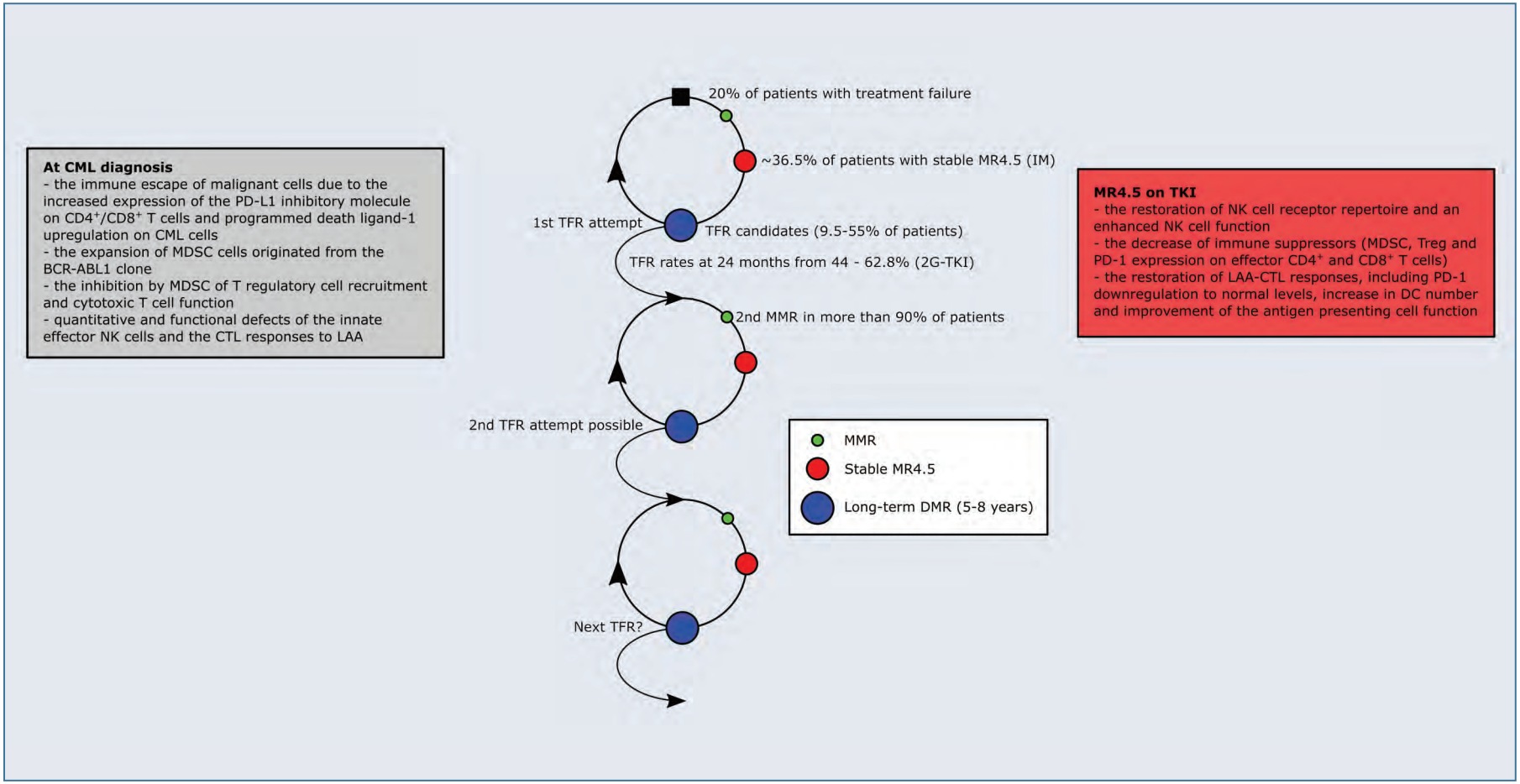


Figure 1. Current concept of chronic myeloid leukemia (CML) treatment with tyrosine kinase inhibitors based on reduction of measurable residual disease and immune effector recovery; CTL — cytotoxic T lymphocytes; LAA — leukemia-associated antigens; MDSCs — myeloid derived suppressor cells; MR — molecular response in log scale; PD-L1 — programmed death-ligand 1

the eradication of leukemic cells with the help of immunotherapy or chimeric antigen receptor–engineered T cells (CAR-T) directed against CXorf48 (cancer testis antigen) or IL1RAP (IL-1 receptor accessory protein) [88, 113]. Recently, quiescent primitive SCs insensitive to IM subpopulation of CML were identified in a CD36+ cell subpopulation with the help of an RNA-seq study [114]. This data forms the basis of the concept of antibody-based therapeutic targeting of CML SCs [112, 114, 115].

Moreover, an innovative strategy based on a liposome loaded with the BCL2 inhibitor venetoclax exploiting begelomab (an anti-CD26 antibody) has been proposed to target positive CML SCs CD26+ [116] more selectively.

In our opinion, its use, in combination with TKI and other drugs targeting alternative CML LCs survival pathways, should be the future of combinatorial therapy for the eradication of CML stem cells.

CML and the future

Integrative genomic analysis reveals cancer-associated mutations at the diagnosis of CML in patients. WES, RNA-seq and gene expression profiling studies have identified a number of molecular aberrations in addition to *BCR-ABL1*, among others affecting epigenetic regulators such as *ASXL1*, *DNMT3A*, *TET2*, *SETD1B* and transcription factors (*IKZF1*, *RUNX1*) [51–53, 117]. Its presence could also potentially influence the process of making therapeutic decisions in future [53, 118].

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; Uniform requirements for manuscripts submitted to biomedical journals.

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REVIEW ARTICLE

CAR-T therapy in mantle cell lymphoma: a literature review

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Abstract

Mantle cell lymphoma (MCL) is a rare lymphoma derived from mature B cells with the presence of translocation t(11;14) resulting in cyclin D1 overexpression, with a variety of clinical symptoms and a variable course. Despite better understanding regarding its pathogenesis, and the use of aggressive immunochemotherapy with autologous bone marrow transplantation, this disease is still considered incurable, with median overall survival of five years. Patients with refractory and relapsed disease have a poor prognosis and the traditional cytotoxic therapy is insufficiently effective in this group of patients. New therapies such as Bruton's tyrosine kinase inhibitors (BTKi), B-cell lymphoma-2 (BCL-2) inhibitors, and immunomodulatory drugs have produced high response rates, but the duration of response is limited, and patients have another relapse diagnosed.

Recently adopted immunotherapy with chimeric antigen receptor (CAR) T-cells directed against the CD19 receptor on lymphoma cells seems to be promising in the population of refractory and relapsed MCL patients. In July 2020, the United States Food and Drug Administration approved brexucaptagene autoleucel CAR-T product for patients with MCL after two lines of therapy and treatment with Bruton kinase inhibitors. In this review, we briefly discuss the treatment options in patients with refractory and relapsed MCL, focusing on BTKi treatment as the targeted therapy required before CAR-T treatment. We summarize our knowledge of CAR-T cell therapy for MCL in clinical trials and real-world clinical practice, and consider the place of CAR-T in future MCL therapy.

Key words: mantle cell lymphoma, CAR-T, refractory, non-Hodgkin lymphoma, cellular therapy

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Introduction

Mantle cell lymphoma (MCL), a B-cell neoplasm, accounts for 2.5–6% of newly diagnosed non-Hodgkin lymphomas (NHL) and is characterized by a broad spectrum of clinical presentations and a highly variable course [1, 2]. MCL is much more frequent in men than in women (3:1) and median age at diagnosis is 60–70 years. The disease is incurable in most patients, and median overall survival is five years [2]. The primary genetic lesion is a translocation t(11;14)(q13;q32) that leads to overexpression of cyclin D1 (*CCND1*) and deregulates cell cycles with uncontrolled cell proliferation [3, 4]. According to the World Health Organization (WHO) 2016 updated classification for lymphoid malignancies, MCL is divided into two distinct entities based on different molecular pathways accounting for the pathogenesis [3, 5]. The nodal subtype occurs in 80-90% of cases, and is characterized by unmutated immunoglobulin heavy chain variable region genes (*IGHV*), sex determining region Y-box 11 (*SOX11*) overexpression, and generally higher genomic instability resulting in an aggressive clinical course. Most patients have advanced disease with nodal and/or frequent extranodal involvement including infiltration of bone marrow

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(50–80%), blood (50%), liver (25%) and gastrointestinal tract (20–60%) [1, 5, 6].

Conversely, the non-nodal, leukemic variant (10–20%) of MCL is characterized by more genetic stability, mutated *IGHV*, *SOX11* negativity and indolent biological behavior. Patients present leukemic disease with leukocytosis, splenomegaly (40%), and bone marrow infiltrations, and the disease resembles chronic lymphocytic leukemia in its course. Acquired genetic lesions during the course of the disease might affect clinical behavior and worsen the prognosis [1, 5].

There are many factors that predict survival outcomes in MCL. The classic clinical factors for a poor outcome include older age, male sex, elevated lactate dehydrogenase, poor Eastern Cooperative Oncology Group (ECOG) performance status, elevated leukocyte count in the blood, advanced stage, and membership of a high-risk group according to the MCL International Prognostic Index (MIPI) [7]. A strong biological prognostic factor is the degree of tumor proliferation expressed as Ki-67 proliferation index [8]. The Ki-67 proliferation index enhances the value of the MIPI score. Other important biomarkers comprise the blastoid variant of MCL, complex karyotype, *TP53* mutation or overexpression, and *MYC* translocation or overexpression [1, 9].

Standard therapeutic approaches for MCL include cytotoxic and anti-CD20 monoclonal antibody immunotherapy. Induction chemotherapy with high-dose cytarabine consolidated with myeloablative chemotherapy and autologous stem cell transplantation (auto-SCT) has been adopted as management for young, fit, transplant-eligible patients [1, 10]. Older patients have been offered less intensive treatment including R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone), RB (rituximab, bendamustine), and VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisolone) [11]. Rituximab maintenance has improved overall survival (OS) and progression-free survival (PFS) post first line treatment. It is recommended to apply it for three years after auto-SCT consolidation in transplant-eligible patients, and after induction therapy in patients who are unfit for auto-SCT [12]. Chemo-free therapy with lenalidomide, Bruton's tyrosine kinase inhibitors (BTKi), and monoclonal antibodies has been tested in a few studies and offers great promise as future standard first line therapy, but its application is still at the clinical trial stage [13–15].

Despite improvements in the efficacy of the first line therapy, MCL is still an incurable disease, and nearly all patients will eventually relapse whatever their initial treatment. Median time to relapse ranges from less than two years (after less intensive therapy or in high-risk patients with *TP53* mutation) to more than 10 years after highly intensive cytarabine-based treatment. Patients with refractory and relapsed disease have a poor prognosis, and traditional cytotoxic therapy is insufficiently effective in this group of patients. Most patients require multiple lines over their disease course. Retreatment with chemotherapy is associated with a progressively lower response rate, shorter remission, and increased hematological toxicity [16].

In recent years, novel target therapies have shown promising activity in the relapsed/refractory (R/R) cohort. Ibrutinib, acalabrutinib, zanubrutinib, lenalidomide and bortezomib have achieved approval from the Food and Drug Administration (FDA) for relapsed and refractory MCL [17]. In July 2020, adoptive chimeric antigen receptor T-cell (CAR-T) immunotherapy with brexucabtagene autoleucel (brexu-cel), a CD19-directed genetically modified autologous T-cells for MCL treatment, received approval from the FDA [17]. This therapy has been intended for adult patients with R/R MCL who have received at least two lines of treatment, including at least one with BTKi.

In this review, we briefly discuss treatment options for patients with refractory and relapsed MCL lymphomas, focusing on BTKi as the targeted therapy required before CAR-T therapy. We summarize the existing data on CAR-T cells treatment as a new immunotherapy for MCL, and we discuss how CAR-T therapy fits into the current MCL treatment landscape.

Bruton tyrosine kinase inhibitors

Bruton's tyrosine kinase (BTK) is an enzyme involved in signal processing after the activation of B-cell receptor (BCR) on lymphoma cells. BTK's role is to participate in the differentiation, proliferation and survival of B lymphocytes and lymphoma cells. An adequate control of BTK activity is important for B-lymphocyte homeostasis. Uncontrolled activation of BTK and, indirectly, the nuclear factor kappa B (NFKB) pathway, is essential for lymphoma cell survival [18]. As mentioned above, three BTKi have been approved by the FDA for the treatment of patients with R/R MCL. They have demonstrated durable responses in relapsed and refractory disease settings, and also when MCL presents high-risk features including *TP53* mutations. BTKi have a common mechanism of action: they bind to the cysteine 481 in the ATP domain of BTK leading to irreversible inhibition. They differ in terms of selectivity, pharmacokinetics, toxicity, and dosage. Ibrutinib was the first BTK inhibitor of which the activity was confirmed in studies with refractory and relapsed MCL patients [19]. Three studies were performed: a pivotal phase II study PCYC 1104-CA, the phase II study MCL 2001, and the phase III study MCL 3001 [19–21]. A total of 370 patients with MCL receiving 560 mg of ibrutinib daily were analyzed [22]. Overall response rates (ORR) and complete remission (CR) rates were established for the three studies: 66% and 20%, respectively, with a median PFS of 13 months. Toxicities included diarrhea (40%), cough 22%, nausea 22%, peripheral edema 20%, atrial fibrillation 5%, and bleeding 5%. Ibrutinib is more effective

in the second line of treatment than in subsequent lines, with ORR of 78% and CR of 37% including a median PFS of 22 months for patients receiving second-line, compared to ORR of 69% and CR of 23% with a median PFS of 8 months among patients after two or more prior lines. Ibrutinib has also demonstrated activity in patients who progressed on bortezomib-containing regimens [22].

The second generation BTKi acalabrutinib and zanubrutinib have demonstrated better efficacy and toxicity profiles than ibrutinib. In the phase II multicenter ACE-Ly-2004 study, acalabrutinib demonstrated ORR of 81% and CR of 40% with a median duration of response of 26 months. Only 1.6% of patients required dose reductions and 6.5% discontinued therapy due to toxicity [23]. The activity of zanubrutinib has been shown in two phase II trials: BGB-3111-206 and BGB-3111-AU-003 [24, 25]. ORR was achieved in 84–90% of patients and CR was confirmed in 22–59% of patients. BTKi appears to be more effective in earlier lines if used in R/R disease settings. BTKi has become the preferred class of agents in second line treatment for MCL, but unfortunately these are not reimbursed in Poland.

Patients who relapse after BTKi have a very poor prognosis, with a median OS of 2.9 months. The optimal therapy for that high-risk group of patients is unknown. One treatment option may be immunochemotherapy with rituximab, cytarabine, and bendamustine [26]. This produces a high ORR (83%) but is not sustained (median PFS of 10 months) and can be used as a bridging strategy to other cell therapies.

Other strategies

Other agents such as lenalidomide and bortezomib were also approved by the FDA, but in monotherapy they have proved less effective in relapsed and refractory disease than in untreated MCL patients. FDA approval for lenalidomide is based on the results of the NHL-002, NHL-003, MCL 001 EMERGE and SPRINT studies. Response to treatment ranged from 28–57%, but the rate of CR was only 7.5%, and the median duration of response (DOR), PFS, and OS were 16.6, 4, and 19 months, respectively. The addition of rituximab to lenalidomide allows for a response in 57% (CR 36%) with a median DOR of 18.9 months, a median PFS of 11.1 months, and a median OS of 24.3 months [27]. The activity of bortezomib in MCL has been demonstrated in several studies. Monotherapy with bortezomib allows for an ORR of 41% and a CR of 20% in heavily pretreated patients (phase II PINNACLE study). The median DOR was 9.2 months. The addition of bortezomib to CHOP chemotherapy induced an ORR of 82% in patients with refractory and relapsed MCL. The combination of rituximab, bendamustine and bortezomib results in ORR of 83% and a 2-year PFS of 47% [27]. Venetoclax is a potent, selective inhibitor of BCL-2 whose activity was also demonstrated in 28 patients with MCL: ORR 75%, CR 21%, median PFS 14 months (phase I study). Venetoclax in combination with ibrutinib acts synergistically and induces ORR of 62% and CR of 42% [27]. Other intensively studied therapies include monoclonal antibodies, bispecific antibodies, antibody-drug conjugates, and CDK4/6 inhibitors as a monotherapy or with other active drugs.

Allogeneic stem cell transplantation

Although allogeneic stem cell transplantation (allo-SCT) is a potentially curative treatment, it is not widely used in relapsed or refractory MCL patients [27]. The risks of early mortality (20%), acute graft-versus-host disease (GvHD) (40%) and chronic (30%) GvHD contribute to the choice of this therapy in patients with relapsed after auto-SCT and other targeted therapies [28]. High non-relapse mortality occurs in 10–24% of patients, even with reduced intensity conditioning. The 5-year OS and PFS are 40–60% and 30–50% respectively [29–31]. Most studies have been retrospective and have usually involved a small number of patients. Recent studies have shown that patients undergoing allo SCT therapy have long-term remission, which may suggest curative potential of this therapy [31–33].

CAR-T products in MCL

The first data on CD19 directed CAR-T activity in MCL disease was reported in a phase I/II study in 2016 [34]. Since then, four CD19 targeted CAR-T cell constructs have been approved by the FDA [17]. Three of them are intended for relapsed and refractory aggressive B cell lymphoma after two prior lines of therapy: axicabtagene ciloleucel based on the results of the ZUMA 1 trial [35], tisagenlecleucel based on the JULIET trial [36, 37], and lisocabtagene maraleucel based on the TRANSCEND-011 trial [38]. One CAR-T product, brexucabtagene, was approved for relapsed and refractory MCL based on the ZUMA 2 study [39]. The first promising results of treatment with lisocabtagene in patients with relapsed and refractory MCL have also been published [40]. Due to the short cut-off time of the data, this still requires confirmation in a long-term follow-up.

The major early toxicities following CAR-T therapy include cytokine release syndrome (CRS), macrophage-activation syndrome, immune effector cell-associated neurotoxicity syndrome (ICANs), tumor lysis syndrome (TLS), cytopenias, infections, and cardiotoxicity [41]. Late complications (28 days after infusion) comprise delayed TLS/CRS/ICANs, prolonged cytopenias, B cell aplasia, hypogammaglobulinemia and associated infections [41]. Various toxicity scales are used in the assessment of CRS, but the Lee scale is the most commonly used [42–44]. The 10-point ICE scale — immuno-effector cell encephalopathy has been

used to assess neurotoxicity [44]. Rest toxicity is usually assessed on the Common Terminology Criteria for Adverse Events (CTCAE) or CARTOX — CAR-T therapy associated toxicity scale [43, 44].

Brexucabtagene autoleucel (brexu-cel, Tecartus) is a CD19-directed genetically modified autologous CAR-T immunotherapy approved in July 2020 for adult relapsed and refractory MCL patients. Brexu-cel is a second generation CD19-directed CAR. It comprises an external domain with single-chain variable fragment linked via a hinge to transmembrane domain and two intracellular CD28/CD3ζ domains: CD28 is a costimulatory domain and CD3ζ is a signaling domain [45, 46]. It is transduced into T-cells using a gamma-retrovirus vector [47]. Binding to CD19 receptor on lymphoma cells CAR-T cells stimulates mechanisms of signaling via CD3ζ domain that leads to activate T-cells. CAR-T cells trigger a cascade of cytokines that facilitate neoplasm destruction, and mediate apoptosis of lymphoma through direct release of granzyme B and perforin [48]. The costimulatory domain CD28 improves CAR-T cell expansion, persistence and anti CD19 activity [50].

Brexu-cel has the same CAR construct as axicabtagene autoleucel (axi-cel), the CAR-T approved for aggressive lymphomas. The important difference is to be found in the manufacturing process after collection of autologous mononuclear cells from peripheral blood by leukapheresis [39]. The harvest product is rich in CD4, CD8 and lymphoma cells. During the manufacturing process, it is exposed to magnetic beads that are coated with anti-CD4 and CD8-antibodies to enrich the product with T-cells and remove any CD19 expressing malignant cells [51]. Then the product depleted CD19 cells are cultured with interleukin 2 (IL-2) followed by transduction of the CAR gene with a gamma-retrovirus vector. The CAR-T product is harvested and undergoes quality assurance testing prior to release. Each single infusion bag dedicated to the individual patient contains approximately 68 mL of anti-CD19 CAR-T cells dispersion, yielding a target dose of 2×10^6 viable anti-CD19 CAR-T cells per kilogram of body weight (range 1×10^6 to 2×10^6 cells per kg body weight) with a maximum number of viable anti-CD19-CAR--T cell of 2×10^8 per kg body weight. Before infusion, the CAR-T product must not be irradiated and no leukocyte depletion filter must be used for infusion [52].

The role of brexu-cel for patients with relapsed and refractory MCL was investigated in the multicenter phase II ZUMA-2 trial [39]. This was the first clinical trial with CAR-T in this population. The results of this study have contributed to the approval of brexu-cel by the FDA for patients with relapsed and refractory MCL. The study cohort contained patients who had received up to five prior therapies, with at least one line including BTK inhibitors. Sixty eight of 74 enrolled patients were administered brexu-cel infusion. Median age was 65 (range: 38–79), and high-risk features of disease such as blastoid or pleomorphic morphology, Ki-67 >30%, and *TP53* mutation were reported in 31%, 82% and 17% of patients respectively. Forty two patients (62%) had disease that had not responded to BTKi, and in 18 (26%) patients the relapse occurred during BTKi treatment. Therefore, 88% of the treated patients were considered to have disease refractory to BTKi. Bridging therapy was given to 25 patients, and 75% of them received BTKi, mainly ibrutinib. A primary efficacy analysis showed that brexu-cel induced high incidence of ORR (93%) and CR (67%) in the first 60 assessed patients. Looking at the entire study population, 85% of patients responded to CAR-T infusion with 59% of patients achieving CR. The response to CAR-T administration was fast and it deepened over time. The median time to initial response was 1.0 month (range: 0.8–3.1) and median time to complete remission was three months (range: 0.9–9.3). Over half of the patients who initially had a partial response or stable disease achieved CR with a longer follow up, and 57% of 60 patients were still in remission at 12 months. Minimal residual disease (MRD) was investigated in 29 patients, and 83% of them had no detectable disease four weeks post infusion. 15/19 (79%) had no detectable MRD six months after infusion. The responses to CAR-T were similar among various subgroups. Patients with a high MIPI score had a similar response to those with a low MIPI score (94% vs. 92%). Also, the use of bridging therapy did not affect response to brexu-cel. Follow up ranged between 7–32 months with a median of 12 months, with PFS and OS of 61% and 83% respectively [39].

All 68 patients experienced at least one adverse event of any grade, with adverse events of grade 3 or more in 99% of patients. Most common toxicity was hematological complications (94%) followed by neutropenia (85%), thrombocytopenia (51%), and anemia (50%). In 26% of patients, cytopenia grade 3 was detectable more than 90 days after CAR-T infusion. The next most common adverse events were infections (32%) grade 3 with pneumonia (9%), and cytomegalovirus infection (2%). CRS in any grade and CRS of grade 3 were reported in 91% and 15% of patients respectively. Median time to CRS was two days (range: 1–13), all symptoms of CRS resolved within a median 11 days, and no patient died of CRS. A total of 63% of patients developed neurological events (NEs), but none of them was fatal. NEs of grade 3 or more occurred in 31% of patients, and median time to NE onset of any grade was seven days. A total of 16 (24%) patients who received brexu-cel died, mainly due to progressive disease (21%) or because of grade 5 adverse events (3%) attributed to lymphodepleting chemotherapy [39].

Apart from the ZUMA study, there are some reports of the efficacy and safety of brexu-cel use in MCL patients (*see* Tables I, II) [53–56]. The first report was based on data from the standard of care practice from centers in the US Lymphoma CAR-T Consortium [53]. In this study, a total of 107 patients underwent leukapheresis, and 93 (87%)

Table I. Comparison of efficacy between ZUMA-2 study and other reports

Study [ref.]	Number of patients who received Brexucel	ORR [%]	CR [%]	Median follow-up in months	Median PFS	Median OS
ZUMA-2 [39]	60	93	67	12.3 (7–32)	NR	NR
US Lymphoma CAR-T Consortium [53]	92	88	66	12	NR	NR
US academic center [54]	52	88	69	4.1	NR	NR
DESCART — France [55]	48	87.2	63.8	3.3 (1–10)	6.3 months	NR
European study [56]	28	89	61	5 (1–10)	NR	NR

ORR — overall response rate; CR — complete remission; PFS — progression-free survival; OS — overall survival; NR — not reached

Table II. Comparison of toxicity between ZUMA-2 study and other reports

Study [ref.]	Number of patients who received Brexucel	CRS grade 3 in [%]	ICAN grade 3 in [%]	Neutropenia grade 3 in [%]	Persistent cytopenia +100	TRM in [%]
ZUMA-2 [39]	60	15	31	16	26	3
US Lymphoma CAR-T Consortium [53]	92	8	35	UNK	UNK	UNK
US academic center [54]	52	14	37	37	15	9
DESCART — France [55]	48	8.7	8.7	UNK	UNK	1
European study [56]	28	5	26	15	12	0

CRS — cytokine release syndrome; ICAN — immune effector cell-associated neurotoxicity syndrome; TRM — treatment-related mortality; UNK — unknown

patients were administered brexu-cel. Median age was 67 years (range: 34–89). Looking at the study population, more patients had unfavorable factors such as blastoid or pleomorphic morphology (45%), *TP53* (46%), Ki-67 >30% (77%), high risk MIPI (32%), and central nervous system (CNS) involvement (7%), and 73% of patients would have not met the ZUMA-2 trial eligibility criteria. Prior BTKi treatment had been given for 82% of patients, and refractory disease was reported in 44%. Bridging therapy was applied in 60 (65%) patients, including ibrutinib (45%), venetoclax (23%), chemotherapy (32%), CD20 monoclonal antibodies (43%), and others. Median follow up was three months (range: 0.1–9). At 30 days post infusion, ORR and CR were 86% and 64% respectively.

Interestingly, patients with a high-risk disease feature had high incidences of response and complete remission: the ORR/CR rates were 94%/70% for blastoid/pleomorphic variants, 82%/50% for *TP53* mutation, and 88%/67% for those who did not meet eligibility criteria for the ZUMA study. 3 months PFS was 80.6% and 6 months OS was 82.1%. CRS occurred in 88% of patients, but only 8% had CRS of grade 3. Neurological complications appeared in the same percentage, 58%, of patients as in the ZUMA-2 study, also a grade 3 NAs (33%). The authors confirmed encouraging results in activity and safety of brexu-cel in relapsed and refractory disease in real world practice, especially as 75% of patients would never receive CAR-T as participants in the ZUMA-2 study [54].

A second study concerns a safety and efficacy analysis of 52 patients treated with brexu-cel in 12 US academic centers [55]. Median age was 66 (range 47–79): seven patients had a history of CNS involvement, 50% of patients relapsed within 24 months of their initial treatment, all patients had previously received BTKi, and 77% of patients received a bridging therapy mainly including BTKi. The ORR and CR were 88% and 69% respectively. With a median follow up of 4.2 months, the estimated 6 months PFS and OS rates were 82.7% and 89% respectively. Patients with CNS involvement had no relapse at the final follow up. The incidence of adverse events were similar as in previously described reports: CRS occurred in 84% of patients with 10% grade 3, median time to CRS onset to max grade was five days (range: 0–10), and neurotoxicity of any grade developed in 57% of patients with a median time to onset of seven days. In 31% of patients, NEs of grade 3 or more were observed. One patient died due to neurotoxicity. Persistent neutropenia and thrombopenia were detectable in 12–15% of patients. Fatal infections occurred months after infusion: septic shock on +40 day and COVID infection on +80 day. Two patients died due to progressive disease. No adverse factors were found for survival in univariate analysis [54].

