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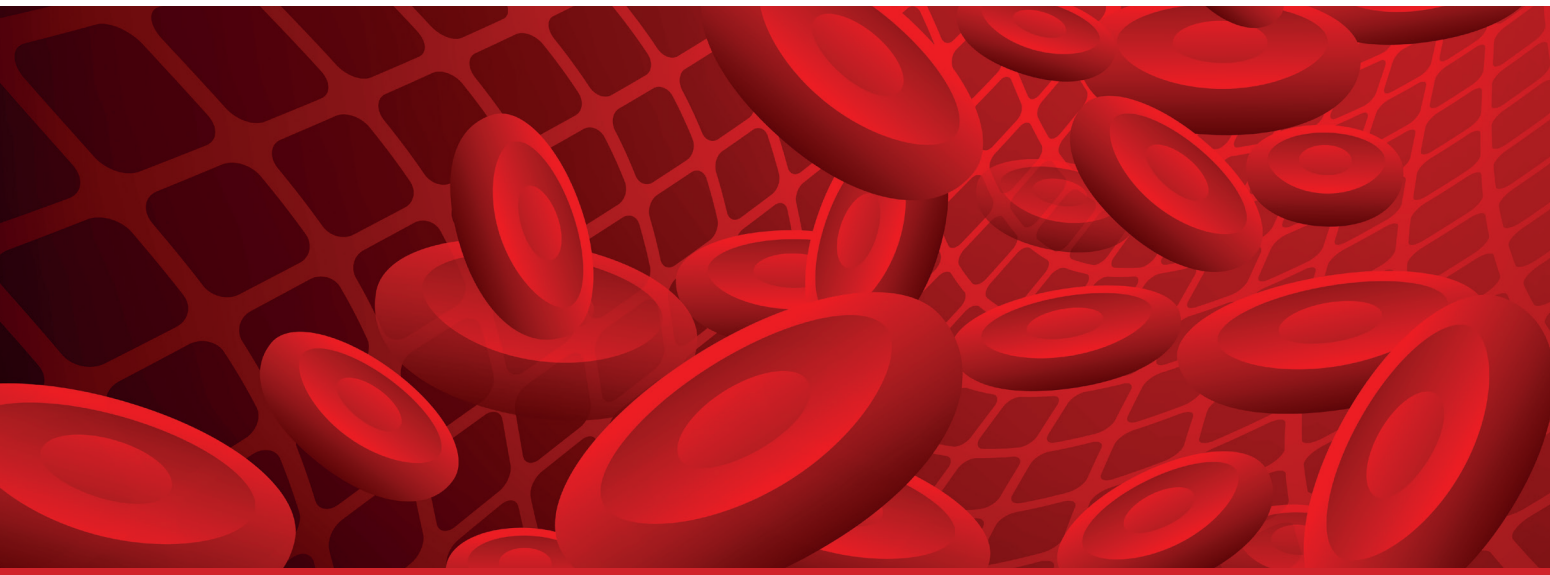

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VIA MEDICA

Lek XOSPATA

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

Rozpoznanie

Nawrotowa AML
z obecnością mutacji FLT3-TKD

Lucyna, 57 lat

XOSPATA | Nawrót | Dobry stan ogólny

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

Rozpoznanie

Oporna na leczenie AML
z obecnością mutacji FLT3-ITD

Józef, 67 lat

XOSPATA | Odporność | Dobry stan ogólny

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

Rozpoznanie

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

Paweł, 43 lata

XOSPATA | Nawrót | Dobry stan ogólny

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

Rozpoznanie

Nawrotowa AML
z mutacjami
FLT3-ITD, NPM1 i IDH1

Joanna, 77 lat

XOSPATA | Nawrót | Gorszy stan ogólny

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

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

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

1. Charakterystyka Produktu Leczniczego XOSPATA.

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

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MAT-PL-XOS-2023-00042 | Listopad 2023

XOSPATA™
gilterytynib 40 mg tabletki

Informacja o leku

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

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

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What's new in chronic myelogenous leukemia and COVID-19?

Bartosz Puła

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In this issue, I would like to highlight two important review articles.