We now turn to two works from European centers. The first report was from DESCAR-T, the French national registry for all patients treated with CAR-T, and contained real-life data regarding the use of brexu-cel in relapsed and refractory MCL in France [55]. A total of 57 patients were

registered, and CAR-T cell product was ordered for 55 patients, but only 47 of them were infused with brexu-cel. Two patients decided against CAR-T. Eight patients did not administer the CAR-T product due to disease progression (three patients), manufacturing failure (three), infection (one) and cardiac disease (one). Most patients were treated with a median three lines of treatment (range: 2–8), and 30% of them presented a high-risk MIPI score. All patients received BTK inhibitors as one line of therapy. Median time between leukapheresis and CAR-T infusion was 56 days (range: 35–134) and up to 87% of patients required bridging therapy. The results of treatment were assessed in 42 patients and were similar to those in earlier studies: ORR in 88% and CR in 61.9% of patients. At 6 months, PFS was 57.9%. CRS and neurotoxicity were observed in 79% and 48.9% respectively. Up to 30% of patients required intensive therapy, although CRS and neurological events of grade 3 occurred in 8.5%.

The second report was from seven sites in three European countries [56]. Twenty eight patients were included, but only 19 (68%) received a CAR-T cell infusion. Median age was 67 (range: 51–78) and 89% were male. Unlike the other report, most of the patients had a high risk Mantle Cell Lymphoma International Prognostic Index (MIPI) score (63%) and required bridging therapy (79%), most patients had progressive (53%) or stable (27%) disease, and only 20% of patients responded to bridging therapy. There was a high incidence of ORR (89%) and CR (68%). A median PFS and a median OS were not reached, and at 6 months PFS and OS were 91% and 83% respectively. The toxicity did not differ from other reports, 89% of CRS and 63% of neurotoxicity of any grade, with low incidence of CRS grade 3 or more (5%) and neurotoxicity grade 3–5 (26%). Two patients required treatment in the Intensive Care Unit [56].

In summary, all reports have confirmed the high efficacy of CAR-T therapy with a high percentage of CR in a population with a very poor prognosis (Table I). The median time of follow up in all studies is very short. Toxicity is manageable and acceptable with a low incidence of grade 3 CRS (Table II). The results of all reports require the confirmation to be found in a longer follow up [39, 53–56].

Lisocabtagene maraleucel (liso-cel) is a another CD19-directed genetically modified autologous cellular immunotherapy provided as a defined composition of CD4+ and CD8+ CAR-T cells. CAR is constructed from extracellular FMC63 monoclonal antibody-derived single chain variable fragment, immunoglobulin G4 hinge region, CD28 transmembrane domain, and intracellular 4-1BB (CD137) co-stimulatory domain and CD3ζ signalling domain [45, 57]. During the manufacturing process of liso-cel, CD4+ and CD8+ are separated from the leukapheresis product and independently activated, expanded and administered as two separate infusions at equal target doses of CD^8 and CD^4 CAR-T [57, 58]. Separate activation of CD4 and CD8 cells allows liso-cel to be administered as a defined product, and reduces the dose variability of CD4 and CD8 components. A single dose of liso-cel contains 50–110 × 10^6 CAR-T-positive T-cells. In addition to CAR, genetically modified CD4 and CD8 cells coexpress a non-functional epidermal growth factor receptor that can serve as a surrogate for CAR expression. CAR binding to CD19 expressed receptors on the lymphoma surface, and normal B cells that induce activation and proliferation of CAR-T, release of proinflammatory cytokines and cytotoxic killing cells. The 4-1BB signalling enhances the expansion and persistence of liso-cel [50, 59].

Impressive results on the clinical activity of liso-cel in patients with R/R MCL who attended the ongoing phase I TRANSCEND-NHL study (NCT 02631044) were presented to the American Society of Hematology (ASH) annual meeting in 2020 [40]. Forty one patients had undergone leukapheresis, but only 32 received liso-cel, at a dose level of 50 × 10^6 (n = 6), or at a dose level of 100 × 10^6 CAR-T cells. Median age for 32 patients was 67 (range: 36–80). High risk factors for treatment failure such as blastoid morphology, high Ki-67, TP53 mutation, and complex karyotype were found in 37.5%, 72%, 22% and 34% of patients respectively. Most patients had been heavily pretreated with a median three (range: 1–7) prior treatment lines. Twenty eight patients had been treated with BTKi (87.5%), and 11 (34%) had acquired resistance to BTKi. ORR and CR were achieved in 27 (84%), and 19 (59%) patients, but better results were obtained for the higher dose 100 × × 10^6. Treatment-emerging adverse events (TEAE) occurred in 27 (84%) patients. Toxicity occurred more frequently at the higher dose level of liso-cel infusion (100 × 10^6 CAR-T cells). Over 30% of patients had hematological complications such as neutropenia (41%), anemia (34%), thrombocytopenia (31%), and prolonged cytopenia grade 3 (34%), CRS occurred in 50% of patients, mainly in 1–2 grade, and only one patient developed CRS grade 4. Median time to onset of CRS was six (range: 2–10) days. Nine patients (28%) developed neurological events (NE) with one third grade 3; no NEs grade 4–5 were reported. Median time to NE onset was eight days (range: 2–25). Serious TEAEs grade 5 occurred in two patients, i.e. tumor lysis syndrome and cryptococcal meningoencephalitis. We are awaiting final results that will confirm these findings [50].

Little is known about the long-term efficacy and safety with 4-1BB based CAR-T cells in MCL. Promising results were reported in three high risk patients with relapsed and refractory MCL. All three achieved complete remission and remained in CR during a follow up of 25–34 months. Long-term B cell depletion was observed in two patients, and no recovery of serum immunoglobulin was observed in two patients. However, they did not develop any serious infections [60].

In the above studies, the main emphasis was on toxicity and response according to the Lugano criteria. A work focused on the eradication of minimal residual disease (MRD) was presented by Chinese researchers from the Shenzhen center (NCT0385786) [61]. Two patients, including one with MCL disease with MRD presentation, were administered anti-CD19 scFv TCRz cells: 41BB CAR-T. Before the administration of cells, in the patient with MCL the presence of genetic abnormalities such as TP53, ATM and NOTCH were found. One month after the administration of CAR-T cells in the next-generation sequencing (NGS) test, no genetic changes were found, TP53 negativity was confirmed on day 180 after the infusion. At the end of the observation, TP53, ATM and NOTCH were still negative. The residual disease was fully eradicated. A second patient with Burkitt lymphoma had also eradicated MRD from bone marrow, confirmed at 42 days post infusion. This report also comprised patients who received CAR-T due to refractory aggressive lymphoma. One patient with MCL was included: he had a high tumor burden, and had received two prior lines of therapy. He achieved metabolic PR in the first course of CAR-T and progressed after 29 months of PR. He was reinfused once more and achieved CR within one year. After 65 months, the patient was in CR. This report confirmed the high activity of CAR-T cells in MCL, and the possibility of eradicating MRD in patients with persistent lymphoma cells [61].

Bispecific CAR-T cells might be another therapeutic option for R/R MCL. Bispecific CAR-T cells aim at two tumor target antigens and could reduce the risk of relapse. The first human phase I dose escalation and dose expansion (NCT03019055) [62] trial with bispecific 4-1BB–CD3ζ anti CD20, anti CD19 (LV20.19) CART included 22 patients with relapsed and refractory NHL (seven with MCL) or chronic lymphocytic leukemia. All patients received 4-1BB–CD3ζ (LV20.19) CAR-T. CRS of grade 3-4 occurred in 5% of patients and neurotoxicity grade 3–4 in three (14%) patients. At 28 days, ORR was 82% with complete remission in 64% of patients. For relapsed and refractory MCL, 4/7 patients achieved a durable response with CR.

The development of allogeneic (allo) CAR-T might be the future direction of cellular therapy for R/R MCL. Off-the shelf allo CAR-T could overcome some disadvantages or limitations of autologous CAR-T such as manufacturing failure or variable T-cell fitness and composition [63]. The T-cells for allo CAR-T cells are yielded from healthy donors. Then, like auto lymphocytes, the allo-T cells undergo a manufacturing process to achieve anti CD19-directed CAR-T. They might be used on demand, also repeating doses if needed. This therapy might become an alternative to autologous CAR-T. The disadvantages of such therapy comprise a risk of GvHD, a rejection risk, an unknown risk of mutagenesis, profound immunosuppression with a high infection risk, and unknown long-term safety [64].

Last year, the American Society of Transplantation and Cellular Therapy (ASTCT), the Center of International Blood and Marrow Transplant Research (CIBMTR), and the European Society for Blood and Marrow Transplantation (EBMT) issued recommendations regarding the role, timing and sequence of autologous hematopoietic cell transplantation (auto-HCT), allogeneic hematopoietic cell transplantation (allo-HCT), and CAR-T cell therapy in patients with newly diagnosed and R/R MCL [65].

For first-line treatment, the consolidation of auto-HCT is the standard of care for patients eligible for this procedure. The role of allo-SCT and CAR-T therapy for *TP53* mutation patients as a first line treatment is not fully established and these therapies should be conducted within clinical trials. The optimal time for CAR-T therapy has not been determined. Due to the cost and availability of other active therapies, it has been recommended to use CAR-T therapy in patients who cannot tolerate or fail BTKi therapy.

In December 2020, the European Medicines Agency (EMA) approved CAR-T therapy for relapsed and refractory patients after two lines of systemic therapy including therapy with at least one BTKi. The ASTCT, the CIBMTR and the EBMT agree with the EMA's recommendation. In patients with the presence of *TP53* mutation, CAR-T therapy may be considered in the second line. The allo-SCT procedure is indicated when CAR-T is unsuccessful or impossible [65].

Conclusion

MCL is a rare, aggressive and incurable disease. Its treatment remains a challenge, especially in patients who have relapsed or refractory disease after treatment with Bruton's tyrosine kinase inhibitors. Allo-SCT remains the only potentially curative treatment option, but due to the high risk of early death posed by acute and chronic GvHD, this treatment is rarely chosen. A promising option is CAR-T cell therapy for MCL patients with disease that is relapsed and refractory to BTK inhibitors. The two CAR-T constructs, brexucaptagene and lisocaptagene, show high activity in this poor prognosis population. Brexucaptegene autoleucel has been approved by the FDA for patients after at least two lines of treatment and BTKi therapy (ZUMA-2 study). Various studies confirm the effectiveness and safety of brexucel. The therapy is also effective in patients with *TP53* mutation. Lisocel is also highly effective and safe in patients with refractory and recurrent MCL, but due to the short follow-up time, this needs to be confirmed in a long-term observation. Due to the cost of CAR-T cells and the availability of other active therapies, it has been recommended to use CAR-T therapy only in patients who cannot tolerate or who fail BTKi therapy. New directions in the development of cell therapies include treatment with bispecific CAR-T or allo-CAR-T.

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; Uniform requirements for manuscripts submitted to biomedical journals.

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REVIEW ARTICLE

Artificial intelligence and chimeric antigen receptor T-cell therapy

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Abstract

Therapy with the use of chimeric antigen receptor T-cell (CAR T-cells) is one of the most modern medical technologies in hemato-oncology, using, thanks to the advances in molecular biology, natural anti-cancer immune mechanisms. Nowadays, it is an extremely effective complement to conventional treatment and hematopoietic cell transplantation. Ongoing clinical trials show the enormous potential of this treatment beyond hemato-oncology. We discuss in this paper the potential use of Artificial intelligence (AI) in this setting. AI has been at the cutting edge of science in recent years. It has spread from computer science to areas like medicine, economics, finance and business. The use of and research into AI in medicine have become prominent due to its versatility and capabilities.

Key words: artificial intelligence, machine learning, CAR T-cell therapy

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Artificial intelligence — introduction

In recent decades, the topic of artificial intelligence (AI) has been on the cutting edge of science. It has spread from computer science to areas including medicine, economics, finance and business. With ever-improving technology year-on-year, its uses and applications have significantly expanded. However, to evaluate the use of this technology in CAR T-cell therapy, it is crucial to present an overview of the technology. Currently, there is no scientific consensus on a singular definition of AI, due to its broadness and complexity.

For the purposes of an overview, the 'Oxford Dictionary of Phrase and Fable' definition is sufficient: "the theory and development of computer systems able to perform tasks normally requiring human intelligence, such as visual perception, speech recognition, decision-making, and translation between languages". AI can be categorized into general AI and narrow AI, with the former being able to mimic human intelligence and its ability to adapt and solve an arbitrary problem and the latter being specialized in performing a specific task (IBM Cloud Education, 2020, https://www.ibm.com/cloud/learn/what-is-artificial-intelligence). Currently, general AI has not been achieved, while narrow AI is being actively utilized. AI can be, and is, used without employing machine learning algorithms, and this subtype is categorized as Symbolic Artificial Intelligence or Good Old Fashioned Artificial Intelligence (GOFAI); however, machine learning algorithms have become more prevalent in medical applications. Machine learning is a technique in artificial intelligence characterized by the use of algorithms and statistics that allow the self-improvement of a program. A subset of machine learning is neural networks, which are structures based on interconnected **neurons** or **nodes** in a layered structure comprising an input layer, hidden layers, and an output layer. These nodes pass information from one to another through weighted connections based on activation, or lack of it, in the previous layer. By manipulating

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the activation thresholds of nodes and weights associated with each connection, the network can be optimized to achieve greater accuracy. A further subset of neural networks is deep learning algorithms, defined as neural networks with more than three layers.

Neural networks allow for the processing of unstructured data, making them more autonomous and allowing the use of data such as images or text (IBM Cloud Education; 2020, https://www.ibm.com/cloud/learn/neural-networks; Kavlakoglu E., AI vs. Machine Learning vs. Deep Learning vs. Neural Networks: What's the Difference? 2020 https://www.ibm.com/cloud/blog/ai-vs-machine-learning-vs-deep-learning-vs-neural-networks). These machine learning algorithms can be further divided into four types: supervised, unsupervised, semi-supervised, and reinforcement learning. The first three are defined according to the training data used, where supervised learning utilizes labeled datasets, unsupervised learning utilizes unlabeled datasets, and semi-supervised learning uses a combination of the two. The use of labeled training data allows the machine learning algorithm to check its output against the correct answer, although it is limited by the cost and time required to label the dataset by experts. Nevertheless, this is the most commonly used type in medical imaging [1].

In contrast, unsupervised machine learning trains on unlabeled data and utilizes methods such as clustering to find parallels between elements in the dataset and group them (Delua J., Supervised vs. Unsupervised Learning: What's the Difference? 2021, https://www.ibm.com/cloud/blog/supervised-vs-unsupervised-learning). Semi-supervised learning is a method that uses both types of data, possibly improving the algorithm's accuracy on a smaller set of labeled data, overcoming the limitations of supervised learning. This method is of particular interest in medical imaging where labeled datasets are expensive to produce, although employing unlabeled datasets may result in decreasing the accuracy of the algorithm [2]. Reinforcement learning is a method based on trial and error, where desired outcomes are rewarded or reinforced. It is characterized by states embedded within an environment, in which certain actions are allowed, and based on the interaction with the environment-specific actions on specific states are rewarded allowing improvement with repeated trials. Due to the sequential nature of the algorithm, it is used in dynamic treatment strategies, where the state of the patient has to be periodically evaluated and adjusted [3, 4].

Artificial intelligence in medicine

The use and research of AI in medicine have become prominent due to its versatility and capabilities.. One of the areas with the most promising use of AI is radiology, due to the image processing capabilities of neural networks. Rajpurkar et al. [5] have developed a neural network, CheXNet, that is more accurate at diagnosing 14 thoracic diseases than expert radiologists, although in the study neither CheXNet nor the radiologists had access to patient history.

Machine learning algorithms are also being developed and tested in genome-wide association studies (GWAS), where they show promise in finding causal genes in cardiovascular disease-associated loci [6]. Moreover, AI has also shown possibilities in real-time treatment applications in the treatment of sepsis with the development of a Targeted Real-time Early Warning Score (TREWS) algorithm, which identifies patients with sepsis significantly quicker than competing warning systems, allowing earlier treatment and potentially improving patient outcomes [7].

Artificial intelligence in CAR T-cell therapy

Therapy with chimeric antigen receptor T-cell (CAR T-cells) is a modern, technologically advanced method of cancer treatment based on adoptive cellular immunotherapy. The treatment process uses the patient's own autologous T-cells, which are genetically manipulated *ex vivo* to express the tumor antigen-specific CAR receptor. T lymphocytes reprogrammed in this way, after intravenous administration to the patient, expand, recognize cancer cells, and destroy them. The antigens used so far as targets for modified T lymphocytes are CD19 on B lymphocytes and BCMA (B-cell maturation antigen) on plasmocytes, which allowed the registration of CAR T-cells products for the treatment of B-cell lymphomas, B-cell acute lymphoblastic leukemia and multiple myeloma [8–13]. Nowadays, this is an extremely effective complement to conventional treatment and hematopoietic target transplantation. Ongoing clinical trials show the enormous potential of this treatment, going beyond hemato-oncology.

Chimeric antigen receptor T-cells can produce durable remission in hematological malignancies not responding to standard therapy. Recently published and ongoing studies indicate high efficacy of the treatment in early disease phases, depending on the diagnosis. The treatment is associated however with a unique profile of toxicities that may limit its use [14]. On the other hand, CAR T-cells therapy is a very expensive treatment, and additionally requires the time and involvement of the latest technology to produce it [15]. Therefore, it seems that both the qualification for CAR T-cells therapy, as well as monitoring and possible interventions after the treatment, should be very precise.

From a clinical point of view, Artificial Intelligence could be used to combine biomarkers associated with CAR T-cells' response to built robust prognostic/predictive models. One challenge is that building robust models using AI requires the creation of large datasets, hence the need to aggregate data from multiple institutions to avoid overfitting.

Deep learning could contribute to determining the radiomics signature correlated with survival.

Several simple factors have been proven to be relevant to predict response to CAR T-cells therapy: Eastern Cooperative Oncology Group (ECOG) performance status, lactate dehydrogenase (LDH), C-reactive protein (CRP), and platelet (PLT) number. With AI, analysis of more sophisticated parameters is possible: tumor mutational burden; alteration in antigen presenting pathways; downregulation or tumor antigen loss; tumor microenvironment; and exhausted (senescent) phenotype. This data could be helpful in appropriate qualification to therapy, response prediction, relapse risk and timing (early vs late relapse) [16].

Deep learning could contribute to determining the radiomics signature correlated with survival.

Due to the availability of routinely performed imaging studies, and correlations of images with underlying biological processes, radiomics may serve as a new predictive tool in immune-oncology in the near future. Apart from the non-invasive identification of potential responders to therapy, addressing resistance mechanisms as well as the visualization of drug distribution and of the tumor microenvironment are major goals of radiomics in immune-oncology. Radiomics is based on common imaging modalities such as computed tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI). It aims to extract a large number of quantitative features from medical images using data-characterization algorithms. These features, termed 'radiomic features', have the potential to uncover tumoral patterns and characteristics that fail to be appreciated by the naked eye. This may be useful for predicting prognoses and therapeutic responses for various cancer types, thus providing valuable information for personalized therapy.

Perspectives of AI in CAR T-cell therapy

AI offers potentially endless possibilities in CAR T-cells therapy:

- creating virtual models to analyze safety;
- creating virtual models to analyze efficacy;
- developing a lymphodepleting treatment that ensures safety and efficacy by influencing the expansion of CAR T-cells;
- novel cancer-associated antigens;
- the possibility of designing new molecules.
- The medical community should however always bear in mind the potential hazards of AI.

Authors' contributions

LG, MG — equal.

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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REVIEW ARTICLE

VIA MEDICA

Outpatient CAR-T therapy

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Abstract

Chimeric antigen receptor T (CAR-T) therapy has recently revolutionized the treatment of aggressive lymphomas and acute lymphoblastic leukemia, and will soon do the same for myeloma and other hematological malignancies. Due to the risk of potentially life-threatening complications such as cytokine release syndrome (CRS) and immune effector cell associated neurological syndrome (ICANS), patients have been hospitalized for the time when those symptoms may have occurred. However, due to improved prognostic factors, diagnostics and treatment of CRS and ICANS, it is possible that in the near future certain groups of patients will be treated with CAR as outpatients. That would allow broader access to CAR therapy, lowering overall costs and improving patient quality of life. Patient selection for outpatient CAR treatment is a topic that has been extensively discussed but, even based on the experience we already have, can already be effectively performed. CAR as an outpatient could be particularly useful for younger patients with a low tumor burden who have an educated caregiver and whose CAR center is logistically capable of providing outpatient care.

Key words: CAR-T, outpatient, cellular therapy

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Introduction

Chimeric antigen receptor T (CAR-T) therapy has recently revolutionized the treatment of aggressive lymphomas and acute lymphoblastic leukemia following the registration in 2017 of two first-in-class cellular therapies: axicabtagen ciloleucel and tisagenlecleucel. Further therapies based on CAR-T technology will soon change the landscape surrounding the treatment of myeloma and other hematological malignancies. The high effectiveness of CAR-T therapy is associated with potentially toxic complications that require hospital care. Thus, CAR-T has a significant impact on the healthcare system not only due to the costs of the procedure itself, but also due to the demands of advanced medical care which may limit the development of this fascinating and efficacious technology. Outpatient care of patients being treated with CAR therapy may become an increasingly attractive option.

Experience of outpatient care of patients after CAR therapy

There are several different CAR constructs being used in aggressive lymphomas, acute lymphoblastic leukemias, and recently in multiple myeloma. Due to different variations in CAR structure and signaling, disease entity treatment, and manufacturing differences, the frequency, severity, and timing of two very challenging complications such as cytokine release syndrome (CRS) and neurological complications (ICANS, immune effector cell associated neurotoxicity syndrome) vary between CAR agents. The anticipated timing and probability of these complications may influence outpatient treatment decisions, and can be a determining factor in making inpatient versus outpatient treatment recommendations.

There have been no prospective clinical trials comparing outpatient versus inpatient care of patients being treated

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with CAR. There are, however, some reports on outpatient treatment from published prospective clinical trials. 27% of subjects from the Juliet study were treated with tisagenlecleucel in an outpatient manner [1], while 24% were so treated in the Eliana study [2]. It is worth mentioning that a 7-day hospital stay was mandated in an axicabtagen registration study (ZUMA-1) [3]. Likewise, in three studies on lisocabtagene, a total of 59 (18%) patients were infused and observed as outpatients [4]. Patients were defined as being treated as outpatients if they were infused as an outpatient or were discharged on the same day if they had been hospitalized before the infusion. Only 17% needed to be readmitted within the first four days, and 46% did not require readmission at all. Only 3% of them were eventually admitted to the intensive care unit. Eventually patients who stayed in the hospital upfront were hospitalized for a median 15 days (range: 2–98; n = 272), while those predefined as outpatients were hospitalized for a median of only 6 (range: 2–23 days; n = 18).

In another observation reported as a single center retrospective study of 30 patients treated with tisagenlecleucel, 70% were treated fully as outpatients and only eight needed readmission, due to CRS (five) and infection (three) [5]. Outpatient care of patients treated with CAR is now being widely allowed in clinical studies like the trial of a third generation CD20 targeted CAR (consisting of both CD28 and 41BB costimulatory domains) in patients with aggressive lymphomas or in a phase III study of cilta-cell [recently Food and Druga Administration (FDA) approved B-cell maturation antigen (BCMA) targeted second generation CAR for patient with refractory multiple myeloma] in newly diagnosed multiple myeloma patients [6, 7] suggests that outpatient administration of CAR will become more common and could become the standard of care for certain populations of patients.

Why CAR outpatient?

It is apparent that CRS and ICANS management algorithms used in real-world settings have confirmed the benefit of broader and earlier use of anti-cytokine therapies such as tocilizumab and glucocorticosteroids compared to the conservative and rigorous approach reported in early clinical studies. It has been shown in real-world and clinical trials that the earlier introduction of corticosteroid and tocilizumab does not influence efficacy, although they appear to mitigate CRS intensity and the risk of ICANS. This approach is reflected in today's international guidelines and regular practice in both formally registered CARs and those being used in clinical trials [8].

The commercialization of cellular therapies, which is an obvious consequence of their unprecedented efficacy, comes alongside the need to optimize medical resources. The expanding interest in outpatient care after CAR-T is one of the major factors that may decrease cost and eventually increase access to this procedure looked at from a whole population perspective, while from the individual perspective it improves quality of life.

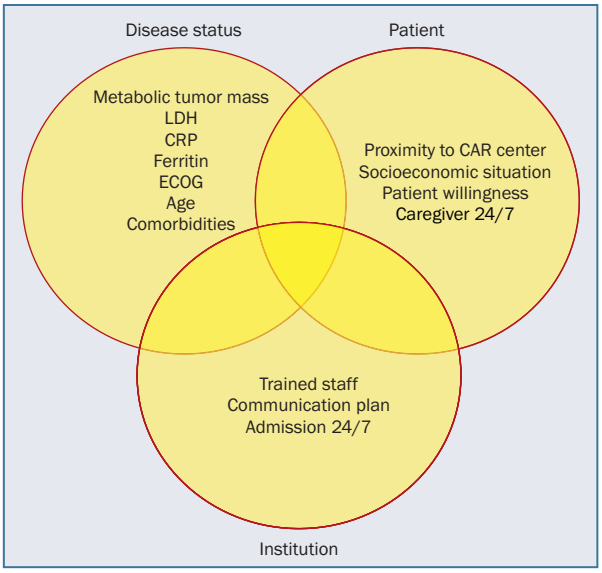

Figure 1. Conditions that need to be analyzed for outpatient chimeric antigen receptor (CAR) therapy; LDH — lactate dehydrogenase; CRP — C-reactive protein; ECOG — Eastern Cooperative Oncology Group

Such an outpatient approach certainly needs to be thoroughly thought through, taking into consideration a risk/benefit assessment, the greater predictability of clinical course, patient preference, and limited resource utilization.

Patient selection

There are several factors that have an impact on the decision as to who can be treated in an outpatient manner (Figure 1). First is the presence of sufficient logistics facilities in the CAR center, such as training classes for patients and caregivers, the 24/7 availability of medical staff for consultation, a developed communication plan within the multidisciplinary team, and the possibility of immediate admission.

The second is the ability of an individual patient and caregiver to stay near to the hospital that is capable of treating specific CAR-related toxicity. One of the most important factors is the caregiver — preferably a family member who will take care of the patient at home. The list of tasks is relatively long and consists of records of administered medications, body temperature, balance of fluids, and eventually the decision to contact medical staff when symptoms of potentially threatening complications occur. Proper patient and caregiver education on the complications that require immediate intervention is key for safe outpatient CAR therapy.

However, the most critical factors are those related to the probability, severity and time to onset of CRS and ICANS. Factors predicting severe CAR-related toxicity that might be contraindications for an outpatient approach are: activity of preinfusion lactate dehydrogenase, preinfusion C reactive protein and ferritin levels, metabolic tumor volume, comorbidities, age and Eastern Cooperative Oncology Group (ECOG) performance status [9], although these factors are not finally conclusive and longer observations need to be performed to create a clear algorithm in the inpatient/outpatient decision process.

Care after CAR infusion

Care given by the non-medical caregiver is important for successful and safe treatment with CAR therapy, although contact with trained medical staff is essential. There are several, slightly different, recommendations on how often and for how long a patient after CAR infusion should be seen by medical professionals. According to the Risk Evaluation and Mitigation Strategy (REMS) developed for tisagenlecleucel, the patient should remain for one month within two hours of the CAR center. Similar recommendations have been created for other CAR products. In an outpatient approach, the patient should visit the CAR center every day during the first week and 2–3 times in the second week to access potential complications in both clinical and laboratory aspects. Close contact is needed especially in the first week with readiness for admission if any severe or potentially severe complication occurs [9]. Additionally, patients and caregivers should have a wallet card setting out how to contact healthcare providers in life-threatening situations.

Patients should be readmitted when there is a fever suggestive of CRS, especially in coexistence with neutropenia. Any other clinical or laboratory symptom of infection should be used as an argument for readmission. Any patient with psychiatric or neurological abnormalities should also be considered for readmission.

Conclusions

CAR therapy is an emerging new standard of care in patients treated due to aggressive lymphomas, acute lymphoblastic leukemias, and (soon) multiple myelomas. Due to the high costs and the need to conduct therapy only in accredited centers, a possibility of outpatient care of patients after CAR therapy is an attractive option that will eventually increase access to cellular therapies. The determination of predictive factors of severity and time of onset of CAR-related toxicities and the optimization of supportive care and treatment of CRS and ICANS will identify patients who can be effectively and safely treated in an outpatient manner that eventually will become the standard of care.

Authors' contributions

DD, LG — wrote the manuscript.

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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Usefulness of training based on outcome of transfusion committee report: assessment by personnel involved in blood therapy

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Abstract

Introduction: We assessed three training formulas i.e. on-site, on-line and e-learning for members of transfusion committees, doctors responsible for blood management, other members of hospital staff, and blood establishment employees involved in blood transfusion.

Fundamental to a successful blood transfusion is the proper education of physicians, nurses and diagnosticians. External inspections of entities involved in blood transfusion revealed that continuous education should be extended to include also other personnel involved in blood transfusion.

Material and methods: Our analysis was based on statistical data from training courses and anonymous satisfaction surveys. Separate questionnaires were prepared for each type of training (on-site, on-line, and e-learning) and questions were adjusted to their specific characteristics. On-site and on-line courses had 659 and 260 participants respectively, and the e-learning module had 6,093. Altogether, 1,101 completed questionnaires were subjected to analysis.

The MS Excel program was used for analysis of questionnaire content and Microsoft Power Business Inteligence (Power BI) was used for data analysis and outcome visualization.

Results: 31% of respondents were members of transfusion committees (49% laboratory diagnosticians, 47% physicians, 4% nurses). On a 5-point scale, an average score of 4.3 was ascribed to sessions that helped upgrade professional qualification (4.37 — on-site, 4.59 — on-line and 4.31 — e-learning). 93.5% of the e-learning participants gave a rating of high or very high to the usefulness and effectiveness of such a formula; 95.6% declared their readiness to recommend it.

Conclusions: All three types of training were found to be useful in upgrading professional awareness. Regardless of the formula of training in which they participated, the responders acknowledged the importance and benefits of continuous training.

Key words: training, blood, transfusion committee

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Introduction

The proper training of medical personnel is one of the prerequisites of safe and effective blood therapy. Supervision over the transfusion chain is one of the responsibilities of the Institute of Hematology and Transfusion Medicine (IHTM) within the framework of the hemovigilance system. An analysis of TC reports and inspections performed by blood establishments (BEs) in hospitals, immunohematology laboratories and hospital blood banks revealed that many areas appertaining to blood transfusion still require improvement, from the basic organization of blood therapy right through to the principles of BE/hospital cooperation and supervision over blood transfusion. Lack of adequate knowledge was determined to be the main reason for the identified non-compliances, and so training of medical personnel became one of the prerequisites of safe and effective blood therapy. Knowledge and expertize are transferred to the medical personnel during external and internal training sessions. The transfusion practice in hospitals is supervised either by physicians appointed responsible for blood management or by transfusion committees. The tasks include monitoring the safe administration of blood components, the analysis of adverse events and reactions, as well as the organization of training courses for medical personnel [1, 2]. For many years now, attention worldwide has been focused on the role of transfusion committees [3, 4].

Ensuring an adequate educational background of physicians, nurses and diagnosticians is fundamental to safe blood collection and transfusion. In Poland, physicians employed in BEs or hospitals have the opportunity to pursue specialization in clinical transfusion medicine. Since 2001, all laboratory diagnosticians with higher education have been offered the opportunity to specialize in laboratory transfusion medicine.

External inspections and analysis of TC reports revealed that continuous education should also be offered to other staff involved at all stages of the blood transfusion chain, and not only to the personnel trained during specialization courses. The two data sources revealed insufficient awareness as regards blood transfusion practices, alternative blood sources, special blood components (i.e. irradiated, inactivated, *etc.*), and handling of adverse reactions and events (ARE) [5, 6].

Knowledge and skills are acquired via training. In Poland, a different scope of training applies to BE personnel and to hospital staff directly involved in transfusion procedures. In-house training has been obligatory for BE staff for many years now, but this has not been the case for hospital staff.

Since 2005, hospitals performing transfusions have appointed physicians responsible for blood management who are obliged to participate in training courses every four years [7]. The same is true of nurses licensed to participate in blood transfusions; after initial theoretical and practical training, they must participate in training every four years. The quality of blood components is also safeguarded by transfusion committees (TCs) which, pursuant to Polish regulations, are established in every transfusion-performing hospital with a minimum of four wards.

Extremely important is continuous training. In 2005–2009, the IHTM cooperated with the Portuguese Blood Institute (*Instituto Português do Sangue e da Transplantação*) in organizing a major training campaign within the Transition Facility project [8]. This program was dedicated primarily to BE staff. Continuious training of BE personnel is mandatory and should be controlled by the IHTM as the competent authority.

The project outcome captured the attention of the Polish Ministry of Health, and its 2010 health policy program allocated separate ministerial funds for countrywide training.

The health policy program 'Ensuring the self-sufficiency of the Republic of Poland in blood and blood components for the years 2015–2020' provided funds for on-site training as well as e-learning in 2017–2020. Training activities also included the publication of the 'Standard for Activity of the Transfusion Committee' [9, 10]. Until then there had been no clear guidelines for the training of TC members. The publication of 'Standard for Activity of the Transfusion Committee'filled the gap between self education and training courses.

The SARS-CoV-2 pandemic induced a broader outlook on training and educational activity. On-site training had to be replaced by new forms of educational activity.

Our study aim was to assess the three training formulas (i.e. on-site/stationary, on-line, and e-learning) addressed to TC members, physicians responsible for blood management, and also to other members of hospital staff involved in blood transfusion, as well as to BE and hospital laboratory diagnosticians performing tests for transfusion.

Material and methods

Our material for analysis was statistical data from training courses as well as from anonymous satisfaction surveys completed by participants. Separate questionnaires were developed for each of the three training formulas: stationary/on-site, on-line, and e-learning. The questions were adjusted to the specific characteristics of each type of training, but some items were common to all three. Representatives of hospitals performing blood transfusion participated in each of the three training modules, while BE employees participated only in e-learning and on-line sessions.

Table I presents the number of training sessions and participants in two types of training (stationary and on-line) organized in 2017–2020. E-learning was launched in November 2018. Figure 1 shows the number of participants

Table I. Data referring to on-site and on-line training courses

Year	Type of course	Professional group							
		Physicians		Nurses and midwives		Laboratory diagnosticians		Total	
		No. courses	No. participants	No. courses	No. participants	No. courses	No. participants	No. courses	No. participants
2017	On-site	1	32	1	45	1	42	**3**	**119**
2018	On-site	2	80	2	86	2	85	**6**	**251**
2019	On-site	2	84	2	84	2	84	**6**	**252**
2020	On-site	0	0	0	0	1	37	**1**	**37**
2020	On-line	2	94	2	92	1	74	**5**	**260**
Total		**7**	**290**	**7**	**307**	**7**	**322**	**21**	**919**

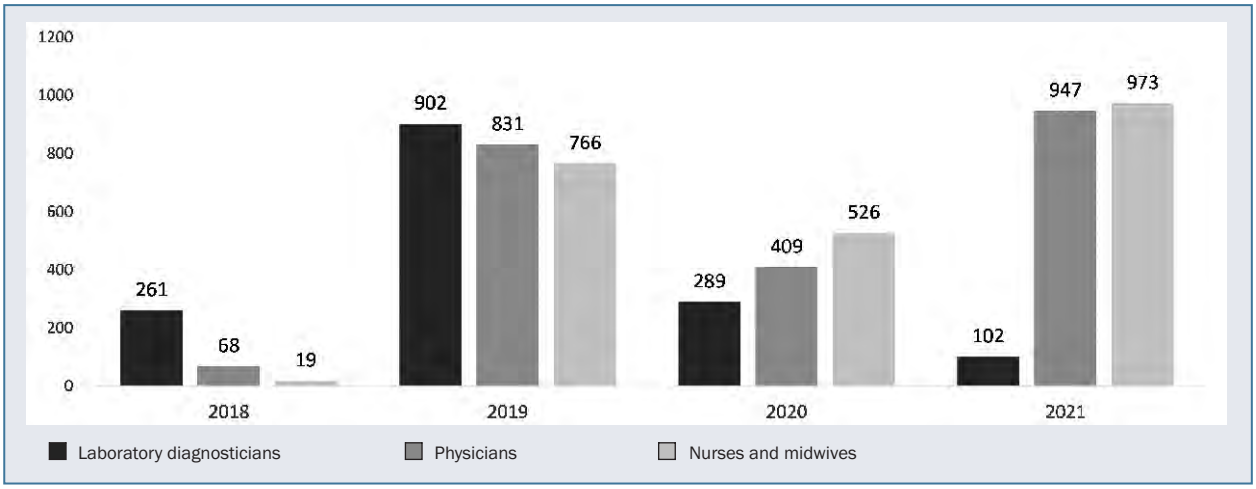

Figure 1. E-learning platform users in period November 2018 to April 2021

of e-learning training between November 2018 and April 2021. A total of 6,093 participants were recorded: 1,554 diagnosticians, 2,255 physicians, and 2,284 nurses. By the end of 2020, a total of 4,071 participants had completed training; 1,452 diagnosticians, 1,308 physicians, and 1,311 nurses. In 2021, the e-learning formula was the only form of educational training.

Lecture topics were adapted to each professional group and covered issues related to the transfusion of blood components. The educational material was tailored to each professional group, with the emphasis on daily routine performance. Each on-site and on-line course consisted of 15 lectures (a 40 min presentation and a 5 min Q&A). The e-learning course comprised 17 lectures divided into 2–3 parts of approximately 10–15 min each. The Q&A module was accessible. Formal tests followed each course. These test results are not the subject of this paper. The topics discussed during training courses were:

- blood transfusion service in Poland, with emphasis on legal acts, organization of blood transfusion therapy in hospitals;
- preparation, use and storage of blood components and blood products;
- indications for the use of blood components and blood products;
- principles of patient blood management (PBM);
- therapeutic procedures — aspects of safe transfusion;
- role of nurse in transfusion process (from ordering of transfusion to adverse reaction/event);
- autologous transfusion and PBM implementation in hospital setting;
- aspects of safe transfusion of blood and blood components;
- adverse events and reactions including serious and clinical cases;
- immunohematology: significance for safe transfusion;
- appropriate provision of blood components;
- organization and tasks of blood banks;
- cooperation between hospital ward, immunohematology laboratory, and blood bank;
- pathogens in transfusion medicine;

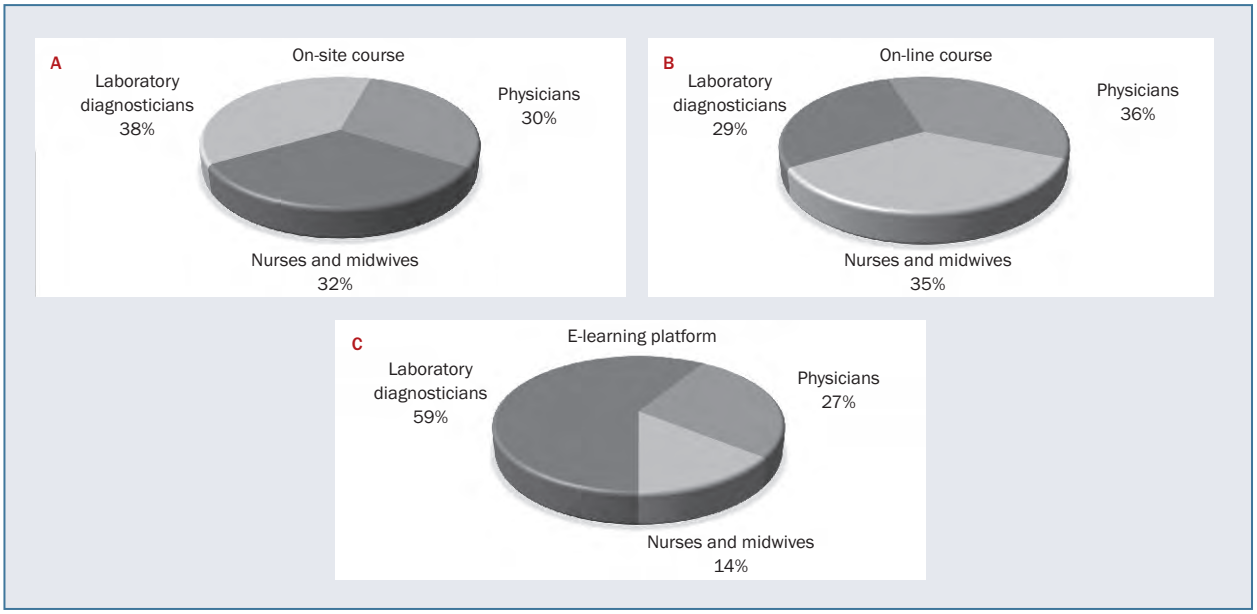

Figure 2A–C. Percentage distribution of professional groups as participants in three types of training course

- tasks of transfusion committee and doctor responsible for blood management;
- importance of IT in transfusion medicine;
- quality assurance system;
- risk management in transfusion medicine;
- and hemovigilance.

Questionnaires

Apart from confirmed participation and passing the test, on-site and on-line training required completion of an anonymous satisfaction questionnaire. Only then were certificates issued. For e-learning participants, the survey was anonymous and voluntary.

Stationary training provided 659 paper questionnaires which were subjected to analysis. On-line training contributed 260 computer-administered questionnaires collected in digital form with special online survey software and subjected to analysis. E-learning platform users were asked to complete an online satisfaction survey in January 2021. The survey link provided via Google Forms remained active only for five weeks, during which 182 participants responded.

The three training formulas thus rendered altogether 1,101 questionnaires.

Methods

For more effective analysis, three MS Excel tables were developed to include survey responses in each training module.

Paper-responses (i.e. to on-site training) were entered into a special table, while electronic responses (i.e. to on-line training and e-learning) were sorted out and transferred into two separate table-templates.

Microsoft Power Business Intelligence (Power BI) was used for data analysis and visualization of the outcome.

Results

In the on-site formula, the highest number of questionnaires was completed by laboratory diagnosticians (248), then by nurses and midwives (215), and then by physicians (196). Among on-line participants, the most numerous group were physicians (94), then nurses and midwives (92), and laboratory diagnosticians (74). The number of completed questionnaires corresponded to that of participants.

While the survey link was active, the questionnaire was completed by 182/4,071 e-learning platform users (4.47%). The 182 comprised laboratory diagnosticians (107), physicians (49), and nurses and midwives (26).

Figure 2 presents the percentage distribution of professional groups with regard to responders of all three training modules.

A very large majority of all responders were women (86%). Figure 3 presents the percentage distribution of women and men broken down by professions.

The e-learning platform survey included questions referring to age. For all three professions, the 25–33 and 34–41 age groups were the most numerous (28% for both). The 49–57 and 41–49 age groups had 24% and 15%, respectively, and the 58–65 age group was the least numerous (5%). Another question referred to membership in the hospital TC and rendered 31% affirmative answers. Most TC members were laboratory diagnosticians and physicians (49% and 47% respectively). Only 4% of nurse-responders declared TC membership.

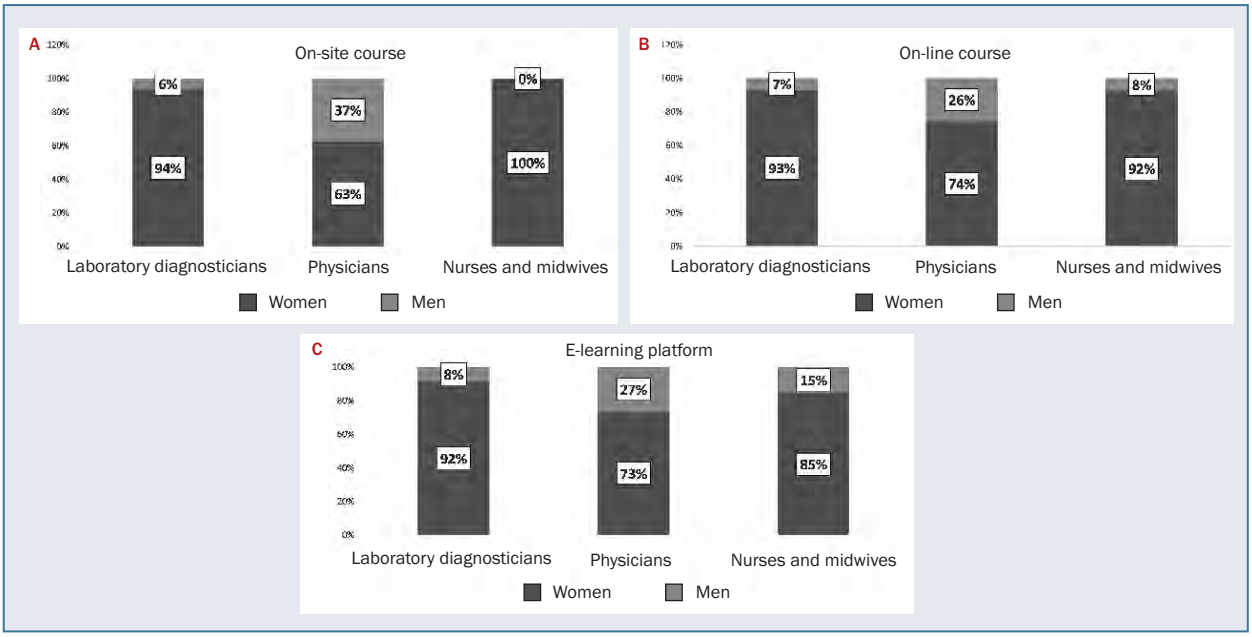

Figure 3A–C. Percentage distributions of men and women as participants in three types of training course broken down into professional groups

Usefulness of the educational content in terms of gaining professional qualifications was estimated by all participants (three modules) on a five-point scale. The educational material was rated very high by all (>4.3 on average, and the highest scores went to on-line training (average rating: 4.59). Participants of the stationary courses and platform users estimated the usefulness of the acquired knowledge at 4.37 and 4.31, respectively. Table II presents the outcome for each professional group.

As regards the uselessness of any lecture, affirmative answers were provided only by 11% of e-learning responders, 6.4% of stationary training responders, and 6.2% — on-line trainees.

Most responders found all topics useful for their daily practice; the least useful referred to organizational issues, legal regulations, immunohematological tests, and blood component administration. Suprisingly, other participants found these very topics worth expanding. The topics indicated as being the least useful were usually those not directly related to the responders' routine tasks. These topics were included in the program to broaden knowledge about transfusion medicine and upgrade the overall performance level.

Regarding the topics to be expanded, most affirmative answers came from e-learning users (37.4%), on-line training participants (15.8%), and in-house training participants (2.4%). The following subjects were the most frequent:

- practical classes, clinical cases;
- immunohematology tests — new challenges, regulations, difficult cases;
- blood therapy in specific patients (e.g. children, transplant recipients);

Table II. Average score in response to survey question: "How useful is the knowledge gained during training for upgrading professional qualifications? (5-point scale)"

Professional group	On-site course	On-line course	E-learning platform
Laboratory diagnosticians	4.33	4.65	4.47
Physicians	4.34	4.49	4.27
Nurses and midwives	4.43	4.62	4.19
Mean	**4.37**	**4.59**	**4.31**

- hemovigilance, serious adverse events and reactions (SARE);
- pathogens;
- and indications for transfusion of blood components on specific examples.

Users of the e-learning module were also asked to assess the usefulness and effectiveness of this form of training, and to declare willingness to recommend it to others. Figure 4 presents the provided answers.

The e-learning platform users were also asked their opinion of the most valuable, and the most burdensome, aspects of such training. They indicated as the most advantageous:

- free access to educational material;
- availability of the course at any time;
- possibility of coming back to previous lectures;

Figure 4. Response to "How do you assess the usefulness and effectiveness of this form of training?" (**A**) and "Would you recommend this training to other people?" (**B**)

- possibility of listening to lectures regardless of location;
- advantage of recorded audio material over 'stationary' lectures;
- and time saving.

They emphasized the extensive knowledge and experience of the lecturers, and appreciated the Q&A option and formal tests after each lecture.

The aspects they found the most inconvenient were:

- problems with concentrating for long periods in front of a computer monitor;
- and no face to face or direct contact with lecturer, and no possibility of asking questions during replay of video-recorded lectures.

Most participants found no negative aspects, while some others suggested making all submitted questions and answers seen to other users. The platform provided the option of a discussion forum, but not all participants were eager to make use of this.

Discussion

In Poland there have been to date no evaluation studies on the activity of TCs, nor countrywide-training dedicated to TC members and other personnel involved in transfusion. There has been no available data for assessment of the current state of knowledge. Preliminary analysis of TC annual activity protocols indicated inadequate knowledge among personnel.

This study offers extensive material for assessment of the effectiveness of educational training. Our evaluation criteria referred not only to the assessment of blood transfusion procedures or to the number of observed ARE, but also to the up-grading of procedures for reporting SARE to the competent authority. According to the data forwarded to the IHTM, the number of reported SARE has markedly increased recently [11]. The significance of reporting such incidents as well as their interpretation have been strongly emphasized during training sessions. Clinical cases were discussed at length to illustrate what should be reported and how to improve self-awareness in this respect. In 2017–2019, the number of SAREs reported to the Institute (as the competent authority) increased from 71 to 196. The 152 reports in 2020 may be attributable to a SARS-CoV-2–related smaller number of donations and transfusions [own information]. Feedback from trainees revealed better self awareness as a result of the completion of courses to be positively associated with a higher reporting rate for SAREs.

Education in transfusion medicine for medical students and residents is often insufficient. It therefore seems necessary to develop formal training programs/curricula to assess the outcome and enforce cooperation both at national and international levels [12]. Although traditional classroom training has always been considered adequate, training based exclusively on printed material is usually ineffective [2, 4]. Recently, attention has focused on new training techniques targeted at medical students and residents. One such example is e-learning [13–15].

Miller et al. [16] draws attention to the role of transfusion practitioner (TP) and the TC. In both cases, solid background knowledge about transfusion medicine is essential for adequate daily performance. Special training programs for TPs and TC members are required to upgrade the safety of transfusion as well as new techniques and modalities [16].

Our study demonstrates that the trainees who completed the courses found all three modules to be beneficial for training of personnel in transfusion medicine.

The current epidemiological situation has enforced the remote training formula as one of the most advantageous solutions. Adjusting the training modality to the needs of the particular professional group seems to be a top priority [17]. The impact of the SARS-CoV-2 pandemic on the number of e-learning participants is evident. In Poland, the obligatory 4-year interval between training courses for physicians responsible for blood management and for nurses was extended by nine months. In 2020, the interest in the e-learning platform was lower, most likely because medical personnel had more pandemic-related tasks. The first months of 2021 however witnessed a rapid increase in the number of trainees, most likely due to the expiry of licenses for medical staff as well as the absence of opportunity to organize in-house training.

Analysis of the e-learning questionnaires demonstrates high (45%) and very high (48%) satisfaction rates. Almost 78% were willing to recommend this form of training.

The e-learning trainees were also asked about practical application of the acquired knowledge. The average rating was 4.3 (on a 5-point scale), while the level of satisfaction was rated 4.45. The tutors (stationary and online training) were assessed for content and lecture presentation; the purpose was to confirm the choice of the lecturing team. A high level of tutorial knowledge was confirmed: 91.2% of respondents (e-learning platform) declared the training course to have met their expectations and that the acquired knowledge improved the quality of their daily performance.

Discussions with trainees revealed greater self-awareness of the significant role of TCs and doctors responsible for blood management because lecturers strongly emphasized some aspects related to safety, risk management and SARE. Focus on TCs activity helped the participants realize its significance for transfusion-related activities.

As mentioned earlier, in 2017–2020, on-site training for medical staff who were members of transfusion committees was financed from the health policy program. The aim was to expand education in transfusion medicine. The e-learning platform launched as part of this program was dedicated to continuous and regular self-education in blood transfusion. This platform comprised the educational material presented during stationary and on-line courses: 176 films, 291 quizzes, 30 PDF files and 30 presentations with additional materials, and 30 video files in mp4 format.

Unlimited access to the e-learning platform also provided opportunities for medical personnel who were not directly involved in transfusion practice activities but who were eager to acquire skills in this field. Such was the approach of most responders of the e-learning platform. A similar approach has also been observed in other countries [18].

Adequate training of medical personnel is essential for safe transfusion. Morgan assessed the effectiveness of training in transfusion medicine for medical students and residents, and stressed the value of such training [2]. The courses contributed to the development of theoretical and practical skills, and were highly rated. Numerous studies have emphasized the need to upgrade knowledge in all professional groups involved in transfusion medicine. Inadequate knowledge means poor cooperation between the professional groups involved in transfusion procedures, which may lead to higher morbidity and mortality and ultimately to higher treatment costs [1, 4, 13–15]. Study results (our own included) indicate satisfaction with the training and awareness of the significance of continuous training. Peterson et al. have presented an excellent example of an e-learning module conducted since 2007, with over 400,000 trainees from 1,500 hospitals and organizations. A survey completed by 3,885 responders revealed that 89.3% gained additional knowledge in transfusion practice, and 87.6% believed that this knowledge would impact on therapy outcomes and patient safety [19]. Our survey outcome was similar. Training could be implemented both on a national scale and in hospitals [20]. Internal training programs could be tailored to the hospital profile while a uniform educational training program is recommended to facilitate the exchange of experience.

Participants' comments revealed numerous topics as requiring more profound discussion. Growing awareness regarding transfusion procedures and of ARE/SARE, as well as the necessity of reporting them to the competent authority (IHTM), was also observed. Our analyses identified the areas of transfusion medicine that still require improvement and implementation of advanced regimens and methods of blood and blood component therapy as well as novel solutions, guidelines and regulations for strengthening donor and recipient safety.

To this purpose however, training and educational activities must be supported by legal regulations, guidelines and governmental financing.

Authors' contributions

JAP — conceived and planned study design. JAP, AM and KS — performed research and contributed to data analysis. JAP wrote paper with input from all authors. All authors approved 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; Uniform requirements for manuscripts submitted to biomedical journals.

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Treosulfan-based conditioning vs. low-dose busulfan-based conditioning for allogeneic hematopoietic stem cell transplantation: a cost-utility analysis in Poland

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Abstract

Introduction: In Poland, busulfan conditioning is used for allogeneic hematopoietic stem cell transplantation (allo--HSCT). Cost-utility analyses comparing alternative conditioning regimens in patients undergoing allo-HSCT have not been conducted so far.

Material and methods: A United Kingdom-based partitioned survival model was adapted to the Polish setting to compare treosulfan to low-dose busulfan conditioning regimen from the public payer's perspective in Poland. Patient characteristics, overall survival (OS), event-free survival (EFS), and the rate of adverse events were obtained from the randomized MC-FludT.14/L trial. Parametric survival models of up to 5 years (the cure threshold), with subsequent mortality defined using survival of the general population of Poland adjusted for cancer survivors, were used to extrapolate OS and EFS beyond the trial duration. Published utilities were adjusted for age using age-dependent general population utilities. The costs of treatment, adverse events, and inpatient/outpatient care were assessed via official remuneration schemes.

Results: Treosulfan-based conditioning outperformed low-dose busulfan, i.e. it was more effective with incremental quality-adjusted life years (QALY) of 0.78 and less expensive by 1,139 PLN per patient over the lifetime horizon. Deterministic sensitivity analyses revealed treosulfan was highly cost-effective (i.e. incremental cost-utility ratio was lower than the gross domestic product per capita in Poland) compared to low-dose busulfan, if most uncertain parameters are changed or alternative scenarios are implemented. The probability of treosulfan being cost-effective with a threshold of 155,514 PLN was 99.6%.

Conclusions: Compared to low-dose busulfan, treosulfan is a highly cost-effective conditioning regimen for allo-HSCT patients ineligible for standard conditioning regimens.