The first article outlines new therapeutic options for chronic myelogenous leukemia (CML), with a special focus on the use of asciminib [1]. Asciminib is a new category of BCR-ABL1 tyrosine kinase inhibitor specifically targeting the myristoyl pocket of ABL tyrosine kinase. This new therapeutic option appears highly promising, especially for patients ineligible for ATP-competitive inhibitor treatment due to previous therapy resistance or intolerance. Moreover, asciminib may diminish long-term cardiovascular toxicity observed in patients treated with next-generation competitive inhibitors [1].

The second review summarizes the published studies concerning the clinical course and prevention of COVID-19 infection in hematological patients [2]. The rapid introduction of vaccines and anti-SARS-CoV-2 agents have improved patient outcomes. The clinical course in most patients is mild. Even so, some groups of patients under specific treatment modalities are at risk of developing severe infection.

It is with great sadness that we announce that Professor Euzebiusz Krykowski passed away in March 2024. His life's achievements are described by Professor Tadeusz Robak and his colleagues in an obituary in this issue [3].

Article information and declarations

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VIA MEDICA

Professor Euzebiusz Krykowski (3 January 1927–21 March 2024)

Anna Korycka-Wołowiec, Joanna Góra-Tybor, Jacek Treliński, Krzysztof Chojnowski, Tadeusz Robak*, Agnieszka Wierzbowska

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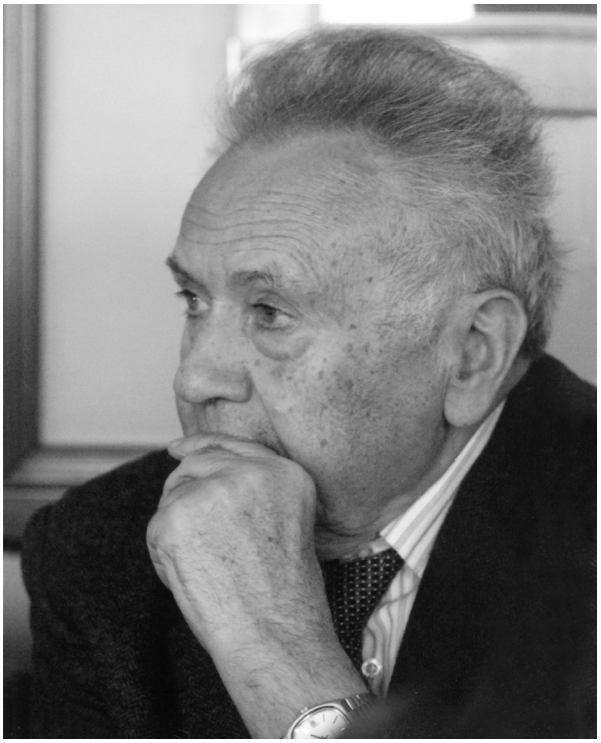

Professor Euzebiusz Krykowski

We recently bade farewell to Professor Euzebiusz Krykowski, a specialist in Hematology and a wonderful doctor, who has died at the age of 97.

Professor Krykowski was born in Brzeziny in 1927. He spent his childhood in the Vilnius region, which remained close to his heart for the rest of his life. He returned to his childhood home many times, initially in his memories, and in later years on sentimental journeys.

Euzebiusz Krykowski graduated from high school in Vilnius and participated in secret classes. As a young boy during the war, he fought in the Home Army (under the nickname 'Lech'), and took part in the battle for Vilnius in 1944. He was later deported across the USSR, to Kaluga in distant Siberia, where he spent almost two years in a Soviet forced labour camp. He returned to Poland in January 1946, where he passed his high school leaving examination, and began his studies at the Faculty of Medicine of the newly-established Medical Academy of Lodz. He obtained his medical diploma in 1952.

After graduating, Euzebiusz began his professional career as an Assistant at the 2nd Department of Internal Diseases, S. Sterling Memorial Hospital, under Prof. Jerzy Jakubowski. From 1958 to 1959, he took part in a scholarship at the Rockefeller Foundation, at Boston University in the USA, where he worked under the supervision of Prof. William Dameshek, the founder of modern Hematology; this experience would have a considerable influence on Prof. Krykowski's professional life. After returning to Poland, he began to expand his interest in Hematology. Later, he completed short research posts in several other American centres, as well as in London, Paris, Innsbruck and Lyon. In 1964, he was awarded the academic degree of Doctor of Medical Sciences by the Council of the Faculty of Medicine; in 1981 he became a Habilitated Doctor, and in 1991, he obtained the title of Professor.