Key words: cost-effectiveness, cost-utility, treosulfan, busulfan, hematopoietic stem cell transplantation

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Introduction

Myelodysplastic syndrome (MDS) is a group of diverse bone marrow abnormalities associated with ineffective hematopoiesis, which manifest as morphologic dysplasia as well as ineffectual production of blood cells resulting in peripheral blood cytopenias. The incidence of MDS is approximately 3–4 cases/100,000, with about 20,000 cases annually being high risk. However, it should be stressed that the actual incidence of this disease could be significantly higher due to its nonspecific symptoms, which often include anemia, fatigue, weakness, intolerance of physical exertion, angina, as well as cognitive impairment [1–3]. Due to its symptom burden, MDS significantly negatively affects quality of life. Moreover, it can be associated with a high social and economic burden, as well as significant utilization of health care funds [3]. In many patients, especially those with indolent or rapidly progressive MDS, along with those with complications secondary to profound cytopenias, myelodysplastic syndrome can progress to acute myeloid leukaemia (AML) [2, 3]. AML consists of multiple clonal hematopoietic disorders which result in proliferation of immature myeloid cells in the bone marrow. Accumulation of the leukemic blasts of myeloid lineage leads to an impairment of hematopoietic function, which results in the occurrence of cytopenias, with or without leucocytosis [3]. Acute myeloid leukaemia is the most common form of adult acute leukaemia, with 18,860 diagnosed cases and 10,460 deaths in the USA in 2014 [4].

Allogeneic hemopoietic stem cell transplantation (HSCT) plays a crucial role in the management of adult patients with myelodysplastic syndrome or acute myeloid leukemia [5, 6]. In fact, these two diseases account for more than half of the HSCT indications for malignant diseases worldwide, while in the USA alone in 2010, AML was the most common indication for this procedure [5, 7]. This is because, to date, hemopoietic stem cell transplantation remains the only curative treatment for acute myeloid leukemia and intermediate-to-high-risk myelodysplastic syndrome [3, 8]. However, HSCT itself can be associated with a plethora of significant adverse events, as well as increased treatment-related mortality [7]. Therefore, before allogeneic hematopoietic stem cell transplantation, it is necessary for patients to undergo conditioning treatment aimed at eradicating disease remnants and weakening the recipient's immune system [9].

For this purpose, myeloablative therapy is used, which usually uses high-dose cyclophosphamide in combination with whole-body radiotherapy or high-dose busulfan. Nevertheless, due to the relatively high toxicity, as well as veno-occlusive diseases, and significant risk of mortality after such therapy, it can only be used by relatively young patients (up to 50–55 years of age) who are in good general condition. Older patients, as well as those in poor general condition, with lower performance status, and greater burden of comorbidities, may be referred to a lower-intensity conditioning treatment, usually involving lower doses of intravenous busulfan and an infusion of fludarabine [3, 10]. However, using the reduced-intensity conditioning can be problematic, because such a regimen, aimed to induce sufficient immunosuppression to enable engraftment, mostly relies on the graft-versus-malignancy effect for the curative results. Therefore, conditioning treatments of reduced intensity are associated with a higher risk of relapse compared to standard regimens. This is a significant limitation and poses a major obstacle to successful transplantation [11].

Therefore, the current development of preparative regimens before allogeneic HSCT is addressing an unmet medical need for the growing number of patients with myelodysplastic syndrome or acute myeloid leukemia. Providing better access to the therapy for patients would seem to be crucial in order to improve clinical outcomes [5] It is a particularly significant unmet need because myelodysplastic syndrome is usually diagnosed among older adults (80% of adult diagnosed patients are ≥70 years), while the diagnosis of acute myelogenous leukemia most often happens between the ages of 68 and 72. Additionally, considering the phenomenon of population ageing, it can be assumed that both MDS and AML in years to come will be ever more frequently encountered in geriatric practices [3, 5].

A conditioning treatment prior to allogeneic hematopoietic cell transplantation that could be used in older patients is treosulfan therapy in combination with fludarabine. The results of a study [5] indicate that the effectiveness of this therapy may be even higher than the standard of conditioning treatment with reduced activity [5], but therapy with intravenous busulfan and fludarabine is unavailable in Poland. Currently, treosulfan is not financed from public resources in Poland. Among the drugs containing the active substance treosulfan, the drugs authorized in Poland are powders for solution for infusions: treosulfan (5 g and 1 g in 50 mg/mL; 1 or 5 vials) [12, 13].

So we performed a cost-utility analysis to compare treosulfan and fludarabine conditioning to low-dose busulfan and fludarabine-based conditioning prior to allogeneic hematopoietic stem cell transplantation (allo-HSCT) in patients considered ineligible for standard conditioning regimens in Poland.

Material and methods

A partitioned survival model developed for a UK setting and positively appraised by the Evidence Review Group (ERG), commissioned by the National Institute for Health and Care Excellence (NICE) [14], was adapted to a Polish setting by the inclusion of input data specific to patients from Poland. In the model, patients started in the induction/allo-HSCT health state, before transitioning to allo-HSCT recovery

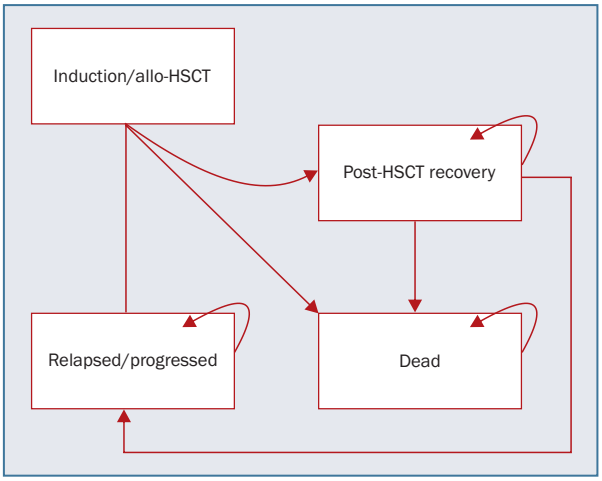

Figure 1. Model diagram; allo-HSCT — allogeneic hematopoietic stem cell transplantation

(remission), relapse/progression/graft failure, and/or death after the first model cycle (Figure 1). A cycle length of 28 days and half-cycle correction were applied. The time horizon was a lifetime (50 years). The costs and QALYs were discounted by 5.0% and 3.5% annually, respectively.

The population was the same as in the MC-FludT.14/L trial [5], which was a randomised non-inferiority phase 3 trail in 31 transplantation centres in France, Germany, Hungary, Italy, and Poland. Eligible patients were 18–70 years, had acute myeloid leukaemia in first or consecutive complete haematological remission (blast counts <5% in bone marrow and included patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) considered ineligible for standard conditioning regimens before allo-HSCT. The regimens were as follows: intravenous treosulfan at a dose of 10 g/m^2 of body surface area daily for 3 days and intravenous busulfan at a dose of 0.8 mg/kg every 6 hours (or 3.2 mg/kg daily) for 2 days, both with 30 mg/m^2 of intravenous fludarabine daily for 5 days.

Data on patient characteristics, overall survival (OS), event-free survival (EFS), and adverse events [stage III/IV acute and extensive chronic graft-versus-host disease (GvHD), other grade 3+ adverse events with ≥1% incidence in either treatment arm] were collected from the MC-FludT.14/L trial. Parametric survival models were used to extrapolate OS and EFS beyond the trial duration. Standard parametric models, commonly used (Weibull, lognormal) mixture-cure models (MCM), and commonly used (Weibull, lognormal) non-mixture-cure models (NMCM) were fitted to the full survival datasets from the MC-FludT.14/L trial. Survival analyses were conducted for the pooled AML and MDS cohorts, as well as separately for the AML and MDS subpopulations stratified by treatment arm. For consistency, the same model type was used for each arm both for treosulfan and busulfan [15]. The NMCM log-normal distribution for EFS and NMCM Weibull distributions for OS were selected in a base-case analysis on the basis of their statistical fit (Akaike information criterion), visual inspection, and clinical validity. The base-case model used an extrapolation method selected by the Evidence Review Group in the UK [5]. Five different variants of long-term extrapolation were considered: 1) parametric models fitted to trial data; 2) parametric models or general population life tables, depending on which had the higher mortality rate; 3) parametric models or standardized mortality ratio (SMR)-adjusted general population life tables, depending on which had the higher mortality rate; 4) parametric models up to a cure threshold, followed by a switch to general population life table mortality rates; and 5) parametric models up to a cure threshold, followed by a switch to SMR-adjusted general population life table mortality rates. The latter variant was considered in a base-case analysis as allo-HSCT is a potentially curative treatment: the relapse rate after 5 years is minimal according to clinical experts and the assumption was incorporated in other economic evaluations on the topic [5]. Prior to the cure threshold, the parametric curves for OS and EFS were used. After the cure threshold, mortality was determined by using life tables for the general population [16] adjusted with SMR for HSCT (2.3. calculated in [17] based on data from Martin et al. [18]). In the base case analysis, the cure threshold was assumed to be 5 years post-HSCT, as patients surviving allo-HSCT for at least 5 years are considered to be cured in clinical practice.

Quality-of-life data was not collected during the MC-FludT.14/L trial. Therefore, health-related utilities were sourced from published studies. For estimating post-HSCT recovery utility, data from Grulke et al. 2012 [19] was mapped to the utilities using an algorithm by Proskorovsky et al. 2014 [20] (data from Castejon et al. 2018 [21] were used in a scenario analysis). Relapse/progression and adverse event utilities were based on previous models submitted to the NICE [22], while disutilities for graft-versus-host disease events were obtained from Kurosawa et al. 2016 [23] with the assumption that disutilities for grade 3–4 acute GvHD are the same as for chronic GvHD. The utilities were adjusted according to the difference in the mean age of patients in studies used for utility calculation and the mean age of patients at baseline in the MC-FludT.14/L trial (59.6 years) as well as during each cycle of the time horizon. The adjustment was made with age-dependent utilities of the general Polish population [24].

Detailed information on the original model is available in the studies by Westwood et al. [14] and Bungey et al. [25].

The economic analysis was conducted from a public payer's perspective, i.e. the National Health Fund (*Narodowy Fundusz Zdrowia* or NFZ in the Polish acronym). Conditioning treatments are not directly financed from public funds in Poland. The NFZ does not directly finance

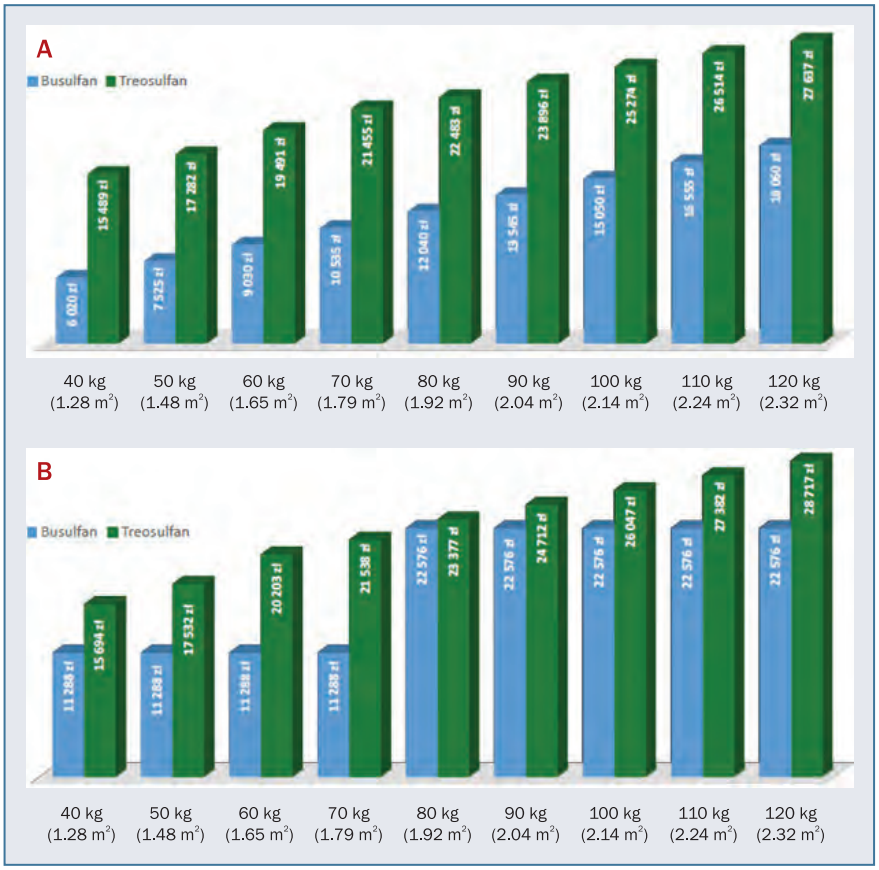

Figure 2. Comparison of treosulfan and low dose busulfan costs per patient by body weight and body surface area: cost of drug administered to patient without cost of unused portion of vial, i.e. scenario without wastage (**A**); cost of drug administered to patient and cost of unused portion of vial with assumption that 100% of unused drug is disposed of, i.e. scenario with full wastage (**B**)

treosulfan, busulfan, and fludarabine used in this indication. Polish hospitals buy these drugs from the funds allocated to diagnosis-related groups [in Polish: *jednorodne grupy pacjentów* (JGP)] designed for allo-HSCT (i.e. JGP S22 'Transplantation of allogeneic hematopoietic cells from siblings identical in HLA' or S23 'Transplantation of allogeneic hematopoietic cells from an alternative donor'). The JGPs are designed to cover the costs of mobilization, conditioning, transplantation, and post-transplant hospitalization up to 30 days, with an additional cost for each day of inpatient stay beyond 30 days. Because of the difference in the total costs of treosulfan and busulfan treatment (treosulfan has a higher acquisition cost compared to low-dose busulfan, Figure 2), and lack of direct reimbursement from the public purse (the hospital acquires these drugs using the funds allocated to the allo-HSCT procedure), treosulfan is not commonly used in Poland.

To assess whether the higher price of treosulfan vs. low-dose busulfan is justified, we assumed that the NFZ would directly finance the cost of treosulfan, while busulfan and fludarabine would not be separately financed by the NFZ. Hence, in the base-case analysis, the cost of conditioning treatment and allo-HSCT included: 1) the cost of treosulfan and allo-HSCT (JGP S22 or S23) in the treosulfan arm; and 2) the cost of allo-HSCT alone (JGP S22 or S23) in the busulfan arm. The remaining costs (i.e. adverse events, post-HSCT care, disease relapse/progression) were the same for both arms, while only the risk of these events differed between the arms.

The cost of treosulfan and busulfan was based on average gross wholesale prices in Poland (445.07 PLN and 1,948.05 PLN for 1,000-mg and 5,000-mg vials of treosulfan, respectively; 1,410.97 PLN for a 60-mg vial of busulfan). The cost of allo-HSCT procedure was based on the current unit cost of JGP S22 or S23 [26] and related statistics in 2019 (number of patients and length of hospital stay for each JGP) [27]. The average cost of allo-HSCT with healthcare provided up to 42.1 days after the admission to hospital for allo-HSCT was 237,865.89 PLN. The cost of drugs used for disease relapse/progression was estimated based on the average unit price of those drugs in 2020 [28] with utilization obtained from the original model [5, 25] (based on treatment guidelines and clinical expert opinions, with the usage assumed to be equally distributed among patients relapsing/progressing in the first year as well as patients relapsing/progressing after

Table I. Main inputs for base-case model

Parameter	Value	Source
Age (mean) [years]	59.6	MC-FludT.14/L trial
Weight (mean), kg/body surface area [m^2]	80.2/1.93	
Matched unrelated donor [%]	76.4%	
Sex (male) [%]	60.8%	
Cure threshold	5 years	Assumption
SMR after cure threshold	2.3	Martin 2010 [21]
Utility of induction/allo-HSCT	0.558	Grulke et al. 2012 [22] (algorithm by Proskorovsky et al. 2014 [23]) adjusted with data from [27]
Post-HSCT recovery utility: discharge	0.660	
Post-HSCT recovery utility: ≤6 months	0.756	
Post-HSCT recovery utility: 7–12 months	0.818	
Post-HSCT recovery utility: year 2	0.822	
Post-HSCT recovery utility: year 3	0.822	
Post-HSCT recovery utility: year 4+	0.870	
Relapse/progression	0.623	[25] adjusted with data from [27]
Graft-versus-host disease disutility	–0.120	[26]
Grade 3+ adverse events disutility	–0.024	[25]
Cost of allo-HSCT with treatments and care up to 42.1 days after procedure: treosulfan arm	261,507.71 PLN (with total cost of treosulfan at 23,376.60 PLN included)	Data from selected drug wholesalers on treosulfan price [29–31], assumption
Cost of allo-HSCT with treatments and care up to 42.1 days after procedure: busulfan arm	240,583.59 PLN without separate cost of busulfan	[29–31]
Cost of allo-HSCT recovery/remission — <12 months	2,448.56 PLN per cycle	[29, 30, 32]
Cost of allo-HSCT recovery/remission — 12–24 months	2,031.64 PLN per cycle	[29, 30, 32]
Cost of allo-HSCT recovery/remission — >24 months	83.38 PLN per cycle	[29, 30, 32]
Cost of early relapse/progression (<12 months)	5,094.91 PLN per cycle*	[18–30, 32]
Cost of late relapse/progression (≥12 months)	120,291.79 PLN per 1st cycle, 4,552.34 PLN per cycle**	[18–30, 32]
End-of-life cost	7,197.94 PLN per event	[32]
Additional cost of graft-versus-host disease	17,593.00 PLN per event	[32]
Grade 3+ febrile neutropenia, lung infection, or syncope	10,440.00 PLN per event	Assumption [29, 32]
Grade 3+ sepsis	11,789.00 PLN per event	Assumption, [29]
Grade 3+ other adverse events	71.00 PLN per event	Assumption [29, 32]

*Assumes equal probability of receiving hypomethylating agents (azacitadine), salvage chemotherapy [etoposide + cytarabine + mitoxantrone (MEC)] and palliative chemotherapy (hydroxycarbamide) treatment regimens; **assumes equal probability of receiving FLAG/Ida [fludarabine + cytarabine + granulocyte colony-stimulating factor (G-CSF)/idarubicin) or secondary allo-HSCT. Secondary allo-HSCT costs applied as one-off cost in first cycle of relapse/progression; SMR — standardized mortality ratio; allo-HSCT — allogeneic hematopoietic stem cell transplantation

1 year based on clinical experts agreeing to that assumption). The cost of outpatient and inpatient procedures was estimated using official unit prices [26] with their shares obtained from data on incidence in 2019 in Poland and/or data presented in other economic analyses submitted to the Agency for Health Technology Assessment and Tariff System in Poland [29].

The main model's inputs are presented in Table I.

The primary outcomes of the analysis included: 1) the incremental cost-utility ratio (ICUR), estimated in terms of the cost per quality-adjusted life year (QALY), which was compared to the threshold of 3 x the gross domestic product per capita in Poland (155,514 PLN in 2021); 2) the incremental net monetary benefit (INMB) expressed as: $INMB = WTP \times \Delta QALY - \Delta C$, where WTP is the threshold, while $\Delta QALY$ and ΔC denote a difference between arms in QALYs and total costs, respectively. When the INMB is higher than or equal to zero, this indicates that the treatment is cost effective, with the willingness to pay per additional QALY at 155,514 PLN. Costs were expressed in PLN (€1 =

Table II. Results of base-case analysis

Parameter	Treosulfan	Busulfan	Incremental
Mean event-free survival, years	9.84	7.96	1.87
Mean overall survival, years	10.51	9.27	1.23
Life years (discounted)	7.85	6.94	0.91
QALY (discounted)	5.74	4.96	0.78
Cost of treosulfan/busulfan	23,377 PLN	0 (included in cost of HSCT procedure)	23,377 PLN
Cost of HSCT procedure (including fludarabine, busulfan and others)	238,131 PLN	240,584 PLN	–2,453 PLN
Cost of healthcare after HSCT (discounted)	44,858 PLN	40,545 PLN	4,313 PLN
Cost of adverse events treatment (discounted)	3,904 PLN	4,453 PLN	–549 PLN
Cost of event-free survival (discounted), overall	309,290 PLN	284,680 PLN	24,610 PLN
Cost of relapsed/progressed disease (discounted)	19,831 PLN	44,725 PLN	–24,895 PLN
End-of-life cost (discounted)	5,464 PLN	6,319 PLN	–854 PLN
Total cost (discounted)	334,585 PLN	335,724 PLN	–1,139 PLN
ICUR	–	–	Dominant
INMB	–	–	122,764 PLN

QALY — quality-adjusted life year; HSCT — hematopoietic stem cell transplantation; ICUR — incremental cost-utility ratio; INMB — incremental net monetary benefit

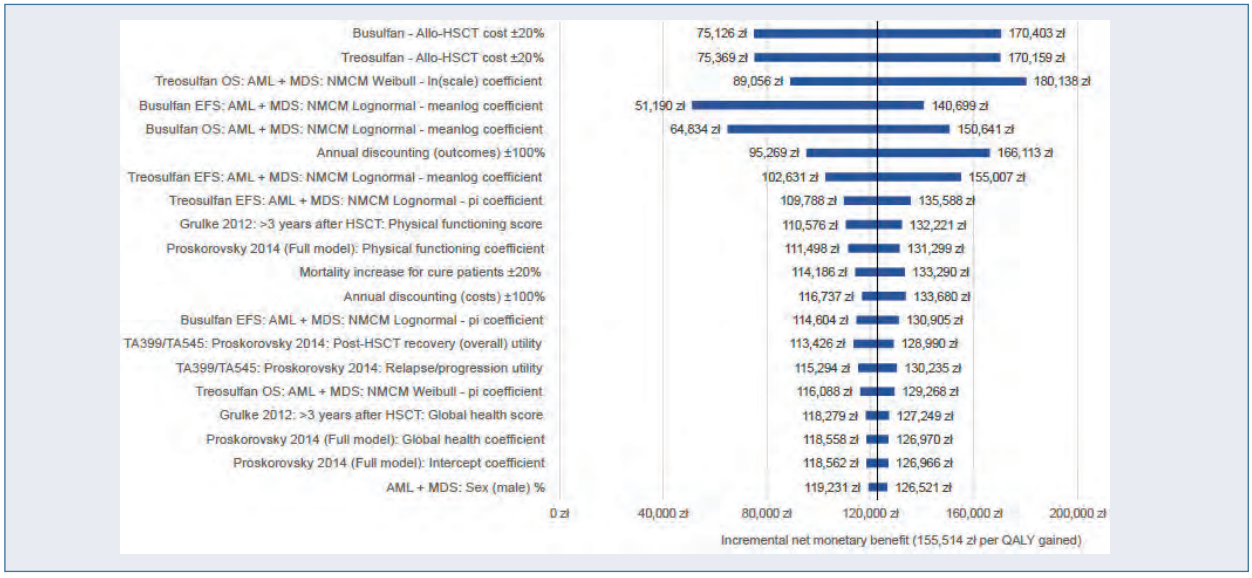

Figure 3. Tornado diagram for deterministic sensitivity analyses; allo-HSCT — allogeneic hematopoietic stem cell transplantation; OS — overall survival; AML — acute myeloid leukemia; MDS — myelodysplastic syndrome; NMCM — non-mixture-cure models; EFS — event-free survival

= 4.47 PLN). The study was reported in adherence with the Consolidated Health Evaluation Reporting Standards [30] and Polish guidelines [31].

One-way deterministic sensitivity analyses were performed for all parameters. Additionally, the alternative source or assumption was tested via scenario analyses, which included optional extrapolation distributions and scenarios (with or without the cure threshold), optional sources of utilities, and optional assumptions regarding the cost of treosulfan and/or busulfan (e.g. with treosulfan-only cost that exceeded busulfan cost financed by the NFZ, without treosulfan wastage, with treosulfan financed by the NFZ: with full wastage, without wastage, or with partial wastage, which assumed that only the unused part of the last vial is dispensed with).

A probabilistic sensitivity analysis, based on 5,000 sets of randomly drawn input parameters, was carried out to calculate the confidence intervals around the base-case

Table III. Results of scenario analyses

Parameter	Incremental QALY	Incremental costs	ICUR (PLN/QALY gained)	INMB
Base-case analysis	0.78	–1,139 PLN	Dominant	122,764 PLN
AML subpopulation only	0.71	–12,545 PLN	Dominant	123,095 PLN
MDS subpopulation only	0.89	11,557 PLN	13,051 (<155,514)	126,145 PLN
Pooled separate modelling for AML and MDS patients	0.77	–3,840 PLN	Dominant	124,196 PLN
Without cost of treosulfan wastage	0.78	–2,001 PLN	Dominant	123,626 PLN
EFS and OS extrapolation: variant 1	1.35	–26,907 PLN	Dominant	236,329 PLN
EFS and OS extrapolation: variant 2	0.97	–9,559 PLN	Dominant	161,115 PLN
EFS and OS extrapolation: variant 3	0.79	2,777 PLN	3,532 PLN (<155,514)	119,502 PLN
EFS and OS extrapolation: variant 4	0.99	–7,725 PLN	Dominant	161,301 PLN
EFS model: gamma	0.75	9,504 PLN	12,743 PLN (<155,514)	106,481 PLN
EFS model: MCM lognormal	0.79	–1,655 PLN	Dominant	123,779 PLN
EFS model: Gompertz	0.78	1,505 PLN	1,934 PLN (<155,514)	119,533 PLN
OS model: gamma	0.75	–3,726 PLN	Dominant	120,594 PLN
OS model: MCM Weibull	0.79	–709 PLN	Dominant	123,242 PLN
OS model: MCM Lognormal	0.78	–1,162 PLN	Dominant	121,731 PLN
OS model: NMCM Lognormal	0.78	–770 PLN	Dominant	121,790 PLN
Cure threshold: 3 years	0.82	12,377 PLN	15,090 PLN (<155,514)	115,177 PLN
Cure threshold: 7 years	0.79	–5,879 PLN	Dominant	129,425 PLN
Busulfan directly financed by NFZ with partial cost of wastage	0.78	–13,855 PLN	Dominant	135,480 PLN
Busulfan directly financed by NFZ with full cost of wastage	0.78	–23,745 PLN	Dominant	145,371 PLN
Only treosulfan cost that exceeds busulfan cost financed by NFZ	0.78	–13,790 PLN	Dominant	135,415 PLN
Post allo-HSCT utilities from Castejon et al. 2018	0.64	–1,139 PLN	Dominant	100,596 PLN

QALY – quality-adjusted life year; HSCT – hematopoietic stem cell transplantation; ICUR – incremental cost-utility ratio; INMB – incremental net monetary benefit; AML – acute myeloid leukemia; MDS – myelodysplastic syndrome; EFS – event-free survival; OS – overall survival; MCM – mixture-cure models; NMCM – non-mixture-cure models; NFZ (*Narodowy Fundusz Zdrowia*) – National Health Fund

analysis results and to calculate the probability of treosulfan being cost-effective.

Results

The base-case model indicated that patients receiving the treosulfan conditioning regimen did not experience cancer-related events for an additional 1.87 years compared to patients receiving a low-dose busulfan conditioning regimen. Moreover, the mean OS was prolonged by 1.23 years.

Compared to busulfan, treosulfan-based conditioning led to a gain of 0.78 QALYs with a reduced cost of 1,139 PLN per patient.

The results indicate that treosulfan outperforms busulfan in Poland, in that it is more effective and less expensive (Table II).

The sensitivity analyses confirmed the results of the base-case analysis. Neither the change of any model parameter (Figure 3) nor the implementation of any scenario (Table III) affected the cost-effectiveness of treosulfan at a threshold of 155,514 PLN per QALY gained. Treosulfan was either dominant or highly cost effective (i.e. ICUR less than the gross domestic product per capita in Poland) compared to low-dose busulfan. Of the model parameters and extrapolation variants, the allo-HSCT cost, EFS, and OS had the greatest impact on the results.

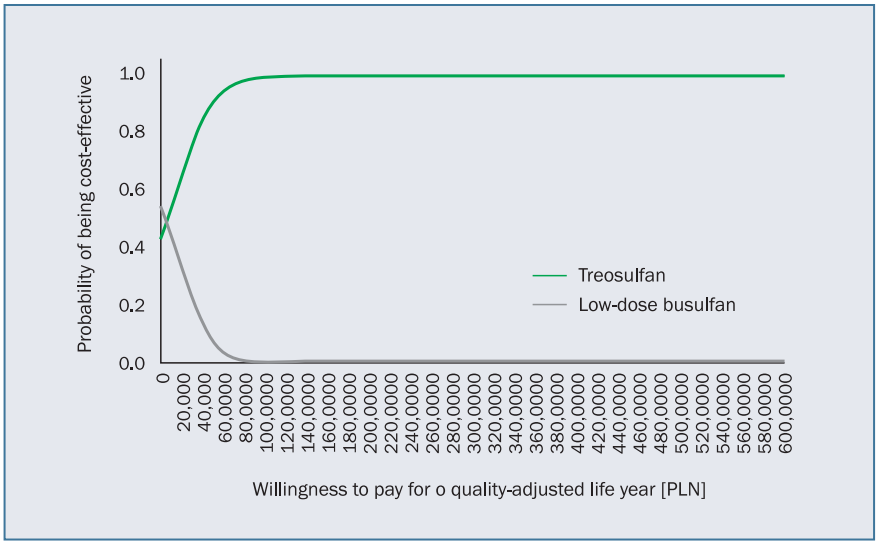

Figure 4. Cost-effectiveness acceptability curve

The probabilistic sensitivity analysis indicated a probability of 99.6% for treosulfan being cost-effective at a threshold of 155,514 PLN per QALY gained (Figure 4).

Discussion

Treosulfan is an alkylating agent viewed as a well-tolerated alternative to other chemotherapy drugs (including other alkylating agents) in conditioning regimens for allo-HSCT; in combination with fludarabine, it is indicated as part of conditioning treatment prior to allo-HSCT in adult patients with malignant and non-malignant diseases, and pediatric patients older than one month with malignant diseases [13]. It is also important to stress that, as demonstrated in a recently published meta-analysis, treosulfan is characterized by a strong activity against AML cells, as well as strong immunosuppressive effects, but is associated with low release of inflammatory cytokines.

These qualities promote the engraftment of the transplanted cells while limiting the risk of GvHD [8]. Additionally, the safety and clinical effectiveness of treosulfan-based regimens as a conditioning treatment have also been confirmed in a dose-escalation study carried out among patients with a variety of hematological malignancies, as well as research including patients with a high risk of both regimen-related toxicity and graft failure [11].

Therefore, thanks to the described characteristics, treosulfan-based regimens are considered to have effectiveness analogous to, or better than in the case of overall survival, conventional myeloablative conditioning regimens, with lower risks of toxicity, the occurrence of GvHD, and transplant-related mortality [8].

This makes treosulfan-based conditioning a great option for patients who are not well enough for standard conditioning, and gives them a chance to undergo a potentially curative procedure.

High clinical effectiveness of treosulfan-based conditioning regimens has also been demonstrated in a pivotal clinical study that aimed to evaluate the efficacy and safety of conditioning with treosulfan plus fludarabine compared to reduced-intensity busulfan plus fludarabine in patients with acute myeloid leukemia or myelodysplastic syndrome. Patients included in the study were at an increased risk of adverse events with the use of standard conditioning therapies because of their older age (≥50 years) or comorbidities [Hematopoietic Cell Transplantation — Comorbidity Index (HCT-CI) score >2]. In this study, 2-year event-free survival reached 64% [95% (CI, confidence interval) 56–70.9] in the treosulfan group and 50.4% (42.8–57.5) in the busulfan group [hazard ratio (HR) 0.65 (95% CI 0.47–0.90)]. The most frequently reported adverse events of grade 3 or higher included abnormal blood chemistry results [33 (15%)/221 for the treosulfan group vs. 35 (15%)/240 patients in the busulfan group] as well as gastrointestinal disorders [24 (11%) vs. 39 (16%) patients]. Serious adverse events were observed in 18 (8%) patients in the treosulfan cohort and in 17 (7%) in the busulfan group. Deaths noted during the study were, generally, transplantation-related [5].

The described study has several significant strengths, which should be pointed out. These include the randomization and multicenter character of the study, as well as a fairly large population of patients included in the study (476 patients). Additionally, due to the open-label model, the researchers decided to choose a robust primary endpoint, which was as independent as possible from the subjective view of both the patient and the investigator. Moreover, investigators and other personnel included in the research were blinded to aggregated data analyses

until database lock. This reduced the risk of bias associated with lack of blinding, which was one of the most significant limitations of the study. Other limitations included the limited use of disease-specific risk scores, such as the disease risk index to adjust for transplantation-related risks, as well as not implementing measurable residuals as the disease-independent prognostic indicator for the post-transplant relapse risk [5].

Despite these limitations, the results of the described clinical study provide important information regarding the conditioning treatment of patients who are not fit for standard regimens utilized before allo-HSCT. They allow us to conclude that treosulfan is non-inferior to busulfan when used in combination with fludarabine as a conditioning treatment utilized before allo-HSCT for patients with acute myeloid leukemia or myelodysplastic syndrome, who are elderly and/or have significant comorbidities which have made the use of standard conditioning treatments impossible.

These findings suggest that treosulfan-based regimens have significant potential to become the standard preparative regimen among such patients [5].

Our study confirms that the conditioning regimen with treosulfan instead of low-dose busulfan is highly cost effective in Poland. However, the analysis has several major limitations. Firstly, there may be differences in the characteristics of patient populations in the included studies [5, 19, 20, 23]. Secondly, efficacy data is limited due to a relatively short duration of the clinical trial (up to 1,586 days) which was used to inform the model during the lifetime horizon. Nevertheless, optional extrapolation variants and survival models did not change the conclusion from the base-case analysis. Thirdly, the cost input was based on other economic analyses or assumptions because valid cost data on Polish patients was unavailable. Finally, the utilities were sourced from published studies, as quality-of-life data was not collected during the MC-FludT.14/L trial.

Only a single economic study of treosulfan-based conditioning in allo-HSCT patients was identified, namely the original model with UK-specific data [5, 25]. Our results are similar to those obtained in that original model, which may indicate that cost inputs and other country-specific input data do not affect the overall conclusion from the cost-effectiveness point of view. Also in regards to the analysis in the subgroups based on the diagnosis (AML and MDS separately), our obtained results (QUALY 0.71 for AML and 0.89 for MDS) were similar to the findings of the UK study (QUALY 0.71 for AML and 1.03 for MDS) [25].

Therefore, it can be concluded that, in both countries, treosulfan-based regimens are a highly cost-effective conditioning treatment for patients with AML or MDS who can benefit from undergoing allo-HSCT, but who are ineligible for standard conditioning regimens.

Based on the available data, as well as the results of the present study, it can be concluded that myeloablative properties and high cytotoxic activity on hematopoietic cells of treosulfan-based regiments, combined with their low non-hematological toxicity, can significantly improve the survival of patients with myelodysplastic syndrome as well as acute myeloid leukemia. This applies especially to elderly patients, as well as those in poor general condition, with lower performance status and a greater burden of comorbidities. Moreover, it should be stressed that such conditioning regimens are associated with a lower incidence of acute graft-versus-host disease compared to busulfan-based treatment. Additionally, and especially importantly from the socio-economic perspective, treosulfan-based conditioning is highly cost-effective in Poland.

Conclusions

The results of this study indicate that compared to low dose busulfan, treosulfan-based conditioning for allo-HSCT patients with AML or MDS ineligible for standard conditioning regimens is highly cost-effective in Poland.

Authors' contributions

PK, PH — conceived and designed model adaptation. PH — performed analysis and generated figures. GB, OM — designed and constructed original model. PH, MZ — prepared first draft. PK, MM — critically reviewed and edited paper. All authors contributed to and accepted final version of manuscript.

Conflict of interest and financial support

This study was financed by Medac Polska Sp z o.o.

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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Survival in multiple myeloma: a real-life single-center study

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Abstract

Introduction: The development of novel drugs with a different mechanism of action has led to considerable progress in multiple myeloma (MM) treatment. However, the exact associations between overall survival (OS) and different treatment types, response to treatment, as well as clinical and laboratory parameters, have not been fully elucidated.

We aimed to determine the effect of clinical and laboratory parameters, type of induction therapy, and high-dose chemotherapy with autologous hematopoietic stem-cell transplant (auto-HSCT) on OS in patients with MM.

Material and methods: This retrospective study included 413 patients with MM treated between 2006 to 2017. Correlations between selected clinical and laboratory parameters and OS were assessed. The severity of MM was evaluated using the Durie-Salmon classification.

Results: The median OS was 4.08 years. The overall response rate to chemotherapy was 76%. The complete remission (CR) rates were higher in patients receiving bortezomib-based therapy than in those receiving thalidomide-based therapy or standard chemotherapy (p <0.001). The CR rate was positively correlated with OS. The use of auto-HSCT with bortezomib-based therapy was associated with longer OS. Renal failure and elevated urinary protein levels were inversely correlated with OS. The severity of MM at diagnosis was also associated with OS. The percentage of bone marrow plasma cell infiltration did not correlate with OS.

Conclusions: MM is still diagnosed too late, by which time patients have developed almost irreversible complications. However, we confirmed that novel treatments improve OS in these patients, especially when used in addition to auto-HSCT. These findings may facilitate clinical therapeutic decision making.

Key words: autologous hematopoietic stem-cell transplant, bortezomib, chemotherapy, multiple myeloma, overall survival

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Introduction

The approach to the care and management of patients with multiple myeloma (MM) is been evolving rapidly. Today, the greatest challenge is the choice of individualized therapy in this highly diverse population. Historically, the median overall survival (OS) in patients with MM was about three years. However, in the era of novel highly active treatment options, a marked improvement in patient outcomes has been observed, with median OS reaching 5–7 years

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[1]. Even so, progress in MM treatment has complicated clinical decision making. The development of a treatment plan should include individual patient evaluation, defining treatment goals, as well as the assessment of therapy- and disease-related risk factors. Undoubtedly, for newly diagnosed patients, first-line treatment choice has the most important effect on overall response and survival rates.

Real-world registry studies have concluded that c.40% of patients with MM do not meet the inclusion criteria for clinical trials [2]. Patients who are ineligible for enrolment due to poor performance status, high comorbidity index, or organ dysfunction are thus commonly overlooked, and so the outcomes of this population are underreported in the literature.

One of the largest prospective studies to describe real-life treatment of MM patients has revealed a great diversity of treatment modalities, the availability of novel agents, and ever-evolving treatment recommendations [3].

The aim of our study was to assess the effect of selected clinical and laboratory parameters, the type of induction therapy, and response to therapy on OS in patients with MM. Moreover, we aimed to evaluate the role of high-dose chemotherapy with autologous hematopoietic stem cell transplant (auto-HSCT) in the treatment of patients with MM, and to identify patients with short OS despite the use of auto-HSCT as well as patients with long OS who did not receive auto-HSCT.

Material and methods

This retrospective study included 413 patients with MM [234 women (56.7%) and 179 men (43.3%); mean age, 66.9 years (range: 27–89)] treated at the Department of Hematology at the Rydygier Hospital in Kraków, Poland, from 2006 to 2017.

Data on the following clinical and laboratory parameters was collected and included in a dedicated database: lactate dehydrogenase, urinary protein (<1 g/L, 1–2 g/L, and >2 g/L), and total protein levels (<100 g/L, 101–120 g/L, and >120 g/L); monoclonal antibody class; type [immunoglobulin G (IgG), IgA, IgM, light chain], form (systemic, localized), and clinical stage of MM (Durie-Salmon classification); and prognosis according to the International Staging System (ISS) and Revised ISS (R-ISS). Data regarding the number of treatment lines, regimens, outcomes, and follow-up duration was also collected. The results of cytogenetic studies were assessed. Risk factors for bone lesions and surgical treatment of bone lesions were evaluated. In the case of unselected proteinuria >0.5 g/24 hours, Bence-Jones protein was assessed. Finally, we assessed associations of OS with laboratory parameters, complete remission (CR), disease severity, ISS and R-ISS stages, the extent of bone marrow infiltration, induction therapy, as well as single and tandem transplant.

Statistical analysis

Qualitative variables such as selected laboratory parameters were presented as mean and SD, median, and minimum-maximum values. The variables were compared between subgroups divided according to risk, treatment, or selected clinical parameters (such as disease severity) using a nonparametric Mann-Whitney test for comparisons between two variables and a Wilcoxon test for comparisons between more than two variables. The rank correlation coefficient between lactate dehydrogenase (LDH) levels and selected laboratory parameters was calculated. Ranked or qualitative variables were presented as number and percentage of patients. The independent χ^2 test was used to assess outcomes for consecutive lines of chemotherapy. Survival analysis was used to compare OS depending on selected risk factors, type of treatment, treatment outcomes after each line of chemotherapy, and selected clinical parameters. Patients receiving auto-HSCT constituted a separate subgroup. The independent χ^2 test was used in this subgroup to assess OS depending on selected factors as well as to assess the effect of selected risk factors on OS shorter or longer than five years. Results with a p value of 0.05 or lower were considered significant. Statistical analysis was conducted using Statistica 13 PL (StatSoft, Kraków, Poland).

Results

Depending on the analyzed parameter, data completeness ranged from 15.2% (31 of 204 patients) for the analysis of the causes of death to 96.6% (399 of 413 patients) for the analysis of the type of MM.

At diagnosis, 95.6% of patients had symptomatic MM. The most common type of MM was immunoglobulin (Ig) G kappa, observed in 155 patients (38.8%). Most patients (n = =214; 54.7%) had stage IIIA MM according to the Durie-Salmon classification. Stage IA MM was noted in 26 patients (6.6%), stage IB in two (0.5%), stage IIA in 34 (8.7%), stage IIB in five (1.3%), and stage IIIB in 110 (28.1%).

Using the ISS, MM was classified as stage III in 55.9% of patients (n = 124) and as stage II in 30.2 % of patients (n = 67).

Cytogenetic study for both karyotype and FISH (t(4;14), t(14;16), del17p) determination was known in 43 patients (10.4%). Classical cytogenetics is not part of the R-ISS classification, but karyotype can be helpful in detecting additional cytogenetic abnormalities such as hypodiploidia.

The most common cytogenetic abnormality was t(4;14), observed in 11 patients (25.6%), while more than half of the study group had normal karyotype (n = 22; 51.1%) (Table I).

Chemotherapy regimens used in the study group allowed the achievement of an overall response rate of 76% in 202 patients. CR and stringent CR was achieved in 60 patients (22.6%; Table II). The CR rate was higher

Table I. Cytogenetic study results in study group (n = 43)

Result	N	[%]
Normal	22	51.1
t(4;14)	11	25.6
del *TP53*, t(4;14)	3	7
del 13	1	2.3
del *TP53*	3	7
Hyperdiploidy	1	2.3
Trisomy 17, 17p13	1	2.3
Trisomy 17, del *TP53*	1	2.3

Table II. First-line chemotherapy outcomes (n = 266)

Outcome	N	[%]
CR	55	20.7
sCR	5	1.9
PR	100	37.6
VGPR	42	15.8
SD	36	13.6
PD	27	10.2
Patients remaining under follow-up	1	0.4

CR — complete remission; sCR — stringent complete remission; VGPR — very good partial remission, PD — progressive disease; SD — stable disease

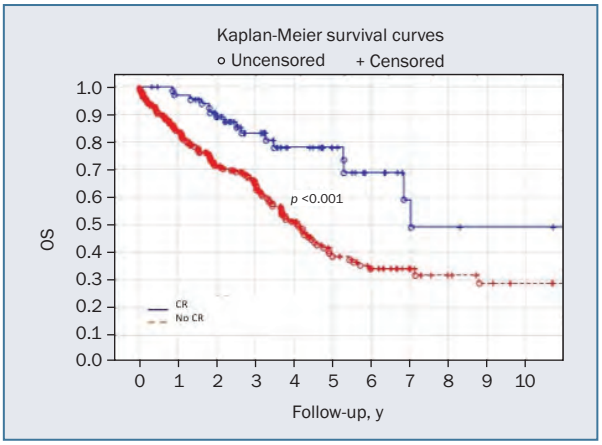

Figure 1. Kaplan-Meier survival plot showing overall survival (OS) in patients with multiple myeloma who achieved and did not achieve complete remission (CR) after first-line chemotherapy

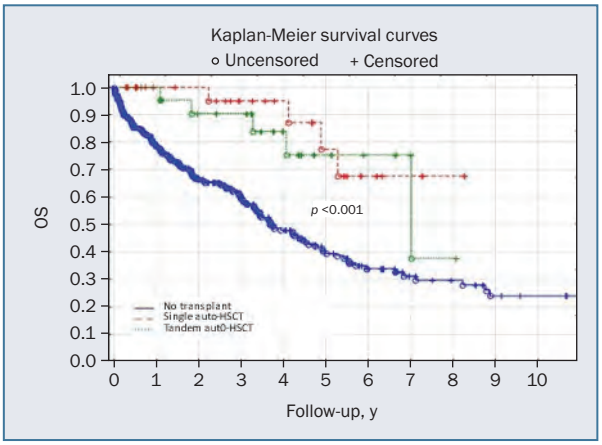

Figure 2. Kaplan-Meier survival plot showing overall survival (OS) in patients with multiple myeloma depending on use of autologous hematopoietic stem-cell transplant (auto-HSCT), single auto-HSCT, tandem auto-HSCT, or no transplant

(p <0.001) in patients treated with bortezomib-based therapy (VTD, VCD, VD, VMP, PAD) 36.1% than in those treated with thalidomide-based therapy (MPT, CTD, TD) 24.7%, and standard chemotherapy (VAD, CD, COP, CP, MD, MP, P) 10.3%. 8.2% of patients received both thalidomide and proteasome inhibitor (VTD regimen) (n = 29), and separate analysis for OS was not assessed in this group. Monoclonal antibodies were not available in Poland until July 2019 in routine practice.

Patients received a maximum of nine lines of treatment. The follow-up duration and maximum OS was 23 years. Achievement of CR after the first-line chemotherapy was associated with longer OS (median OS 7 vs. 4 years) (p <0.001) (Figure 1). Transplant treatment (both auto-HSCT and tandem transplant) was also associated with longer OS (median OS 7 vs. 3.75 years) (p <0.001) (Figure 2), regardless of age divided into two groups <60 years and 60–75 years, but this lacked statistical significance (NS, n = 50).

Elevated serum LDH levels (>248 U/L) correlated positively with leukocyte count (p = 0.037), percentage of bone marrow plasma cell infiltration (p = 0.009), and ISS stage (p = 0.025), (LDH assessment as a part of R-ISS staging was an auto-control parameter), while negatively correlated with serum IgA levels (p <0.001).

Bone lesions associated with MM were observed in 215 patients (74.4%) at diagnosis, and they were more common in men than in women (p = 0.002). The presence of bone lesions was not correlated with patient age, percentage of bone marrow plasma cell infiltration, or ISS stage. Surgical treatment such as vertebroplasty, transpedicular spondylodesis or intramedullary nailing was necessary in 50 of the 303 patients (16.5%) assessed for the presence and treatment of bone lesions. Surgical patients included 27 women (54%). 31 individuals aged 60 to 75 years (62%) were not analyzed for overall survival.

The median OS in the study group was 4.08 years. The OS for the whole study group is presented in Figure 3. Overall survival was associated with the severity of MM at diagnosis (Figure 4) and the ISS stage (Figure 5). However, no associations were shown for the R-ISS stage, probably because of a small sample size (the cytogenetic study was performed only in 43 patients). The percentage of bone

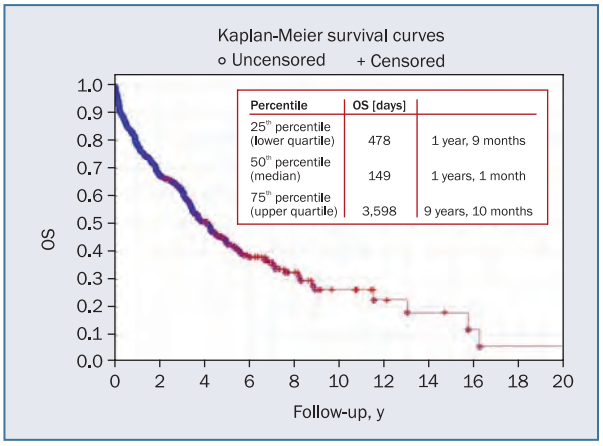

Figure 3. Overall survival (OS) for whole study group (n = 413)

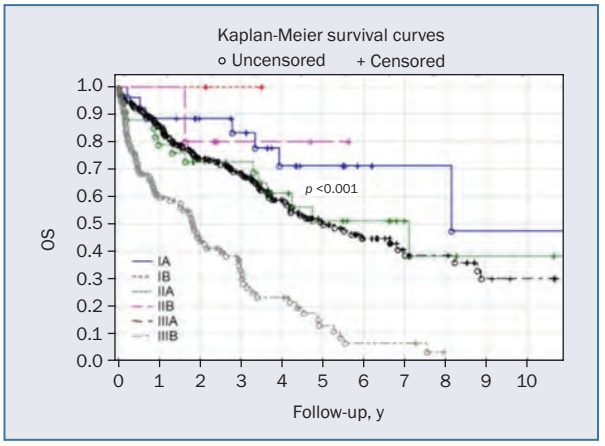

Figure 4. Kaplan-Meier survival plot showing overall survival (OS) of patients with multiple myeloma depending on disease severity according to Durie-Salmon classification (n = 391)

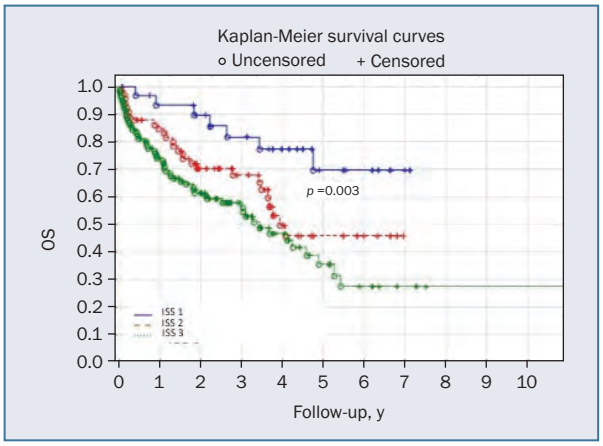

Figure 5. Kaplan-Meier survival plot showing overall survival of patients with multiple myeloma depending on International Staging System stage (n = 222)

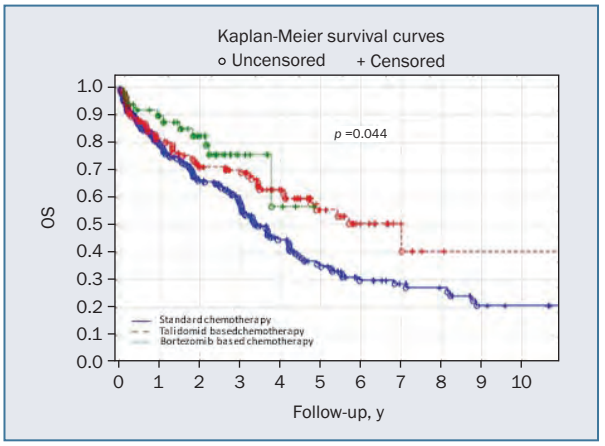

Figure 6. Kaplan-Meier survival plot showing overall survival of patients with multiple myeloma depending on type of first-line chemotherapy (n = 341)

Table III. Association between autologous hematopoietic stem-cell transplant and overall survival of less than, and more than, five years

Transplant	N	OS <5 years	OS >5 years	Censored observations <5 years	*p* value
No transplant	256	47 18.4%	124 48.4%	85 33.2%	<0.001
auto-HSCT	29*	8** 27.6%**	3** 10.3%**	18 62.0%	
Tandem auto-HSCT	21*	6** 28.6%**	4** 19.0%**	11 52.5%	

*Patients included in survival analysis; **patients included in subsequent χ^2 test analysis; auto-HSCT – autologous hematopoietic stem-cell transplant; OS – overall survival

marrow plasma cell infiltration did not correlate with OS, although the survival curves may imply a potential relationship (data not shown). Finally, induction therapy with the proteasome inhibitor bortezomib was significantly associated with longer OS (Figure 6).

A separate analysis was conducted to identify patients who do not benefit from transplant treatment. In a group of 50 transplant recipients, there were seven (three after auto-HSCT, four after tandem auto-HSCT) with a survival longer than five years. 29 patients (18 after auto-HSCT, 11 after tandem auto-HSCT) were alive at the time of the study (censored observations). The total number of patients with survival longer than five years in this group was 36 (72%) (Table III).

In patients after auto-HSCT, there were no associations between OS and sex, age, or elevated LDH levels. Moreover, no significant association between the presence of renal failure and OS was observed. There was no association between OS and urinary protein or total protein levels. No associations were noted for the ISS stage, which may suggest that these patients have a similar OS despite differences in prognostic factors (ISS, R-ISS) at baseline. However, the study group was too small (n = 43) to draw firm conclusions. Finally, OS was not significantly associated with the percentage of bone marrow plasma cell infiltration (<40%, 41%–59%, or >60%) or the achievement of CR after the first-line treatment.

Discussion

Most studies suggest that survival improvement in older adults with MM is less pronounced compared to that in younger individuals. Older adults with MM are particularly vulnerable to adverse events (AEs) associated with multidrug combinations, which can lead to dose reductions or treatment discontinuation, both of which are associated with poorer outcomes. The goals of care for older adults may differ from those in younger adults; older adults facing serious illness are more likely to prioritize symptom control and the maintenance of independence rather than prolonged survival [1].

Thus, although the effectiveness of ASCT in older patients in the era of novel agents remains an important area for investigation, ASCT can be a feasible and efficacious component of therapy for selected older patients with MM. Exactly which older adults are eligible for ASCT remains poorly defined [1].

Multiple myeloma is still diagnosed too late when the disease stage is advanced [most patients (n = 214; 54.7%) had stage IIIA according to the Durie-Salmon classification], when the tumor mass is large, and complications are almost irreversible.

Our study showed that OS, the most important survival indicator, is associated with Durie-Salmon and ISS stages at diagnosis. We also observed a positive effect of achieving CR on OS. Moreover, the CR rate was significantly higher in patients receiving chemotherapy with the proteasome inhibitor bortezomib than in those receiving thalidomide and standard chemotherapy. Longer OS was also related to auto-HSCT, both single and tandem transplant.

In recent years, there has been considerable progress in the treatment of MM due to the introduction of novel drugs and their subsequent generations, including immunomodulatory drugs (thalidomide, lenalidomide, pomalidomide), proteasome inhibitors (bortezomib, carfilzomib, ixazomib) [1, 3–6], anti-CD38 monoclonal antibodies (daratumumab), anti-SLAMF7 antibody (elotuzumab), signaling pathway inhibitors (panobinostat) [7], and immunotherapy with chimeric antigen receptor (CAR) T cells, namely, genetically engineered autologous T-cells (anti-BCMA CAR T-cells) [8].

The use of drugs with an alternative mechanism of action in the treatment of MM has improved survival of these patients, with an increase in median OS from 3/4 years to 5–7 years over the last 20 years. It is estimated that survival since diagnosis is still less than two years in 25% of patients. In 50–70% of patients, survival is five years or longer, depending on response to therapy, treatment tolerance, use of immunomodulatory drugs, and eligibility for auto-HSCT [9].

Our study had a retrospective design and a relatively long follow-up (2006–2017). Considering the study duration and the Polish setting, the treatment outcomes and OS in the study group seem to be relatively good compared to other national and international centers. However, since the completion of our study, new generations of drugs such as carfilzomib, lenalidomide, and pomalidomide and drugs with new mechanisms of action such as monoclonal antibodies daratumumab and belantamab mafodotin have been developed, although they are not available as first-line regimens in clinical practice in Poland. This may be considered a limitation of the study.

Our study has important implications for therapeutic decision making. In the Polish setting, patients with MM should receive induction therapy based on bortezomib and should be more often referred for auto-HSCT. Bortezomib-based regimens in individuals eligible for auto-HSCT include VRD (bortezomib, lenalidomide, dexamethasone), VTD (bortezomib, thalidomide, dexamethasone), VCD (bortezomib, cyclophosphamide, dexamethasone), PAD (bortezomib, doxorubicin, dexamethasone), or, in exceptional cases, CTD (cyclophosphamide, thalidomide, dexamethasone) [7].