In 1973, together with Prof. Aleksandra Mazurowa, Professor Krykowski jointly took over the running of the 2nd Department of Internal Diseases in the newly-established M. Copernicus Memorial University Hospital in Lodz. In this hospital, between 1984 and 1995, he served as Head of the 2nd Department and Head of the Department of Internal Medicine.

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Prof. Krykowski was the 'father' of Hematology in Lodz, being the architect of its current organisation and programme shape. In 1995, he created the Hematology Clinic of the Medical University of Lodz, which he headed until his retirement in 1997. As he himself emphasised many times, he was a student of three Professors: Jerzy Jakubowski, Włodzimierz Musiał senior, and William Dameshek.

Professor Euzebiusz Krykowski was a co-founder of the Polish Society of Hematology and Transfusion Medicine, a member of the Polish Medical Society and of the Society of Polish Internists, the Clinical Hematology Committee, the Pathophysiology Committee of the Polish Academy of Sciences, and the Lodz Scientific Society. He served as the voivodship consultant in the field of Internal Medicine. He was the supervisor of several doctoral theses and a reviewer of many other doctoral theses and scientific articles. Above all, he was an outstanding scientist and an excellent practitioner and teacher, and one who served as a role model for subsequent generations of doctors. He was devoted to his patients, and dedicated his considerable clinical intuition to their care.

Many indeed owe their return to health to him.

Even after retiring, Professor Krykowski remained professionally active and continued to work in the Hematology Clinic for many years. He maintained an interest in the affairs of the clinic and enjoyed keeping touch with the successes of his students and former colleagues, with whom he remained on friendly terms until the end of his life.

Euzebiusz Krykowski was an undisputed authority in the field of Internal Medicine and a pioneer in the development of Hematology in Poland. For his outstanding achievements in research and teaching work, and in the development of healthcare, he was awarded the Officer's Cross of the Order of Polonia Restituta.

Professor Euzebiusz Krykowski was buried in Lodz at the Doły Municipal Cemetery, but he will remain in our hearts and memories for ever.

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REVIEW ARTICLE

VIA MEDICA

Asciminib a new player in treatment of TKI-resistant/intolerant chronic phase chronic myelogenous leukemia

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Abstract

The introduction in 1998 of imatinib mesylate (IM), a first-generation BCR-ABL1 tyrosine kinase inhibitor (1G-TKI), to the treatment of chronic myelogenous leukemia patients in the chronic phase (CML-CP), significantly improved the prognosis of a previously incurable disease with a prognosed 5-year-long overall survival and progression-free survival of 91.7% and 94.7%, respectively. Long term follow-up studies of CML-CP patients verified the initial results, showing a 10-year overall response rate of 82–83.2%. In about one quarter of CML-CP patients, IM primary/secondary resistance or intolerance is diagnosed. After switching to a second generation BCR-ABL1 TKI (dasatinib, nilotinib, bosutinib), a complete cytogenetic response is obtained in only c. 50% of CML-CP patients. Also the frequency of deep molecular responses (DMR: $MR^{4.0}$ and $MR^{4.5}$) is relatively low. The results of 2G-TKI treatment are particularly unsatisfactory in patients carrying the TKI resistant BCR::ABL1 kinase domain mutants (BCR::ABL1 KD), especially BCR-ABL1 T315I. For this reason, other orally biocompatible compounds have been developed to target BCR-ABL T315I. One of these is ponatinib, which allows a major molecular response (MMR) and $MR^{4.5}$ to be obtained in 40% and 24% of severely TKIs-pretreated CML-CP patients, respectively. The latter represent a new class of allosteric BCR-ABL1 tyrosine kinase inhibitor [asciminib (ABL001)], specifically targeting the ABL myristoyl pocket of BCR-ABL tyrosine kinase. Its application in CML-CP patients previously treated with at least two TKIs resulted in an MMR rate and a $MR^{4.5}$ rate of 37.6% and 10.8%, respectively, at 96 weeks. The favorable asciminib response and tolerance profile was also confirmed in real-life conditions, even in subjects with previous ponatinib therapy failure ($MR^{4.5}$ in 10.5%). Recent data suggests that asciminib may be used in the first line or in combination with a 1G- or 2G-TKI. This latter strategy may enhance the rate of DMR obtained and increase the number of patients eligible for an attempt at treatment-free remission.

Keywords: chronic myelogenous leukemia, tyrosine kinase inhibitors, cytogenetic response, molecular response, BCR::ABL1 KD mutations, asciminib

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Introduction

The introduction in 1998 of imatinib mesylate (IM), a first-generation BCR-ABL1 tyrosine kinase inhibitor (1G-TKI), to the treatment of chronic myelogenous leukemia patients in the chronic phase (CML-CP), significantly improved the prognosis of a previously incurable disease [1–4]. The results of the International Randomized Study of Interferon and STI571 (IRIS) study confirmed the high therapeutic efficacy of IM in CML-CP patients, with an estimated probability of

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event-free survival (EFS) of 8 years of 81% and an 8-year-long overall survival (OS) of 85% [5].

Long-term treatment results (with a median follow-up of almost 11 years) showed an estimated OS rate of CML-CP patients receiving IM therapy of 83.3% [6]. Also, the results of a German CML IV trial including 1,551 patients with CML-CP treated with imatinib-based regimens showed a 10-year OS rate of 82%. Moreover, the study showed that about one quarter of the studied patients (26.5%) required therapy change to first-generation BCR-ABL1 tyrosine kinase inhibitor (2G-TKI) due to resistant disease (10%) and IM intolerance, as well as for other reasons [7]. This was also confirmed by the EUTOS population-based registry based on a long-term observation of 2,904 CML-CP patients, documenting IM primary/secondary resistance or intolerance in 28% of the patients qualified for the IM 1-line therapy [8].

IM resistance/intolerance is an important clinical problem, especially in the light of data documenting that the administration of the 2G-TKIs (dasatinib, nilotinib or bosutinib) in a 2-line setting in CML-CP patients with IM intolerance/resistance resulted in complete cytogenetic response (CCyR) rates of 49%, 44%, 41%, PFS of 90%, 64%, 81% and OS of 96%, 87%, 91%, respectively [9–11]. In addition, data concerning the frequency of deep molecular response (DMR: $MR^{4.0}$ and $MR^{4.5}$) after a 2-line treatment with 2G-TKI is unsatisfactory. A real-life comparison of nilotinib versus dasatinib as second-line therapy in CML-CP patients with IM therapy failure showed that only 47% and 38% of 108 evaluable patients achieved an major molecular response (MMR) BCR::ABL1 [on the International Scale (IS) <0.1%], and 18.2% and 16.2% a DMR, with dasatinib and nilotinib, respectively, after 12 months of treatment [12].

The implementation of the 2G-TKI to the first line treatment of CML-CP did not significantly improve the therapy results in terms of PFS and OS. During a 10-year follow-up of the ENEST trial, the estimated 10-year OS rates in the nilotinib 300 mg twice-daily, nilotinib 400 mg twice-daily arms were 92.7%, 94.5%, respectively [13]. Analysis of the DASISION trial showed similar rates for PFS and OS at 5 years across both treatment arms (IM 400 mg once daily vs. dasatinib 100 mg once daily) [14]. Also, the results of treatment with another 2G-TKI, bosutinib, in first-line settings showed a 5-year OS rate of 94.5% [15].

It has been documented that compared to imatinib, the administration of 2G-TKIs in the 1-line setting resulted in faster and deeper molecular responses in CML-CP patients. In the ENEST trial, the frequency of $MR^{4.5}$ after 10 years of treatment with nilotinib 300 mg twice daily or nilotinib 400 mg twice daily was established to be 61% and 61.2%, respectively. Meanwhile in the imatinib (400 mg once daily) treated patients, the $MR^{4.5}$ rate was 39.2% only [16]. In the DASISION study, the administration of dasatinib at a dose of 100 mg once a day resulted in $MR^{4.5}$ in 42% of participants after five years of follow-up [14]. Interestingly, despite lower response dynamics in the IM treated patients, compared to 2G-TKIs, the cumulative $MR^{4.5}$ rate in CML-CP patients treated with IM 400 mg/d after nine years of follow-up was established to be 70% in the CML-atudy IV participants [17].

According to the 2020 recommendations of European LeukemiaNet (ELN), the main goal of the CML management is the prolongation of OS with a normal life expectancy, and reducing the risk of the disease progressing to more advanced phases. The introduction of IM into clinical practice reduced the risk of CML progression to 1–1.5% per year from more than 20% per year in the pre-TKI era [4, 18–20]. The maintenance of a normal quality of life and avoiding early and late toxicity of the TKI applied are equally important. Recently, the implementation of the above-mentioned idea has become possible in CML patients achieving and maintaining stable DMR, while avoiding the TKI administration that had resulted in early and long-term organ toxicities [21].