Authors' contributions

MRo — study conception and desing, manuscript writing. AMK — data collection and analysis. MRa — revision of mauscript. BJ — revision of manuscript et paper design.

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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Vaccinations following CAR-T cell therapy: summary of reported cases and state-of-the-art review of current recommendations

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Abstract

Introduction: Chimeric antigen receptor T-cell (CAR-T) therapy is a modern breakthrough technology used in the treatment of B-lineage lymphoid malignancies. These malignancies include acute lymphoblastic leukemia, non-Hodgkin lymphoma, and plasma cell disorders. CAR-T therapy combines cellular therapy, gene therapy, and individualized therapy. The objective of this paper was to review the latest clinical knowledge, and summarize the reported data pertaining to vaccinations in patients after CAR-T therapy.

Material and methods: We carried out a review of published original studies as indexed in PubMed, and a review of abstracts presented during major hematology meetings.

Results: Overall, 22 original studies were reviewed and considered suitable for analysis regarding the efficacy of vaccinations for patients who had received CAR-T therapy. Data was divided into three groupings: the efficacy of vaccination against coronavirus disease 2019 (COVID-19)/severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); the efficacy of vaccination against influenza; and the efficacy of post-CAR-T immunization persistence of vaccination performed before CAR-T therapy. Humoral and cellular response to SARS-CoV-2 vaccination was positive for 36.5% and 72.2% of patients, respectively. The positive response to the influenza vaccine was 40% when administered prior to CAR-T therapy, as opposed to 31% after. Seroprotection for vaccine-preventable infections within 3–6 months after CAR-T was comparable to that of the general population, although it was determined to be less effective against specific pathogens (S. pneumoniae, B. pertussis, H. influenzae) in most patients.

Conclusions: In cases of incomplete immune reconstitution, there is a high likelihood of a limited response to vaccination. Regarding the SARS-CoV-2/COVID-19 vaccine, T-cell-induced protection is relatively significant. Therefore, B-cell aplasia is not a contraindication for vaccination in CAR-T patients. The consensus of European Society of Blood and Marrow Transplantation/European Hematology Association experts is that vaccination after CAR-T therapy is beneficial in order to reduce the rates of infection, and eventually to improve clinical course.

Key words: CAR-T, vaccination, acute lymphoblastic leukemia, non-Hodgkin lymphoma, multiple myeloma, SARS-CoV-2, COVID-19, influenza

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Introduction

Chimeric antigen receptor T-cells (CAR-T) therapy is a modern breakthrough technology used in the treatment of B-lineage lymphoid malignancies including acute lymphoblastic leukemia, non-Hodgkin lymphoma, and plasma cell disorders. CAR-T therapy combines cellular therapy, gene therapy, and individualized therapy. This treatment has been shown to be highly effective and safe for patients with an otherwise resistant, relapsing or refractory stage [1–5]. Even so, various complications can occur.

Approximately three to six months after commencing CAR-T therapy, the immune recovery of T-cells has been observed, while humoral response obviously occurs much later [6, 7]. Nevertheless, in the majority of patients who have achieved remission, B-lineage suppression and hypogammaglobulinemia were present. This condition results from expected activity of anti-CD19 CAR-T cells [8, 9]. Prevention of infections is of great importance in these patients [10, 11]. Supplementation of immunoglobulins is also important, especially in children [12].

Thus far, little is known about the use of vaccinations and the respective immune response in this cohort of patients. Therefore, the objective of this paper was to review the current clinical knowledge and to summarize reported data on vaccinations in patients after CAR-T therapy.

Material and methods

Design of study

Analysis and summary of available original data on the efficacy of vaccinations in patients after therapy with CAR-T cells, reported up to 28 February 2022.

Source data

Review of published original reports indexed in PubMed and review of abstracts presented during meetings of American Society of Hematology (ASH), American Society of Transplantation and Cellular Therapy (ASTCT), Center for International Blood and Marrow Transplant Research (CIBMTR) Tandem Meetings and European Society of Blood and Marrow Transplantation (EBMT) up to 28 February 2022 (including the 2022 ASTCT and EBMT meetings, because these abstracts were already available online). No vaccination issues were presented at the 4th European CAR T-cell Meeting (10–12 February 2022).

Inclusion criteria

We included patients after CAR-T therapy, and original data on humoral or cellular response to vaccination performed 1) after, and 2) before, the application of CAR-T therapy. Only studies reporting data of at least three patients after CAR-T therapy, with available information on their response to vaccination, were included in our analysis.

Literature search and selection

A literature search was conducted by two researchers (TS, JSa), and checked by all other study group members. The key words used in data search were: 'chimeric receptor antigen' or 'CAR-T' or 'CAR T-cell' as well as 'vaccination' or 'vaccine'. The following data was retrieved from these reports: vaccination target disease, number of patients included, analysis of their response to vaccination, time elapsed between CAR-T infusion and vaccination, type of response to vaccination (humoral or cellular), and the response rate.

Definitions

- CAR-T — lymphocytes T with chimeric antigen receptor directed against B-cell antigens (CD19, BCMA).
- BCMA — B-cell maturation antigen, analyzed in patients with multiple myeloma.
- CAR-T products (registered up to the end of 2021): tisagenlecleucel, axicabtagene ciloleucel, brexucabtagene autoleucel, idecabtagene vicleucel, and lisocabtagene maraleucel.
- Vaccination response — both humoral and cellular response. Humoral response to vaccination was measured by the presence of specific antibodies. Cellular response was measured by the presence of specific T-cells.
- Immune reconstitution — absolute number of CD4 T-cells >0.2 × 10^9/L, number of CD19 or CD20 positive B-cells >0.2 × 10^9/L, without concomitant cytotoxic or immunosuppressive therapy.

Statistical analysis

Chi-square test of the Fisher exact test was used to analyze the differences of categorical variables between groups. Odds ratio (OR) and 95% confidence intervals (CI) were determined, if p-value was significant (<0.05).

Results

Reported data

Overall, 22 original studies were deemed suitable for analysis of the efficacy of vaccinations in patients who had been administered CAR-T therapy (Table I).

According to the objective and design of our study, data were grouped and analyzed in three topics:

- efficacy of vaccination against coronavirus disease 2019 (COVID-19)/severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2);
- efficacy of vaccination against influenza;
- efficacy of post-CAR-T immunization persistence of vaccination performed before CAR-T therapy.

Table I. Potentially relevant and selected for analysis original reports on vaccination after chimeric antigen receptor T-cell (CAR-T) therapy

Source	Period analyzed	CAR-T reports	Vaccination after CAR-T	Potentially relevant	Selected for analysis
PubMed	Up to 28.02.2022	6,135	148	10	10
ASH 2021	63rd Annual Meeting, 11–14 December 2021, Atlanta, USA	388	15	7	7
ASTCT 2022	2022 Tandem Meetings, 23–26 April 2022, Salt Lake City, USA	108	7	7	4
EBMT 2022	48th Annual Meeting, 20–23 March 2022, Prague, Czech Republic	44	2	1	1

ASH — American Society of Hematology; ASTCT — American Society of Transplantation and Cellular Therapy; EBMT — European Society of Blood and Marrow Transplantation

Vaccination against COVID-19/ /SARS-CoV-2

A total of eight published studies and 11 meeting reports were found relevant for this topic (Table II) [6, 13–19]. Overall response to the SARS-CoV-2 vaccination was positive for 88/241 (36.5%) patients in criteria of humoral response, and for 26/36 (72.2%) patients in criteria of cellular response. Thus, patients after CAR-T therapy produced a better cellular than humoral response after vaccination against SARS-CoV-2, with OR = 4.5 (95% CI = 2.1–9.8), p <0.001 (Fisher exact test).

Vaccination against influenza

Only one study has been published [20], with 18 vaccinated patients including five prior to and 13 after the administration of CAR-T therapy. The time between vaccination and CAR-T therapy was 14–29 days prior (n = 5) or 13–57 months following the infusion (n = 13). In this study, commercially available inactivated influenza vaccines were used in adult patients. Response to vaccination was measured in the pre-CAR-T cohort 90 days following CAR-T therapy, and in the post-CAR-T patients approximately 90 days after vaccination. Humoral immunogenicity was analyzed and response to vaccination was defined by hemagglutination inhibition (HAI) titer. Seroprotection against influenza was defined as an HAI titer ≥40. Response to vaccination was 2/5 (40%) before, and 4/13 (31%) after CAR-T.

Response to vaccine-preventable infections after CAR-T therapy

In two studies, the proportion of patients with antibody levels above a threshold value was analyzed for seroprotection for vaccine-preventable infections (Table III). Overall humoral response within 3–6 months was comparable to the general population. However, seroprotection for specific pathogens (*Streptococcus pneumoniae, Bordetella pertussis, Hemophilus influenzae*) was found to be lacking in most patients. Additionally, even with these different patient cohorts, it was clear that protective seroconversion decreased between the third and the sixth month after CAR-T therapy. Walti et al. [21] underscored that CD19-CAR-T cell recipients had better seroprotection than BCMA-CAR-T cell patients. Neither total IgG concentration over 4 g/L, nor immunoglobulin supplementation, was associated with improved seroprotective IgG titers [21]. Prophylactic immunoglobulin replacement therapy did not confer immunization protection (ASH #3857).

Discussion

From the introduction of CAR-T technology into the treatment of patients with B-cell-lineage acute lymphoblastic leukemia, then in non-Hodgkin lymphoma and multiple myeloma, the question of how to prevent infections before, during, and after CAR-T infusion has been a vital topic in patient management [11, 22–24], although there is a lack of evidence [10]. As a consequence of the COVID-19 pandemic, a new generation of vaccines was developed, and a universal vaccination program was introduced worldwide. By 1 March 2022, almost 5 billion people had been vaccinated with at least one dose of the SARS-CoV-2/ /COVID-19 vaccine, 63.8% of the entire world population (https://ourworldindata.org). Data on vaccination in CAR-T patients is very limited, but more and more studies have been presented at hematology, transplantation and cellular therapy forums.

In our study, we have summarized the available data regarding the response to vaccinations in patients who had been administered CAR-T therapy. The overall humoral response to SARS-CoV-2/COVID-19 vaccine, based upon 18 studies, was 36.5%. A similar percentage was found in a small cohort of patients vaccinated against influenza. On the other hand, cellular response to the SARS-CoV-2/ /COVID-19 vaccine was much better, and reached 72.2%. The importance of this result, based on three small studies, cannot be overstated [10, 25].

Table II. Summary of reported data in abstracts and full papers on vaccination against coronavirus disease 2019 (COVID-19)/severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Source	Patients included	Patients analyzed	Time of vaccination after CAR-T (median, range)	Final response	Follow-up
ASH #254	23	20	401 (113–819) days	6/20 (30%)	No COVID-19 infection after 77 days (range: 49–127)
ASH #754	47	47	NA	11/47 (23.4%)	Booster vaccination 5 months after initial vaccination
ASH #1750	17	17	250 (32–881) days	13/17 (76.4%)	MM higher titer response than NHL
ASH #1757	12	12	40.6 months (1,230 days)	8/12 (66.7%)	Vaccine-specific antibody was strongly associated with level of circulating B cells
ASH #2504	8	8	>12 months	1/8 (12.5%)	Treatment with CAR-T was associated with lower immune response than HCT
ASH #2537	7	7	>12 months	1/7 (14.3%)	Treatment with CAR-T was associated with lower B titers
EBMT #P113	8	8	48 months	8/8 (100%)	Cellular response
ASTCT #475	6	6	Within 12 months after CAR-T therapy	0/6 (0%)	No CAR-T recipients responded to first dose
ASTCT #264	11 prior 22 post CAR-T	10 prior 22 post	NA	5/10 (prior) 50% (n = 11/22 post) developed positive anti-S IgG 59% (n = 13/22 post) developed S-specific T cells	Antibody responses appeared more frequently later after CAR-T cell therapy
ASTCT #239	104	17	250 (32–881) days	13/17 (76.4%)	More patients with MM had a higher titer response to vaccine (>250 U/mL) compared to NHL counterparts
ASTCT #476	11 prior	3	250 (32–881) days	1 (33.3%)	At days 30 and 100 post HCT/CAR-T, pre-cellular therapy titers were low in most patients and decreased soon post therapy
Ram et al. [13]	6	6	NA	1 (16.6%) humoral 5 (83.3%) cellular	Humoral and cellular response was measured
Dahiya et al. [14]	18	18	33 (24–447) days	1 (5.5%)	Antibody response to common pathogens (e.g. influenza, Epstein-Barr virus, and tetanus toxoid) was preserved
Abid et al. [15]	10	10		4 (40%)	After third dose
Ram et al. [16]	14	14	9 (3–17) months	5/14 (36%)	Humoral immune response
Dhakal et al. [17]	14	14	24 (8–31) months	21% (3/14)	Humoral immune response
Greenberger et al. [18]	12	12	NA	BCMA– or CD138-CAR T: 80% (4/5) CD19 + CAR-T: 14% (1/7)	Humoral immune response
Gastinne et al. [19]	23	20	13 (4–27) months	30% (6/20)	Humoral immune response
Tamari et al. [6]	7	7	218 (66–825) days	2 (28.5%)	Humoral immune response
TOTAL	372	241		88/241 (36.5%) humoral 26/36 (72.2%) cellular	Humoral and cellular response was measured

CAR-T — chimeric antigen receptor T-cell; ASH — American Society of Hematology; MM — multiple myeloma; NHL — non-Hodgkin lymphoma; HCT — hematopoietic cell transplantation; EBMT — European Society of Blood and Marrow Transplantation; ASTCT — American Society of Transplantation and Cellular Therapy; NA — not applicable; IgG — immunoglobulin G; BCMA — B-cell maturation antigen

Table III. Seropositivity for routine immunization analyzed after chimeric antigen receptor T-cell (CAR-T) therapy

Vaccine-preventable infection	Bansal et al. (ASH #3857)	Walti et al. [21]
Time	+3 months	+6 months
Number of patients	87	65
Streptococcus pneumoniae	14%	0%
Bordetella pertusis	NA	0%
Hemophilus influenzae	NA	15%
Hepatitis B	71%	39%
Hepatitis A	64%	43%
Mumps	86%	50%
Measles	86%	80%
Rubella	95%	90%
Varicella zoster virus (VZV)	98%	90%
Tetanus	100%	89%
Diphtheria	NA	89%
Polio	NA	89%

ASH — American Society of Hematology; NA — not applicable

Importantly, it seems that the interval between the infusion of CAR-T cells and the day of vaccination did not influence the humoral response. Moreover, no development of lymphopenia $<1 \times 10^9$/L was observed. We speculate that the development of specific T-cell responses in CAR-T recipients was essential, and more data will provide more information about the humoral and cellular efficacy of vaccination in this context. In the CAR-T cohort patients, despite severe humoral immune deficiency, strong CD4+ T cell responses were observed, suggestive of a sufficient protective immunity (ASH #1757). Therefore, following anti-CD19 or anti-BCMA-CAR-T therapy, patients were able to develop seroprotection which was comparable to that obtained in the general population, despite hypogammaglobulinemia [21]. Nevertheless, exceptions for several specific pathogens, such as pneumococcus, were almost the rule. Also, in BCMA-CAR-T treated patients, lower pathogen-specific antibodies rates were found [2]. This underscores the need for vaccination, as well as for immunoglobulin replacement in these cohorts.

Obviously, the risk factors for a poor response to vaccination in CAR-T recipients are lymphopenia, hypogammaglobulinemia, and B-cell aplasia. Different information was available about other factors which contributed to the response to the vaccination. Compared to NHL, patients with MM had a higher response to the vaccine (>250 U/mL) (ASH #1750). Vaccination prior to CAR-T therapy results in low (if any) antibody titers in most patients, and to a decrease in these titers soon after therapy (ASTCT #476). Importantly, responses appear similar in those vaccinated <6 months vs ≥6 months after treatment (ASTCT #475), which justifies the indication for the SARS-CoV-2/COVID-19 vaccination as soon as three months after CAR-T infusion. With respect to the SARS-CoV-2/COVID-19 vaccination, response in seropositivity seemed to be higher with the mRNA-1273 vaccine, and therefore resulted in a higher spike of mRNA content, as well as a longer duration of response compared to the BNT162b2 vaccine [6, 16–19, 26].

Some authors have emphasized the necessity of an additional booster (third) dose of the SARS-CoV-2/COVID-19 vaccine, approximately five months after the initial vaccination, in order to allow better immune reconstitution prior to vaccination (ASH #754, ASTCT #476). It has previously been shown that a third dose of the anti-COVID-19 vaccine in patients after CAR-T therapy B-cell aplasia is safe, although a humoral response is achieved in a limited number of patients [13]. There is data showing that none of the CAR-T recipients with complete B-cell aplasia exhibited an anti-vaccine humoral response, although cellular response was achieved in 83% of these patients [13]. The third dose of the anti-SARS-CoV-2 mRNA vaccine resulted in lower antibody response in males and corticosteroid recipients. The type of vaccine and the strategy of vaccination had no impact [15].

Data indicates the added rationale for active immunization of CAR-T recipients by the administration of vaccinations. We should clearly keep in mind that there are contraindications for vaccinations with killed or inactivated vaccine in patients with concurrent immunosuppressive or cytotoxic therapy; and contraindications for live and non-live adjuvant vaccines in the period <2 years post allogeneic HCT, and up to eight months after the last dose of immunoglobulin replacement therapy [27–30].

Table IV. Eligibility criteria for vaccination in patients receiving CD19-targeted chimeric antigen receptor T-cell (CAR-T) therapy (adapted from [25])

Type of vaccination	Before CAR-T therapy	After CAR-T therapy
Influenza vaccine	Preferably vaccinate 2 weeks prior to lymphodepleting therapy	Patients should be vaccinated >3 months after CAR-T
	Low likelihood of serological response when B-cell aplasia	Immunological reconstitution is irrelevant
SARS-CoV-19	Preferably vaccinate prior to CAR-T therapy	Patients should be vaccinated >3 months after CAR-T
	Low likelihood of serological response when B-cell aplasia	Immunological reconstitution is irrelevant
Inactivated/killed vaccines		Patients should be vaccinated >6 months after CAR-T and >2 months after immunoglobulin replacement therapy
Live and non-live adjuvant vaccines		Patients should be vaccinated >1 year after CAR-T
		Full immunological reconstitution is mandatory

SARS-CoV-2 — severe acute respiratory syndrome coronavirus 2

The EBMT/European Haematology Association (EHA) cooperative group of experts announced recommendations pertaining to the management of patients undergoing therapy with CAR-T [12]. Their update [25] includes recommendations for patient vaccinations (Table IV). These guidelines are applicable to both adults and children [10, 25].

Based on the initial published data on vaccination against influenza after CAR-T infusion [20], in cases of incomplete immune reconstitution there is a high likelihood of a lower response to vaccination [10]. However, this might not be the case for the SARS-CoV-2/COVID-19 vaccine-induced protection, as it strongly relies on T-cell-mediated immunity. In this case, B-cell aplasia is not a contraindication for vaccination [10, 25]. On the other hand, the T-cell threshold has not been determined. In order to gain more knowledge, monitoring of post-vaccination response is necessary. The consensus view of EBMT/EHA experts is that vaccination in patients after CAR-T therapy is beneficial in order to reduce the rates of infection, and to eventually improve the clinical course [25]. Nevertheless, the use of these guidelines must adhere to specific national schedules. Furthermore, an individualized approach based on a patient's infection history together with laboratory assessments of their humoral and/or cellular immunity is necessary.

Novel active or passive immunization strategies are needed for this population. Further research is expected. Predictors of response to vaccination, including determination of the vaccine's efficacy and safety, optimal timing of vaccination, additional or booster doses of the vaccine, and passive immune and pharmacological prophylaxis and treatment, all need to be determined in CAR-T patients.

List of analyzed meeting abstracts

- ASH #254. Thomas Gastinne, Amandine Le Bourgeois, Marianne Coste-Burel et al. Antibody response after one and/or two doses of BNT162b2 anti-SARS--CoV-2 mRNA vaccine in patients treated by CAR T-cells therapy. American Society of Hematology 63rd Annual Meeting, Atlanta, 11–14 December 2021. Blood 2021; 138 (Suppl) 1: abstract 254.
- ASH #754. Sabine Haggenburg, Birgit I Lissenberg--Witte, Robert S Van Binnendijk et al. For better or for worse: COVID-19 vaccination during or early after (immuno-) chemotherapy or hematopoietic progenitor cell transplantation. American Society of Hematology 63rd Annual Meeting, Atlanta, 11–14 December 2021. Blood 2021; 138, (Suppl) 1: abstract 754.
- ASH #1750. Julia E Wiedmeier, Madiha Iqbal, Javier Muñoz et al. Response to COVID-19 vaccination post-CAR T therapy in patients with non-Hodgkin lymphoma and multiple myeloma. American Society of Hematology 63rd Annual Meeting, Atlanta, 11–14 December 2021. Blood 2021; 138 (Suppl 1): abstract 1750.
- ASH #1757. Kalpana Parvathaneni, Kyabeth Toress-Rodriguez, Wenzhao Meng et al. Adoptive immune responses to SARS-CoV-2 vaccination in CART19 treated patients. American Society of Hematology 63rd Annual Meeting, Atlanta, 11–14 December 2021. Blood 2021; 138 (Suppl 1): abstract 1757.
- ASH #2504. Ning Dong, Akriti G Jain, Elaine S Tan et al. Immunogenicity of SARS-CoV-2 mRNA 1273 vaccine in patients with lymphoid malignancies. American Society of Hematology 63rd Annual Meeting, Atlanta, 11–14 December 2021. Blood 2021; 138 (Suppl 1): abstract 2504.
- ASH #2537. Lauren C Shapiro, Radhika Gali, Astha Thakkar et al. Seroconversion rates after

COVID-19 vaccination amongst patients with hematologic malignancies: results of a rapid vaccination and evaluation program in a minority rich, ethnically diverse inner city cohort. American Society of Hematology 63rd Annual Meeting, Atlanta, 11–14 December 2021. Blood 2021; 138 (Suppl 1): abstract 2537.

- ASH #3857. Radhika Bansal, Paschalis Vergidis, Pritish K Tosh et al. Vaccine titers in lymphoma patients receiving chimeric antigen receptor T cell therapy. American Society of Hematology 63rd Annual Meeting, Atlanta, 11–14 December 2021. Blood 2021; 138 (Suppl 1): abstract 3857.
- EBMT #P113. A Jarisch, E Wiercinska, S Huenecke et al. Humoral and T cell immune responses to anti-SARS-CoV-2 vaccines in pediatric & patients with anti-CD19 CAR-T-induced B-cell aplasia. European Society of Blood and Marrow Transplantation 48th Annual Meeting, 19–23 March 2022, abstract P113.
- ASTCT #475. Marcie L Riches, Joshua A Hill, Michael Martens et al. Humoral Immunogenicity of SARS-CoV-2 vaccination in the first year after hematopoietic cell transplant or chimeric antigen receptor T cell therapy: a CIBMTR and BMT CTN study. Tandem Meetings/American Society of Transplantation and Cellular Therapy 2022 Annual Meeting, Salt Lake City, 23–26 April 2022; abstract 475.
- ASTCT #264. Michael A Gonzalez, Jim Boonyaratanakornkit, Atif Bhatti et al. Comparison of humoral and T-cell response after SARS-CoV-2 vaccination among patients before and after chimeric antigen receptor-modified T cell (CAR-T cell) therapy. Tandem Meetings/ /American Society of Transplantation and Cellular Therapy 2022 Annual Meeting, Salt Lake City, 23–26 April 2022; abstract 264.
- ASTCT #239. Julia Erin Wiedmeier-Nutor, Madiha Iqbal, Javier Muñoz et al. Response to COVID-19 vaccination post-CAR T therapy in patients with non-Hodgkin lymphoma and multiple myeloma. Tandem Meetings/American Society of Transplantation and Cellular Therapy 2022 Annual Meeting, Salt Lake City, 23–26 April 2022; abstract 239.
- ASTCT #476. Gunjan L Shah, David J Chung, Roni Tamari et al. Humoral response to COVID-19 vaccination given pre-cellular therapy wanes in patients after cellular therapy: an argument for full reimmunization. Tandem Meetings/American Society of Transplantation and Cellular Therapy 2022 Annual Meeting,. Salt Lake City, 23–26 April 2022; abstract 476.

Authors' contributions

JS — design of study; JS, TS, JSa — literature search and analysis of data; JS, TS, JSa, MW, DR — writing manuscript; all authors — critical revision and final approval.

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

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VIA MEDICA

CLINICAL VIGNETTE

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Primary refractory primary mediastinal lymphoma treated with CAR-T: new possibilities and challenges

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Introduction

Chimeric antigen receptors T-cells (CAR-T) are autologous, genetically engineered T-cells redirected against a specific antigen. Indications for the use of CAR-T include refractory and relapsed (R/R), large B-cell lymphoma (LBCL), acute lymphoblastic leukemia, mantle cell lymphoma, follicular lymphoma, and multiple myeloma.

Primary mediastinal lymphoma (PMBCL) represents 2–3% of non-Hodgkin lymphomas (NHL), with 10–30% of patients having primary refractory or relapsed disease [1]. The SCHOLAR-1 study reported outcomes of R/R LBCL treatment enabling complete response (CR) achievement only in 7% of cases, among 26% OR [2]. However, superior outcomes with novel therapies emerging are possible. The ZUMA-1 axicabtagene ciloleucel (axi-cel) registration trial reported 52% CR with an 82% overall response (OR) rate in this setting [3].

This clinical vignette highlights the therapeutic opportunities created by CAR-T, and looks at ways of enhancing and sustaining responses and managing severe therapy-associated events.

Patient and treatment

A 39-year-old male patient presented with a bulky lesion located in the mediastinum, infiltrating and exceeding the chest wall (Lugano IV), diagnosed in March 2019. The patient progressed after first-line treatment with dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)-rituximab and second-line with DHAP (dexamethasone, cytarabine, cisplatin)-rituximab, and was qualified for CAR-T therapy. After successful lymphocyte collection, due to disease activity and risk of progression awaiting manufacturing process, BR (bendamustine, rituximab) bridging therapy was implemented. FluCy (fludarabine, cyclophosphamide) lymphodepletion preceded axi-cell infusion. The extrathoracic tumor regressed during the primary 14 days post-infusion, becoming imperceptible (Figure 1).

CAR-T-specific adverse events occurred, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). CRS, classified as grade 3 according to American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading for CRS [4], occurred on day 2, presenting as fever, tachycardia, and hypotension. Based on the standard of care in G3 CRS, symptomatic treatment was implemented and combined with four doses of tocilizumab (8 mg/kg on each dose) started on day 5. Grade 4 ICANS occurred on day 5, presenting as graphomotor disorders with features of cerebral edema in computed tomography (CT). The neurological condition was assessed using the Effector Cell-Associated Encephalopathy (ICE) score [4]. The patient was admitted to the ICU treated with dexamethasone 10 mg every 6 hours and then a methylprednisolone dose of 1,000 mg and sodium valproate dose 2 × 600 mg. Symptoms subsided on day 10, and the patient was referred to the hematology department. On day 12, ICANS recurred following discontinuation of glucocorticosteroids, presenting as motor aphasia and depressed level of consciousness, with features of cerebral edema in CT. Re-admission to ICU and restoration of methylprednisolone treatment resulted in the resolution of symptoms on day 14.

30 days post-infusion, a positron emission tomography (PET) scan showed a partial metabolic response (Deauville Scale 4) (PR, partial response). Due to active residual disease 60 days post-infusion, the patient was referred for mediastinum radiotherapy (20 × 2 Gy). Recurrent fever and abnormal thoracic CT scan following radiotherapy raised

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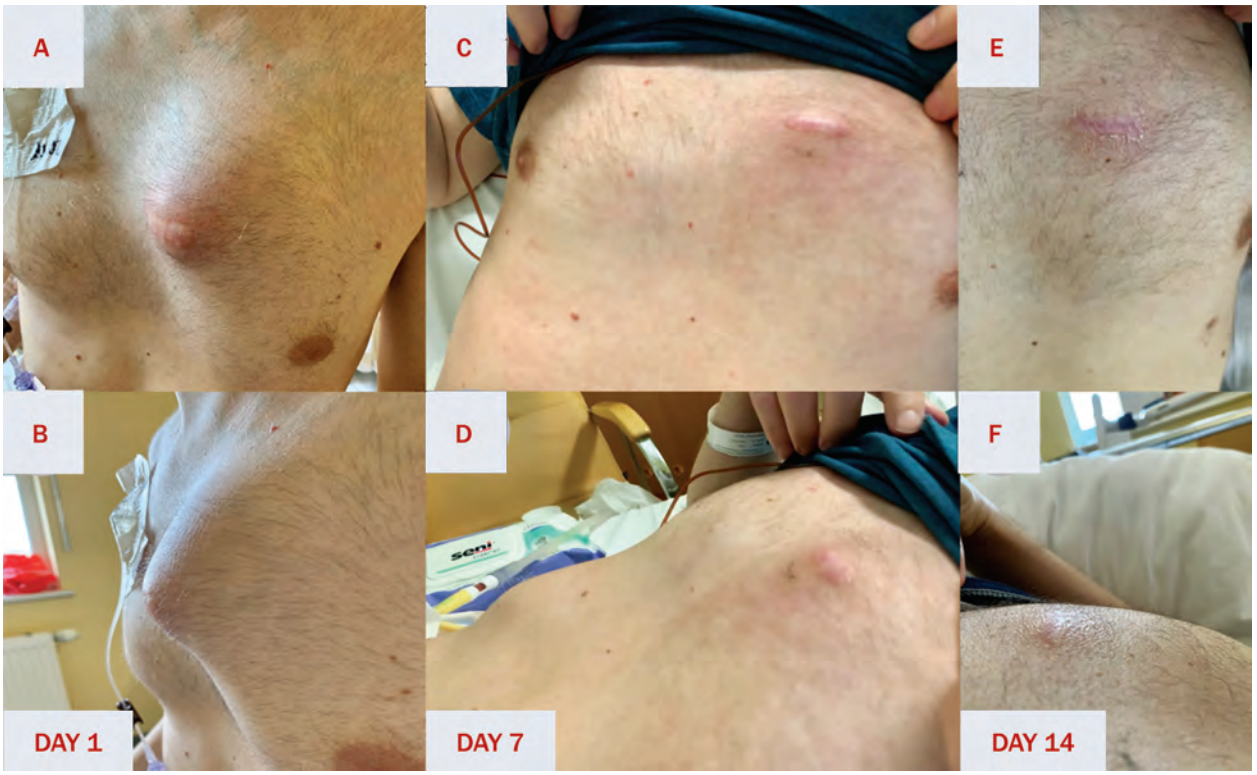

Figure 1. Extrathoracic tumor regression following chimeric antigen receptors T-cells (CAR-T) infusion: **A**, **B**. Large lesion exceeding chest wall on day of axi-cel infusion; **C**, **D**. Tumor regression 7 days post-infusion; **E**, **F**. 14 days after CAR-T infusion, umor is almost imperceptible

a suspicion of invasive fungal disease (IFD). CAR-T therapy increases the risk of infectious complications [3, 5, 6]. Broad-spectrum antibiotic therapy and liposomal amphotericin B resulted in clinical improvement. Due to a bronchopleural fistula found in bronchofiberoscopy, an upper left lobectomy was performed, although histological examination excluded IFD and NHL. Compared to allogeneic hematopoietic cell transplantation (allo-HCT), the incidence of IFDs after CAR-T is rare [5–7]. 180 days post-infusion, the patient achieved complete metabolic response (Deauville Scale 3) (CR).

In November 2020, with persisting CR, 10/10 human leukocyte antigen (HLA)-matched sibling HCT (hematopoietic cell transplantation) with BendaFlu (bendamustine, fludarabine) reduced-intensity conditioning was implemented. Graft-vesus-host disease (GvHD) prophylaxis included cyclosporin A, thymoglobulin, and methotrexate. Hematological recovery was observed on day 14. On day 3 post-allo-HCT, fever and cough occurred, diagnosed as coronavirus disease 2019 (COVID-19). Remdesivir and plasma of convalescent application resulted in resolution of symptoms within 48 h. Cutaneous grade 2 GvHD occurred on day 48. 90 days post-HCT, the patient persisted in CR, Eastern Cooperative Oncology Group (ECOG) Performance Status Scale 0 without symptoms of GvHD with 100% donor chimerism. The recent assessment in February 2022 confirmed CR.

Discussion

CAR-T therapy is a powerful tool in R/R lymphomas treatment, and in this case, resulted in the achievement of immediate disease control leading to PR and enabling effective allo-HCT. Despite a high CR rate, there is still up to a 60% risk of progression or relapse after CAR-T therapy of R/R LBCL. Thus, allo-HCT could be considered to achieve sustainability of response, especially in patients without CR at 30 days post-infusion [8]. Relapses often occur in known pretreatment sites [9]. Therefore, radiotherapy to high-risk lesions could be considered. Also, bridging with radiotherapy prior to CAR-T infusion is an option [10]. Nevertheless, the role of radiotherapy post-CAR-T infusion remains undefined. New strategies and management standardization for responding patients are needed.

The risk of severe adverse events highlights the requirement for complex care and specialized centers prepared to manage them [5]. In the ZUMA-1 trial, CRS occurrence was 93%, and ICANS 64%. However, respectively, only 13% and 28% of cases were G3 or higher [3]. Currently, early use of tocilizumab in CRS and steroids in ICANS is recommended [10].

Considering that CAR-T is a still developing yet successful technology with further indications expanding, this approach will play a significant part in treating hematological

malignancies. Complications might be life-threatening and complex but, due to standardized algorithms, they are now manageable.

Authors' contributions

All authors — data collection, analysis, writing, and manuscript acceptance.

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; uniform requirements for manuscripts submitted to biomedical journals.

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Extramedullary plasmacytoma of larynx manifesting as chronic hypertrophic laryngitis

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Introduction

Extramedullary plasmacytoma (EMP) is a rare variant of plasma cell myeloma (PCM) that is localized to soft tissues in the absence of any detectable signs of systemic disease including marrow plasma cell infiltration, osteolysis or monoclonal protein. EMPs have a strong predilection towards the head and neck region, and more than 80% of cases are located in the upper aerodigestive tract (UADT) [1, 2]. Most UADT EMPs occur in the nasal cavity, paranasal sinuses, oropharynx and nasopharynx, while the larynx is rarely involved (6–18% of cases) [1, 3–5]. Importantly, EMP constitutes less than 0.2% of laryngeal malignancies [1].

A biological basis for EMP's affinity to the UADT has not yet been elucidated. Interestingly, chronic laryngitis, a nonspecific prolonged laryngeal inflammation, is a clinical precancerous condition [6, 7]. However, to the best of our knowledge, any association between chronic laryngitis and EMP of the larynx has yet to be postulated.

Case description

A 70-year-old male patient with a history of gastroesophageal reflux disease (GERD), smoking and asbestos exposure was referred to our Department of Otorhinolaryngology in August 2017 due to recurrent hypertrophic lesions within the larynx causing hoarse voice, cough and mild dyspnea. In the preceding year, the patient had been hospitalized in another Department of Otorhinolaryngology due to hoarseness, and histopathological examination of the larynx had revealed paraepidermal epithelium with strong p16 expression, indicative for human papilloma virus (HPV) infection.

During the first stay, directoscopy with subsequent histopathological examination of laryngeal specimens showed severe inflammatory infiltrates. Endoscopic examinations performed during outpatient follow-up visits revealed periodic recurrence of hypertrophic lesions, primarily affecting the epiglottis, aryepiglottic folds, arytenoids and ventricular folds bilaterally (Figure 1A, B). Moreover, generalized thickening of supralaryngeal structures was found in a computed tomography (CT) scan (Figure 1C, D). Four subsequent diagnostic hospitalizations with microsurgical laser procedures of the larynx provided inconsistent histopathological findings. Proposed differential diagnoses included plasma cell dyscrasia and IgG4-related disease, but the diagnostic criteria of these conditions were not met. No consensus was reached until the last histopathological finding in October 2019 revealed lambda light chains secreting infiltration of plasma cell with aberrant CD19-negative immunophenotype (Figure 1E, F).

The patient was referred to the Department of Hematology for further evaluation. No anemia, hypercalcemia or increased creatin level were found. Electrophoresis and immunofixation of serum and urine were negative for monoclonal component, and the serum concentrations of kappa and lambda free light chains were normal. Bone marrow aspiration, flow cytometry and biopsy did not reveal clonal

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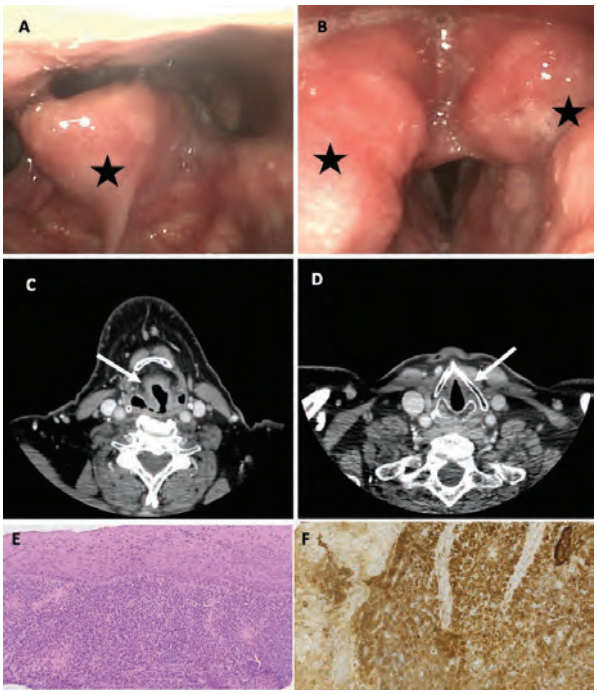

Figure 1. Endoscopic view of edematous epiglottis (black asterisk) (**A**) and hypertrophic aryepiglottic folds, arytenoids and ventricular folds bilaterally (black asterisk) (**B**) and of patient's larynx infiltrated with extramedullary plasmacytoma. Neck computed tomography (CT) scan with enlarged, edematous supralaryngeal structures (white arrow) without increased tissue enhancement (**C**) and without features of thyroid cartilage (white arrow) infiltration (**D**). Histological view of hematoxylin and eosin staining of laryngeal specimen with diffused plasma cell infiltration beneath squamous epithelium layer (**E**), and strong cytoplasmic lambda light chain positivity (**F**)

plasma cells. Low-dose CT body scan revealed no osteolitic lesions.

Based on these results, systemic involvement of PCM was excluded, and the diagnosis of laryngeal EMP was established. The patient was successfully treated with radiotherapy of the larynx area with a cumulative dose of 50 Gy. At the last follow up visit, 18 months following treatment completion, the patient remained in complete remission.

Discussion

EMP of the larynx primarily affects patients aged over 50 years with a strong male predominance (male: female ratio 3:1) [3–5]. The most common symptoms are dysphonia, dysphagia, cough, and dyspnea. In examination, it often presents as a polypoid or sessile mass and occasionally appears to be a diffuse submucosal swelling [3].

Chronic laryngitis is a nonspecific condition of prolonged laryngeal inflammation manifesting mainly with hoarseness and cough resulting from voice overuse, irritation or infection. Chronic hypertrophic laryngitis, leukoplakia and erythroplakia are macroscopically considered to be premalignant lesions [8]. There is a known association between chronic laryngitis and neoplastic transformation. About 90% of malignant tumors of the larynx are carcinomas developing from premalignant lesions [6, 7].

In the presented case, EMP may be the underlying cause and the medium for the development of chronic laryngitis.

However, another, more intriguing, scenario is possible. It could be hypothesized that chronic inflammation, resulting from known chronic irritation in the patient's history (GERD, smoking, asbestos, HPV viral infection), had played a crucial role in the development of EMP. This theory could be supported by the observation by DiStadio et al. [9] who described the development of EMP of the nasal cavity stimulated by chronic inflammation. It is evident that more data needs to be accumulated to prove any causal relationship between these two entities.

Current treatment options for EMP of the larynx include local radiotherapy or surgical excision of the tumor with subsequent local radiotherapy. Potential treatment side effects of radiotherapy are skin reactions, sore throat, dry throat, and voice changes. Based on previous anecdotal reports, both short-term and long-term efficacy seem satisfactory [1, 10].

From the clinical point of view, our case highlights the crucial role of laryngeal biopsy in identifying the cause of chronic laryngitis, and illustrates the difficulties in the diagnostic process of EMP localized in the UADT (e.g. multiple biopsies, ambiguous histopathological findings). Furthermore, it underscores the efficacy of standard treatment

of EMP with radiotherapy [3]. Nevertheless, based on the literature, the risk of transformation to systemic PCM is 11–30% [11]. Such systemic progression of EMP should be treated with standard chemotherapy or immunochemotherapy for PCM, and response needs to be consolidated by a high-dose melphalan with autologous stem cell transplantation in younger patients. Despite the impressive advances in the treatment of plasma cell neoplasms that have been made over the last two decades, evolution to PCM appears to be the main cause of death among patients with EMP.

Authors' contributions

ES — clinical analysis, writing manuscript. AR — clinical analysis, writing manuscript. AK — writing manuscript, critical revision. KN — clinical analysis, critical revision, writing manuscript. IH — clinical analysis, critical revision. JG — histopathological revision, microscopic images, critical revision. KJ — clinical analysis, critical revision, writing manuscript.

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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Role of *Bradyrhizobium enterica* in gastrointestinal graft-versus-host disease

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Bradyrhizobium enterica in cord colitis syndrome was first described as an agent by Herrera et al. Cord colitis syndrome is defined as chronic active colitis and granulomatous inflammation that responds to antibiotics, with late-onset diarrhea after umbilical cord blood transplantation without known infectious agents or graft-versus-host disease (GvHD) [1]. No known infectious agent has been detected in cord colitis syndrome. However, since the colitis clinic responded to antibiotherapy such as metronidazole, alone or in combination with a fluoroquinolone, DNA samples of the newly discovered bacterium *Bradyrhizobium enterica* were detected in the DNA determinations made from samples taken from the intestines of all patients diagnosed with cord colitis.

Bradyrhizobium is a gram-negative, aerobic, slow-growing, non-spore-forming bacillus, a motile bacterial genus with a single subpolar flagella. As a result of comparative genomic analyses and algorithms performed by global alignment of amino acid sequences, the gene structure of *Bradyrhizobium enterica* has been found to be almost identical to that of *Bradyrhizobium japonicum*. The association of the detected sequences with cord colitis suggests that *Bradyrhizobium enterica* may be an opportunistic human pathogen [2, 3]. *Bradyrhizobium enterica* has not been investigated in patients who previously developed gastrointestinal (GIS) GvHD after allogeneic hematopoietic stem cell transplantation (allo-HSCT).

In our study, we investigated *Bradyrhizobium enterica* as a factor in patients who developed GIS GvHD after allo-HSCT.

In our study, 16 patients who were proven with tissue biopsy samples taken from the colon, where GIS GvHD develops according to the Glucksberg criteria [4] after allo-HSCT, were included. Thirteen of the patients were male and three were female. Their mean age was 45 ± 5 years. Eight of the patients were diagnosed with acute myeloid leukemia, three were diagnosed with acute lymphoblastic leukemia, two patients were diagnosed with aplastic anemia, and one patient was diagnosed with each of the following: plasma cell leukemia, mantle cell lymphoma, and chronic lymphocytic leukemia. CMV DNA was found positive in some of the patients, but none of these patients were found to have CMV in their intestinal biopsy, which was evaluated as CMV reactivation. Table I summarizes other information about these patients.

Bacterial DNA needed to be obtained from tissue biopsy samples taken from the colon. In order to obtain DNA, for DNA isolation from tissue samples in the paraffin block, NucleoSpin DNA FFPE XS (Macherey-Nagel), a commercial DNA isolation kit, was used. The obtained DNA samples were stored at –20°C until use. Polymerase chain reaction for detection of *Bradyrhizobium enterica* bacteria, forward for *Bradyrhizobium enterica* search, 5'-TCGAGGGCTACGGCTTGAAGATTT-3' and reverse 5'-ACAACGTGTTGCCGCCAATATGAG-3, a target site was attempted to amplify a 367 base pair. As a control, primers belonging to the human actin gene and the 16S ribosomal RNA gene region, which is a common gene in bacteria, were used. Forward 5'-GCGAGAAGATGACCCAGATC-3' targeting the 102 base pair gene region for the human actin gene; reverse 5'-CCAGTGGTACGGCCAGAGG-3' primers and forward 5'-GTGCAATATTCCCCACTGCT-3 targeting 93 base pairs gene region for 16S RNA; reverse 5′-CGATCCCTA GCTGGTCTGAG-3' primers were used. The following thermal cycling conditions were applied for all PCR tests: denaturation at 95°C for 2 minutes, 35 cycles: 30 seconds at 95°C, 30 seconds at 62.1°C, 40 seconds at 68°C, and final elongation at 68°C for 5 minutes [5]. In order to show

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Table I. Information on patients participating in study

Case number	Age	Gender	GIS GvHD stage	GvHD	allo-HSCT regimen	CMV DNA	Donor*
1	57	F	3	GIS	Nonmyeloablative	–	1
2	34	M	3	GIS, liver, skin	Nonmyeloablative	+	3
3	23	M	3	GIS, liver, skin	Nonmyeloablative	+	3
4	55	F	3	GIS, skin	Myeloablative	+	2
5	40	F	4	GIS, liver, skin	Myeloablative	+	1
6	62	M	3	GIS, liver, skin	Nonmyeloablative	–	1
7	39	M	4	GIS, liver, skin	Myeloablative	+	3
8	24	M	2	GIS, skin	Myeloablative	–	1
9	60	M	2	GIS, skin	Myeloablative	–	1
10	54	M	3	GIS, liver, skin	Nonmyeloablative	+	1
11	58	M	3	GIS, liver, skin	Nonmyeloablative	–	1
12	50	M	2	GIS, skin	Myeloablative	+	1
13	34	M	4	GIS, liver, skin	Myeloablative	+	1
14	44	M	3	GIS, liver, skin	Nonmyeloablative	+	3
15	44	M	3	GIS, skin	Nonmyeloablative	+	3
16	53	M	3	GIS, liver, skin	Myeloablative	+	1

*Donor scoring: 1 — human leukocyte antigen (HLA) identical sibling donor; 2 — haploidentical; 3 — HLA 9–10/10 matched unrelated donor; GIS — gastrointestinal; GvHD — graft-versus-host disease; allo-HSCT — allogeneic hematopoietic stem cell transplantation; CMV; F — female; M — male

the amplified gene regions, the amplification products were observed in UV light by running at 90 V for 45 minutes in gel electrophoresis.

As a result of the PCR experiment, gene region of *Bradyrhizobium enterica* could not be determined in any of the DNA samples isolated from patients' tissues. Control genes were found in all samples. For this study, approval was obtained from the Ethics Committee for Clinical Studies at the Adnan Menderes University School of Medicine (date: June 12, 2021; No: 2020/1368).

The intestinal mucosa is the innermost layer of the four histological layers of the major intestinal tract, followed by the submucosa, muscularis externa and serosa. The epithelium is a single-cell layer lining of the interior lumen of the gastrointestinal tract. Immediately adjacent to the epithelial layer is the lamina propria, an interstitial tissue with a rich vascular and lymphatic network and abundant leukocytes. There are various cell types within the epithelium, such as intestinal epithelial cells, goblet cells, paneth cells, intestinal stem cells and tuft cells, each with their own specific functions, including nutrient absorption and barrier function, mucus production, production of antimicrobial molecules, production of growth factors, and cellular regeneration. In human and animal studies, it has been shown that these cells have been decreased in acute GvHD [6]. In addition, the human intestinal tract contains an estimated 10 trillion bacteria from about 1,000 species. Approximately 15,000 different bacterial species such as *Gemella, Staphylococcus, Enterococcus, Lactobacillus, Streptococcus, Blautia, Eubacterium, Erysipelatoclostridium, Acidaminococcus, and Bacteroides* genus have been identified in human populations [7].

Even though GvHD is an iatrogenic illness, its pathogenesis is not completely understood, and deaths from GvHD are a continuing obstacle to successful transplantation [8]. Although the impact of bacteria on acute GIS GvHD is not fully understood, the loss of enteric flora diversity correlates with the risk of developing acute GvHD. Patients who have lost *Clostridiale* bacteria from the gut and have a significant increase in *Lactobacillales* develop acute GvHD rapidly [9]. Reduced intestinal microbial diversity represents an independent risk for post-transplant mortality [10]. To date, the *Bradyrhizobium* species has not been associated with human disease.

The detection of *Bradyrhizobium enterica* in all patients with cord colitis in our study suggests that *Bradyrhizobium enterica* may be a pathogenic bacterium for cord colitis. In our study, *Bradyrhizobium enterica* was not detected in the tissue samples taken from the colons of patients with acute GIS GvHD. Consequently, we conclude that the bacterium *Bradyrhizobium enterica* has no role in GIS GvHD after allo-HSCT.

Authors' contributions

CS — collected the data, conceived and designed the analysis, wrote the paper,contributed data tools. MT — perform

the analysis microbiology samples review. AZB — performed the analysis. İY — conceived and designed the analysis, performed the analysis ,contributed data tools.

Conflict of interest and financial support

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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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1. NAZWA PRODUKTU LECZNICZEGO: Yescarta, 0,4-2 $\times 10^8$ komórek, dyspersja do infuzji. **2. SKŁAD JAKOŚCIOWY I ILOŚCIOWY: 2.1 Opis ogólny:** Yescarta (aksykabtagen cyloleucel) to genetycznie zmodyfikowane autologiczne limfocyty T skierowane przeciw CD19 stosowane w immunoterapii. Aby przygotować produkt Yescarta, od pacjenta pobiera się limfocyty T, które są następnie genetycznie modyfikowane w warunkach *ex vivo* metodą transdukcji retrowirusowej w celu uzyskania ekspresji chimerowego receptora antygenowego (ang. *chimeric antigen receptor*, CAR) zawierającego mysi jednołańcuchowy fragment Fv anty-CD19 połączony z domeną kostymulującą CD-28 i domeną sygnalizacyjną CD3-zeta. Żywotne limfocyty CAR-T anty-CD19 są namnażane i z powrotem wprowadzane za pomocą infuzji do organizmu pacjenta, gdzie mogą rozpoznawać i eliminować komórki docelowe prezentujące CD19. **2.2 Skład jakościowy i ilościowy:** Każdy worek do jednorazowej infuzji ze swoistym dla danego pacjenta produktem Yescarta zawiera około 68 ml dyspersji limfocytów CAR-T anty-CD19, co umożliwia otrzymanie docelowej dawki wynoszącej 2×10^6 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 opalizującej dyspersja w kolorze od białego do czerwonego. **4. SZCZEGÓŁOWE DANE KLINICZNE: 4.1 Wskazania do stosowania:** Produkt Yescarta jest wskazany w leczeniu nawrotowego lub opornego na leczenie chłoniaka rozlanego z dużych komórek B (ang. *diffuse large B-cell lymphoma*, DLBCL) i pierwotnego chłoniaka śródpiersia z dużych komórek B (ang. *primary mediastinal large B-cell lymphoma*, PMBCL) u dorosłych pacjentów, którzy uprzednio otrzymali co najmniej dwie linie leczenia systemowego. **4.2 Dawkowanie i sposób podawania:** Produkt Yescarta musi być podawany w kwalifikowanym ośrodku leczniczym przez lekarza mającego doświadczenie w leczeniu złośliwych nowotworów krwi oraz przeszkolonego w zakresie podawania i leczenia pacjentów produktem Yescarta. Na wypadek wystąpienia zespołu uwalniania cytokin (ang. *cytokine release syndrome*, CRS) przed infuzją musi być dostępna przynajmniej 1 dawka tocilizumabu i sprzęt ratunkowy. Ośrodek, w którym odbywa się leczenie, musi mieć zapewniony dostęp do dodatkowej dawki tocilizumabu w ciągu 8 godzin od uprzedniego podania każdej dawki. W wyjątkowej sytuacji braku dostępności tocilizumabu uwzględnionym w wykazie produktów leczniczych zagrożonych brakiem dostępności Europejskiej Agencji Leków przed rozpoczęciem infuzji muszą być dostępne odpowiednie, alternatywne leki do leczenia CRS zamiast tocilizumabu. 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 5., 4. i 3. dniu przed infuzją produktu Yescarta należy zastosować chemioterapię limfodeplecyjną, składającą się z cyklofosfamidu w dawce 500 mg/m^2 podawanego dożylnie i fludarabiny w dawce 30 mg/m^2 podawanej dożylnie. *Premedykacja:* Zaleca się podanie paracetamolu w dawce 500-1000 mg doustnie i difenhydraminy w dawce 12,5 do 25 mg dożylnie lub doustnie (lub równoważnej) na około 1 godzinę przed infuzją produktu Yescarta. Nie zaleca się podawania ogólnoustrojowych kortykosteroidów w ramach profilaktyki, ponieważ mogą mieć wpływ na działanie produktu Yescarta. *Monitorowanie:* Po infuzji pacjentów należy monitorować codziennie przez pierwsze 10 dni po infuzji pod kątem objawów przedmiotowych i podmiotowych potencjalnego CRS, zdarzeń neurologicznych i innych toksyczności. Lekarze powinni rozważyć hospitalizację pacjenta przez pierwsze 10 dni po infuzji lub w momencie pojawienia się pierwszych objawów przedmiotowych lub podmiotowych CRS i (lub) zdarzeń neurologicznych. Po pierwszych 10 dniach od infuzji o monitorowaniu pacjenta zdecyduje lekarz. Pacjentów należy poinformować o konieczności pozostania w pobliżu kwalifikowanej placówki klinicznej przez co najmniej 4 tygodnie po infuzji. Specjalne 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 wymagane 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 powinien stosować odpowiednie środki ostrożności (nosić rękawice i okulary), aby uniknąć potencjalnego przeniesienia chorób zakaźnych. *Przygotowanie do infuzji:* Zweryfikować zgodność tożsamości pacjenta (ang. *identity,* ID) z oznaczeniami na kasecie z produktem Yescarta. Nie wolno wyjmować worka z produktem Yescarta z metalowej kasety, gdy brak zgodności informacji na etykiecie dotyczącej danego pacjenta z danymi pacjenta, dla którego przeznaczony jest ten produkt. Po potwierdzeniu ID pacjenta wyjąć worek z produktem Yescarta z metalowej kasety. Sprawdzić, czy dane pacjenta na etykiecie metalowej kasety są zgodne z danymi na etykiecie worka. Przed rozmrożeniem sprawdzić, czy worek z produktem nie ma jakichkolwiek uszkodzeń. W razie uszkodzenia worka postępować zgodnie z lokalnymi wytycznymi dotyczącymi postępowania z odpadami materiałów pochodzenia ludzkiego (lub niezwłocznie przekazać informację do firmy Kite). Umieścić worek do infuzji w drugim worku. Rozmrozić produkt Yescarta w temperaturze wynoszącej około 37°C w kąpieli wodnej lub metodą suchego rozmrażania do momentu, gdy w worku infuzyjnym nie będzie widocznego lodu. Delikatnie wymieszać zawartość worka, aby rozprowadzić grudki materiału komórkowego. Jeśli nadal widoczne są grudki materiału komórkowego, kontynuować delikatne mieszanie zawartości worka. Powinno to doprowadzić do rozproszenia małych grudek materiału komórkowego. Produktu Yescarta nie należy myć, wirować ani powtórnie odtwarzać zawiesiny na nowych nośnikach przed infuzją. Rozmrażanie powinno trwać około 3 do 5 minut. Po rozmrożeniu produkt Yescarta zachowuje trwałość w temperaturze pokojowej (od 20°C do 25°C) do 3 godzin. Infuzję produktu Yescarta należy jednak rozpocząć w ciągu 30 minut od rozmrożenia. *Podawanie:* Tylko do stosowania autologicznego. Tocilizumab oraz sprzęt ratunkowy powinny być dostępne przed infuzją i podczas monitorowania. W wyjątkowej sytuacji braku dostępności tocilizumabu uwzględnionym w wykazie produktów leczniczych zagrożonych brakiem dostępności Europejskiej Agencji Leków przed rozpoczęciem infuzji muszą być dostępne odpowiednie, alternatywne leki do leczenia CRS zamiast tocilizumabu. Nie wolno używać filtra do deplecji leukocytów. Zaleca się założenie centralnego dostępu żylnego w celu podania produktu Yescarta. Ponownie zweryfikować ID pacjenta w celu potwierdzenia zgodności z oznaczeniami pacjenta na worku z produktem Yescarta. Przed infuzją wypełnić zestaw do infuzji roztworem chlorku sodu (0,154 mmol sodu/ml). Cała zawartość worka z produktem Yescarta powinna zostać podana w infuzji w ciągu 30 minut metodą grawitacyjną lub z użyciem objętościowej pompy infuzyjnej. Delikatnie masować worek podczas infuzji produktu Yescarta, aby zapobiec tworzeniu się grudek materiału komórkowego. Po podaniu w infuzji całej zawartości worka, przepłukać zestaw do infuzji roztworem chlorku sodu (0,154 mmol sodu/ml) z tą samą prędkością infuzji, aby upewnić się, że produkt Yescarta został podany w całości. Instrukcja dotycząca postępowania, przypadkowego narażenia oraz usuwania tego produktu, patrz punkt 6.6 ChPL. **4.3 Przeciwwskazania:** Nadwrażliwość na substancję czynną lub którąkolwiek substancję pomocniczą wymienioną w punkcie 6.1 ChPL. Należy uwzględnić przeciwwskazania dotyczące chemioterapii limfodeplecyjnej. **4.4 Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania:** 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 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. Pacjentów należy monitorować codziennie przez pierwsze 10 dni po infuzji w celu wykrycia przedmiotowych i podmiotowych objawów potencjalnego CRS, zdarzeń neurologicznych i innych toksyczności. Lekarze powinni rozważyć hospitalizację pacjenta przez pierwsze 10 dni po infuzji lub w momencie wystąpienia pierwszych objawów przedmiotowych/podmiotowych CRS i (lub) zdarzeń neurologicznych. Po pierwszych 10 dniach po infuzji o monitorowaniu pacjenta zdecyduje lekarz. Należy poinformować pacjentów o konieczności pozostawania w pobliżu kwalifikowanego ośrodka leczniczego przez co najmniej 4 tygodnie po infuzji oraz o konieczności uzyskania natychmiastowej pomocy medycznej w razie wystąpienia przedmiotowych lub podmiotowych objawów CRS lub neurologicznych działań niepożądanych. W zależności od stopnia nasilenia danego działania niepożądanego należy rozważyć monitorowanie parametrów życiowych i czynności narządów. Powody odroczenia leczenia: Ze względu na zagrożenia związane z leczeniem produktem Yescarta podanie infuzji należy wstrzymać, jeśli u pacjenta występuje którykolwiek z następujących stanów: utrzymujące się ciężkie działania niepożądane (w szczególności działania dotyczące płuc, serca lub niedociśnienie), w tym związane z wcześniejszymi chemioterapiami; czynne, niekontrolowane zakażenie; czynna choroba przeszczep przeciwko gospodarzowi (ang. *graft-versus-host disease*, GVHD). Badania serologiczne: Przed pobraniem komórek do wytworzenia produktu Yescarta, należy wykonać badania przesiewowe na obecność HBV, HCV i HIV (patrz punkt 4.2). Oddawanie krwi, narządów, tkanek i komórek: Pacjenci leczeni produktem Yescarta nie powinni 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 (patrz punkt 4.8). O leczeniu CRS decyduje lekarz na podstawie występujących u pacjenta objawów klinicznych oraz zgodnie z algorytmem postępowania w CRS przedstawionym w tabeli 1. W leczeniu CRS o nasileniu umiarkowanym lub ciężkim, związanego z podaniem produktu Yescarta, stosowano terapię opartą na inhibitorze receptora interleukiny 6 (IL-6), takim jak tocilizumab. Ośrodek, w którym odbywa się infuzja produktu Yescarta, musi przystępując do niej dysponować co najmniej 1 dostępną do podania dawką tocilizumabu dla każdego pacjenta. Ośrodek, w którym odbywa się leczenie, musi mieć dostęp do dodatkowej dawki tocilizumabu w ciągu 8 godzin od podania każdej z uprzednich dawek. W wyjątkowej sytuacji braku dostępności tocilizumabu uwzględnionym w wykazie produktów leczniczych zagrożonych brakiem dostępności Europejskiej Agencji Leków ośrodek leczniczy musi mieć dostęp do odpowiednich, alternatywnych leków do leczenia CRS zamiast tocilizumabu. Pacjentów należy codziennie monitorować w kwalifikowanej placówce klinicznej przez co najmniej 10 dni po infuzji pod kątem objawów przedmiotowych i podmiotowych CRS. Po upływie pierwszych 10 dni od infuzji o monitorowaniu pacjentów zdecyduje lekarz. Należy poinformować pacjentów o konieczności pozostawania w pobliżu kwalifikowanej placówki klinicznej przez co najmniej 4 tygodnie po infuzji oraz o konieczności uzyskania natychmiastowej pomocy medycznej w razie wystąpienia objawów przedmiotowych lub podmiotowych CRS. Opracowano algorytmy postępowania mające na celu łagodzenie niektórych objawów CRS występujących u pacjentów przyjmujących produkt Yescarta. Obejmują one stosowanie tocilizumabu lub tocilizumabu z kortykosteroidami w przypadkach CRS o nasileniu umiarkowanym, ciężkim lub zagrażającym życiu, jak przedstawiono w tabeli 1. Pacjentów, u których wystąpi CRS w stopniu 2. lub wyższym (np. niedociśnienie, brak odpowiedzi po podaniu płynów lub hipoksja wymagająca podania dodatkowego tlenu), należy monitorować z wykorzystaniem ciągłej telemetrii kardiologicznej oraz pulsoksymetrii. U pacjentów z ciężkim CRS należy rozważyć wykonanie echokardiogramu w celu oceny czynności serca. W przypadku ciężkiego lub zagrażającego życiu CRS należy rozważyć wdrożenie intensywnej terapii w ramach leczenia wspomagającego. Produktu Yescarta nie należy podawać pacjentom, u których występuje czynne zakażenie lub choroba zapalna, dopóki stany te nie ustąpią. Wiadomo, że CRS jest związany z niewydolnością narządów docelowych (np. wątroby, nerek, serca i płuc). Ponadto w przebiegu CRS może dojść do nasilenia występujących zaburzeń tych narządów. U pacjentów z istotnymi klinicznie zaburzeniami kardiologicznymi należy stosować standardy opieki w stanach krytycznych oraz rozważyć takie środki, jak echokardiografia. W celu rozpoznania CRS należy wykluczyć inne przyczyny ogólnoustrojowej odpowiedzi zapalnej, w tym zakażenie. W razie wystąpienia gorączki neutropenicznej należy dokonać oceny pod kątem zakażenia i zastosować antybiotyki o szerokim spektrum działania, płyny oraz leczenie podtrzymujące zgodnie z istniejącymi wskazaniami medycznymi. W przypadku pacjentów z ciężkim lub nieodpowiadającym na leczenie CRS należy rozważyć możliwość wystąpienia limfohistiocytozy hemofagocytarnej/zespołu aktywacji makrofagów (ang. *haemophagocytic lymphohistiocytosis/macrophage activation syndrome*, HLH/MAS). Produkt Yescarta nadal rozprzestrzenia się i utrzymuje w organizmie po podaniu tocilizumabu oraz kortykosteroidów. Nie zaleca się stosowania antagonistów czynnika martwicy nowotworu (ang. *tumour necrosis factor*, TNF) w leczeniu CRS związanego z zastosowaniem produktu Yescarta. **Tabela 1: Algorytm postępowania w zespole uwalniania cytokin (CRS).** Nasilenie CRS[a]: 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 hipotensja odpowiadająca na podanie płynów lub małej dawki jednego leku wazopresyjnego, lub toksyczność narządowa 2. stopnia[b]. *Tocilizumab:* Podać tocilizumab[c] w dawce 8 mg/kg dożylnie przez 1 godzinę (nie przekraczać dawki 800 mg). W razie potrzeby podawać tocilizumab co 8 godzin, gdy brak odpowiedzi na dożylne podanie płynów lub rośnie zapotrzebowanie na tlenoterapię. Nie podawać więcej niż 3 dawki w ciągu 24 godzin; maksymalna całkowita liczba dawek to 4 dawki, jeśli brak poprawy klinicznej dotyczącej objawów przedmiotowych i podmiotowych CRS lub jeśli brak odpowiedzi na drugą lub kolejną dawkę tocilizumabu, należy rozważyć zastosowanie alternatywnych sposobów leczenia CRS. *Kortykosteroidy:* Leczenie jak w stopniu 3., gdy brak poprawy w ciągu 24 godzin od podania tocilizumabu. Stopień 3.: Objawy wymagają poważnej interwencji, po której ustępują. Zapotrzebowanie na tlen przekraczające lub równe 40% FiO_2 lub hipotensja wymagająca podania dużej dawki leku wazopresyjnego albo zastosowania wielu leków wazopresyjnych, lub toksyczność narządowa 3. stopnia, albo hipertransaminazemia 4. stopnia. *Tocilizumab:* Leczenie jak w stopniu 2. *Kortykosteroidy:* Podać metyloprednizolon dożylnie w dawce 1 mg/kg dwa razy na dobę lub równoważną dawkę deksametazonu (np. 10 mg dożylnie co 6 godzin). Kontynuować podawanie kortykosteroidów do momentu, gdy zdarzenie zostanie zakwalifikowane jako zdarzenie stopnia 1. lub mniejszego, a następnie stopniowo zmniejszać dawkę. Gdy brak poprawy, zastosować leczenie jak w stopniu 4. (poniżej). 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, które mogą zagrażać życiu lub prowadzić do zgonu (patrz punkt 4.8). Pacjenci z zaburzeniami OUN w wywiadzie, takimi jak drgawki lub niedokrwienie naczyniowo-mózgowe, mogą być narażeni na większe ryzyko. Zgłaszano przypadki zakończonego zgonem i ciężkiego obrzęku mózgu u pacjentów leczonych produktem Yescarta. Pacjentów należy monitorować pod kątem objawów przedmiotowych i podmiotowych neurologicznych działań niepożądanych (Tabela 2). Po infuzji pacjentów należy monitorować w kwalifikowanej placówce opieki zdrowotnej co najmniej codziennie przez pierwsze 10 dni pod kątem objawów przedmiotowych i podmiotowych toksyczności neurologicznej. Po tych pierwszych 10 dniach o monitorowaniu pacjenta zdecyduje lekarz. Pacjentów należy poinformować o konieczności pozostania w pobliżu kwalifikowanej placówki klinicznej przynajmniej przez 4 tygodnie po infuzji i natychmiastowego zwrócenia się po pomoc medyczną, jeśli wystąpią objawy przedmiotowe lub podmiotowe toksyczności neurologicznej. W zależności od stopnia nasilenia danego działania niepożądanego należy rozważyć monitorowanie parametrów życiowych i wydolności narządów. Pacjentów, u których wystąpi toksyczność neurologiczna stopnia 2. lub wyższego, należy monitorować z wykorzystaniem ciągłej telemetrii kardiologicznej oraz pulsoksymetrii. W razie ciężkiej lub zagrażającej życiu toksyczności neurologicznej należy wdrożyć intensywną terapię wspomagającą. Należy rozważyć podanie leków przeciwdrgawkowych niemających działania uspokajającego w ramach profilaktyki przeciwdrgawkowej zgodnie ze wskazaniami klinicznymi dla działań niepożądanych 2. lub wyższego stopnia. Opracowano algorytmy postępowania mające na celu złagodzenie neurologicznych działań niepożądanych występujących u pacjentów przyjmujących produkt Yescarta. Obejmują one stosowanie tocilizumabu (w razie współistniejącego CRS) i (lub) kortykosteroidów w przypadku umiarkowanych, ciężkich lub zagrażających życiu neurologicznych działań niepożądanych, jak przedstawiono w tabeli 2. **Tabela 2: Algorytmy postępowania dotyczące objawów neurologicznych działań niepożądanych.** 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). Pacjentów należy monitorować pod kątem objawów przedmiotowych i podmiotowych zakażenia przed, w trakcie i po podaniu produktu Yescarta w infuzji oraz zastosować odpowiednie leczenie. Należy zastosować profilaktykę przeciwbakteryjną zgodnie z obowiązującymi standardowymi wytycznymi. Po infuzji produktu Yescarta u pacjentów stwierdzano gorączkę neutropeniczną (patrz punkt 4.8) i może ona występować jednocześnie z CRS. W przypadku wystąpienia gorączki neutropenicznej należy ocenić, czy nie jest to zakażenie, i zastosować antybiotyki o szerokim spektrum działania, płyny oraz leczenie objawowe zgodnie ze wskazaniami medycznymi. 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 należy 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 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% maksymalnego dziennego dopuszczalnego spożycia sodu, wynoszącego 2 g dla osoby dorosłej, zgodnie z zaleceniami WHO. Oczekuje się, że pacjenci zostaną wpisani do rejestru pacjentów, na podstawie którego prowadzona będzie obserwacja w celu lepszego poznania długoterminowego bezpieczeństwa stosowania i skuteczności produktu Yescarta. **4.8 Działania niepożądane:** Podsumowanie profilu bezpieczeństwa: Dane dotyczące bezpieczeństwa opisane w tym punkcie odzwierciedlają skutki narażenia na produkt Yescarta w badaniu fazy I/II ZUMA-1, w którym 108 pacjentów z nawrotowym/opornym chłoniakiem nieziarniczym (NHL) z limfocytów B otrzymywało limfocyty CAR-T w zalecanej dawce w zależności od masy ciała. Mediana okresu obserwacji wyniosła 27,4 miesiąca. Do najbardziej poważnych i najczęstszych działań niepożądanych należały CRS (93%), encefalopatia (58%) oraz zakażenia (39%). Ciężkie działania niepożądane wystąpiły u 56% pacjentów. Do najczęstszych działań niepożądanych należały: encefalopatia (22%), zakażenia nieswoistymi patogenami (16%), zakażenia bakteryjne (6%), gorączka neutropeniczna (6%), zakażenia wirusowe (5%) i gorączka (5%). Najczęściej występujące działania niepożądane stopnia 3. lub wyższego obejmowały encefalopatię (31%), zakażenia nieswoistymi patogenami (19%), CRS (11%), zakażenie bakteryjne (9%), afazję (7%), zakażenie wirusowe (6%), stan majaczeniowy (6%), hipotensję (6%) i nadciśnienie (6%). Tabelaryczna lista działań niepożądanych: Działania niepożądane zgłaszane w badaniach klinicznych oraz po wprowadzeniu produktu do obrotu przedstawiono poniżej. Działania te są wymienione według klasyfikacji układów i narządów oraz częstości występowania. Częstości występowania określone są w następujący sposób: bardzo często (≥ 1/10), często (≥ 1/100 do < 1/10), niezbyt często (≥ 1/1000 do < 1/100), rzadko (≥ 1/10 000 do < 1/1000) i bardzo rzadko (< 1/10 000). W obrębie każdej grupy o określonej częstości występowania działania niepożądane wymieniono zgodnie ze zmniejszającym się nasileniem. **Tabela 3: Działania niepożądane związane ze stosowaniem produktu Yescarta.** *Zakażenia i zakażenia pasożytnicze:* Bardzo często: zakażenia nieswoistymi patogenami, zakażenie wirusowe, zakażenie bakteryjne. Często: zakażenie grzybicze. *Zaburzenia krwi i układu chłonnego:* Bardzo często: leukopenia, neutropenia, niedokrwistość, małopłytkowość. Często: koagulopatia. *Zaburzenia układu immunologicznego:* Bardzo często: zespół uwalniania cytokin, hipogammaglobulinemia. Często: nadwrażliwość, histiocytoza hemofagocytarna. *Zaburzenia metabolizmu i odżywiania:* Bardzo często: odwodnienie, zmniejszone łaknienie, hipofosfatemia, hiponatremia, zmniejszenie masy ciała. Często: hipokalcemia, hipoalbuminemia. *Zaburzenia psychiczne:* Bardzo często: majaczenia, lęk. Często: bezsenność. *Zaburzenia układu nerwowego:* Bardzo często: encefalopatia, ból głowy, drżenie, zawroty głowy, afazja. Często: ataksja, neuropatia, drgawki, dyskalkulia, mioklonie. Niezbyt często: obrzęk rdzenia kręgowego, zapalenie rdzenia kręgowego, porażenie czterokończynowe. *Zaburzenia serca:* Bardzo często: tachykardia, arytmia. Często: zatrzymanie akcji serca, niewydolność serca. *Zaburzenia naczyniowe:* Bardzo często: niedociśnienie, nadciśnienie. Często: zakrzepica, zespół przesiąkania włośniczek. *Zaburzenia układu oddechowego, klatki piersiowej i śródpiersia:* Bardzo często: kaszel, duszność, hipoksja, wysięk opłucnowy. Często: obrzęk płuc. *Zaburzenia żołądka i jelit:* Bardzo często: biegunka, nudności, wymioty, zaparcia, ból brzucha, suchość w jamie ustnej. Często: dysfagia*. *Zaburzenia skóry i tkanki podskórnej:* Często: wysypka. *Zaburzenia układu mięśniowo-szkieletowego i tkanki łącznej:* Bardzo często: zaburzenia ruchowe, ból kończyn, ból pleców, ból stawów, ból mięśni. *Zaburzenia nerek i dróg moczowych:* Często: niewydolność nerek. *Zaburzenia ogólne i stany w miejscu podania:* Bardzo często: zmęczenie, gorączka, obrzęk, dreszcze. *Badania diagnostyczne:* Bardzo często: zwiększone stężenie aminotransferazy alaninowej, zwiększone stężenie aminotransferazy asparaginowej. Często: zwiększone stężenie bilirubiny. W tabeli 3 ujęto wyłącznie przypadki cytopenii, które spowodowały (I) wystąpienie nowych lub zaostrzenie istniejących następstw klinicznych, (II) wymagały leczenia lub (III) modyfikacji aktualnego leczenia. * Dysfagię zgłaszano w ramach toksycznego działania na układ nerwowy i encefalopatii. Opis wybranych działań niepożądanych: *Zespół uwalniania cytokin:* CRS wystąpił u 93% pacjentów. U jedenastu procent (11%) pacjentów wystąpił CRS stopnia 3. lub wyższego (ciężki, zagrażający życiu oraz prowadzący do zgonu). Mediana czasu do wystąpienia CRS wynosiła 2 dni (zakres od 1 do 12 dni), a mediana czasu trwania 7 dni (zakres od 2 do 29 dni). U dziewięćdziesięciu ośmiu procent pacjentów (98%) doszło do ustąpienia CRS. Najczęściej występujące objawy przedmiotowe i podmiotowe związane z CRS obejmowały gorączkę (83%), niedociśnienie (44%), tachykardię (24%), hipoksję (23%) i dreszcze (20%). Ciężkie działania niepożądane, które mogą być związane z CRS, obejmowały: ostre uszkodzenie nerek, migotanie przedsionków, tachykardię komorową, zatrzymanie akcji serca, niewydolność serca, zespół przesiąkania włośniczek, niedociśnienie, hipoksję i HLH/MAS. Wskazówki dotyczące monitorowania i leczenia – patrz punkt 4.4. *Neurologiczne działania niepożądane:* Neurologiczne działania niepożądane wystąpiły u 67% pacjentów. U trzydziestu dwóch procent (32%) pacjentów wystąpiły działania niepożądane stopnia 3. lub wyższego (ciężkie lub zagrażające życiu). Mediana czasu do wystąpienia działań niepożądanych wynosiła 5 dni (zakres od 1 do 17 dni). Mediana czasu trwania wynosiła 13 dni (zakres: od 1 do 191 dni). U większości pacjentów neurologiczne działania niepożądane ustąpiły, z wyjątkiem 4 pacjentów, u których niepożądane działania neurologiczne utrzymywały się do momentu zgonu; zgony te były spowodowane innymi przyczynami. Najczęstszymi objawami przedmiotowymi i podmiotowymi związanymi z neurologicznymi działaniami niepożądanymi były: encefalopatia (58%), ból głowy (40%), drżenie (31%), zawroty głowy (21%), afazja (18%) i stan majaczeniowy (17%). Zgłaszano ciężkie działania niepożądane, w tym encefalopatię (22%), afazję (4%), stan majaczeniowy (4%) i drgawki (1%), u pacjentów, którym podawano produkt Yescarta. Inne neurologiczne działania niepożądane były zgłaszane rzadziej w badaniach klinicznych i obejmowały dysfagię (5%), zapalenie rdzenia kręgowego (0,2%) i porażenie czterokończynowe (0,2%). W okresie po wprowadzeniu produktu do obrotu zgłoszono wystąpienie obrzęku rdzenia kręgowego, w kontekście neurotoksyczności. Wskazówki dotyczące monitorowania i leczenia – patrz punkt 4.4. *Gorączka neutropeniczna i zakażenia:* Gorączkę neutropeniczną zaobserwowano u 36% pacjentów po infuzji produktu Yescarta. Zakażenia wystąpiły u 39% pacjentów w badaniu ZUMA-1. Zakażenia stopnia 3. lub wyższego (ciężkie, zagrażające życiu lub prowadzące do zgonu) wystąpiły u 26% pacjentów. Zakażenia nieswoistymi patogenami oraz zakażenia bakteryjne i wirusowe stopnia 3. lub wyższego wystąpiły u, odpowiednio, 19%, 9% i 6% pacjentów. Najczęstszym miejscem zakażenia były drogi oddechowe. Wskazówki dotyczące monitorowania i leczenia – patrz punkt 4.4. *Przedłużająca się cytopenia:* Neutropenia (w tym gorączka neutropeniczna), niedokrwistość i małopłytkowość stopnia 3. lub wyższego wystąpiły u, odpowiednio, 80%, 45% i 40% pacjentów. Przedłużająca się (utrzymująca się w dniu 30. lub pojawiająca się w dniu 30. lub później) neutropenia, małopłytkowość i niedokrwistość stopnia 3. lub wyższego wystąpiła u, odpowiednio, 26%, 24% i 10% pacjentów. Utrzymująca się neutropenia, małopłytkowość i niedokrwistość stopnia 3. lub wyższego po dniu 93. wystąpiła u, odpowiednio, 11%, 7% i 3% pacjentów. Wskazówki dotyczące leczenia – patrz punkt 4.4. *Hipogammaglobulinemia:* W badaniu ZUMA-1 hipogammaglobulinemia wystąpiła u 16% pacjentów. Łącznie 33 (31%) ze 108 pacjentów otrzymywało dożylne leczenie immunoglobulinami w momencie przeprowadzania analizy po 24 miesiącach. Wskazówki dotyczące leczenia – patrz punkt 4.4. Immunogenność: Immunogenność produktu Yescarta oceniano za pomocą testu immunoenzymatycznego (ELISA) wykrywającego przeciwciała wiążące FMC63, z których wywodzą się przeciwciała anty-CD19 CAR. U trzech pacjentów przed leczeniem produktem Yescarta badanie przeciwciał anty-FMC63 dało wynik dodatni. Wpływ tych przeciwciał na skuteczność lub bezpieczeństwo stosowania nie był dostrzegalny. 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 *Departamentu Monitorowania Niepożądanych Działań Produktów Leczniczych Urzędu Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych, Al. Jerozolimskie 181C, PL-02 222 Warszawa, tel.: +48 22 49 21 301, faks: +48 22 49 21 309, strona internetowa: https://smz.ezdrowie.gov.pl.* Działania niepożądane można także zgłaszać za pośrednictwem przedstawiciela podmiotu odpowiedzialnego w Polsce: Gilead Sciences Poland Sp. z o.o., tel.: +48 22 262 87 02 lub e-mail: DrugSafety.Poland@gilead.com. **7. PODMIOT ODPOWIEDZIALNY POSIADAJĄCY POZWOLENIE NA DOPUSZCZENIE DO OBROTU:** Kite Pharma EU B.V., Tufsteen 1, 2132 NT Hoofddorp, Holandia. **8. NUMER POZWOLENIA NA DOPUSZCZENIE DO OBROTU:** EU/1/18/1299/001. **WYDANE PRZEZ:** Komisję Wspólnot Europejskich. **OGÓLNA KATEGORIA DOSTĘPNOŚCI:** Rpz. **9. DATA WYDANIA PIERWSZEGO POZWOLENIA NA DOPUSZCZENIE DO OBROTU I DATA PRZEDŁUŻENIA POZWOLENIA:** Data wydania pierwszego pozwolenia na dopuszczenie do obrotu: 23 sierpnia 2018. **10. DATA ZATWIERDZENIA LUB CZĘŚCIOWEJ ZMIANY TEKSTU CHARAKTERYSTYKI PRODUKTU LECZNICZEGO:** 01/2022. Szczegółowe informacje o tym produkcie leczniczym są dostępne na stronie internetowej Europejskiej Agencji Leków http://www.ema.europa.eu.

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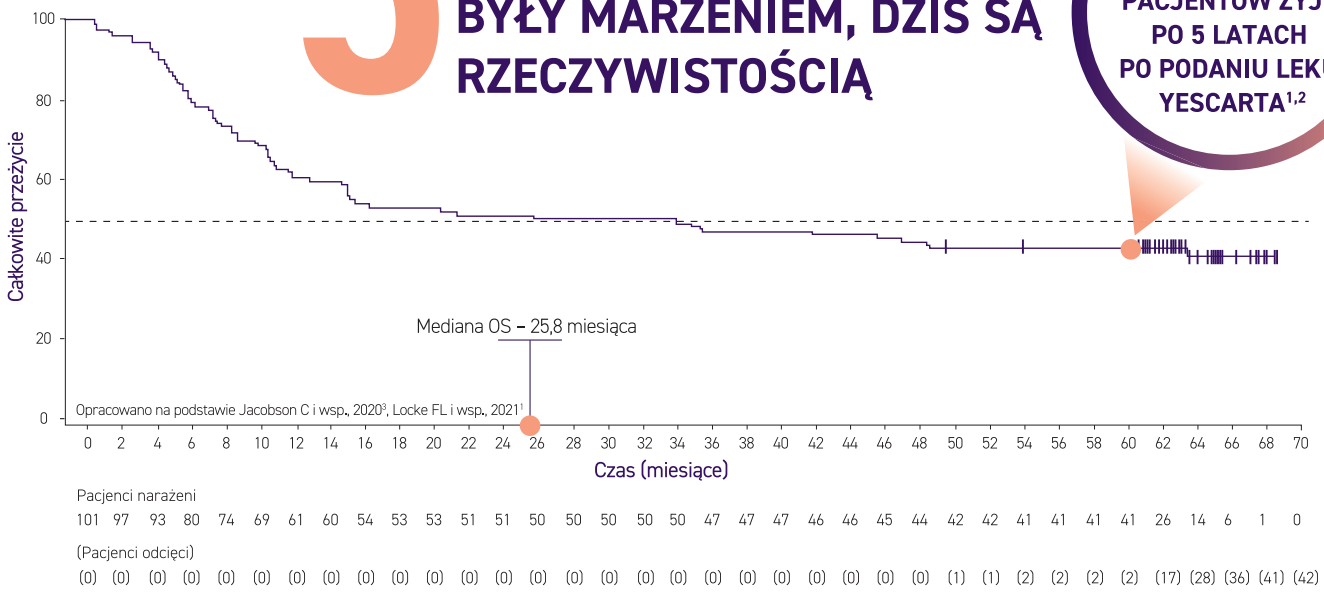

* Wartości szacunkowe wg Kaplana-Meiera dla 5-letniego wskaźnika OS wyniosły 42,6%.

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

PL-YES-0080. Data przygotowania: 06.2022

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