Unfortunately, there is still no precise guideline for patients who fail to qualify for the 2G-TKI treatment according to the ELN 2020 criteria. It has been postulated that the individual decision about the consecutive line of therapy must be based on the patient's age, the TKI toxicity profile with respect to the patient's comorbidities, the disease phase, and the BCR::ABL1 mutation(s) profile at the time of diagnosis of the therapy failure [22, 23]. Nevertheless, the clearly desirable treatment aims [i.e. prolongation of survival, treatment-free remission (TFR) attempt] in individual cases is of similar importance [24, 25].

This paper summarizes data about the therapeutic efficacy and tolerability of subsequent lines treatment in patients with CML-CP, with particular emphasis on new therapeutic options, including therapy with ponatinib [third-generation TKI (3G-TKI)] and the allosteric BCR-ABL kinase inhibitor asciminib. This drug belongs a newly developed class of BCR-ABL kinase inhibitors with a different mechanism of action — it inhibits the kinase activity by blocking the myristoyl pocket of BCR-ABL tyrosine kinase (STAMP).

Impact of IM and 2G-TKI therapy failure/ /intolerance on CML outcome and disease evolution

The main consequence of TKI therapy failure is disease progression to a more advanced stage. It has been shown that in CP-CML patients who are resistant to ≥2 TKIs, the risk of progression to BP is significantly increased [26, 27]. This is the result of selection of CML leukemic stem cells (LSC) and disease clonal evolution [28, 29]. Preliminary reports indicate that TKI-resistant CML cells have high expression levels of DNA damage repair genes, such as RAD51L1, FANCA, and ERCC5, which may reflect CML LSC

genetic instability. This might, at least in part, explain the mechanism of molecular disease evolution and progression to the more advanced phase [30–32].

Another possible mechanism of TKI resistance of leukemic cells includes the activation of alternative signaling pathways (i.e. RAS–MAPK, SRC, JAK–STAT, and PI3K–AKT). Also, abnormal function of transmembrane protein participating in the TKI influx/TKI efflux (i.e. ABCB1, ABCG2, SLCO1B) to/from the leukemic cells may be responsible for the TKI treatment failure. In c. 50% of CML-CP cases, the presence of BCR::ABL1 kinase domain (BCR::ABL1 KD) mutations is responsible for the TKI resistance. BCR::ABL1 KD mutations have emerged during the TKI treatment and they may have single, and combined or compound character (≥2 of BCR::ABL1 mutations in cells from different clones and ≥2 BCR::ABL1 mutations in a single cell, respectively) [33]. The frequency of BCR::ABL1 KD mutations in patients with first-line and second-line TKI treatment failure differs depending on the detection method used. The Sanger sequencing technique and the next generation sequencing method allowed the detection of BCR::ABL1 mutations in 23% and 38% and 47% and 51% of patients, respectively [34]. The negative impact of clonal and/or subclonal BCR::ABL1 KD mutations on the CML evolution and progression is especially evident in the light of data documenting that the sequential use of TKIs is associated with decreased OS and the emergence of new BCR::ABL1 KD mutations, particularly the T315I mutation and compound BCR:ABL1 KD mutations [34, 35]. The above-mentioned data supports the hypothesis that restrained activity of BCR-ABL1 tyrosine kinase and/or increase in the BCR-ABL1 fusion gene amplification status in the CML cells is, at least in part, related to disease molecular evolution and progression [36] (Figure 1).

The results of second-line treatment with 2G-TKI were unsatisfactory in patients carrying the TKI resistant BCR::ABL1 KD mutation(s), especially BCR-ABL1 T315I [14, 38]. For this reason, other orally biocompatible compounds targeting BCR-ABL1 T315I have been developed. This was made possible with the help of computational and molecular structure-based designing. One of the substances identified in this way was ponatinib (3G-TKI), a dual SRC-ABL inhibitor with a documented potential to overcome the T315I and other single BCR::ABL1 KD mutants associated with resistance to IM and 2G-TKIs.

The pivotal phase II ponatinib Philadelphia positive acute lymphoblastic leukemia (Ph+ ALL) and CML evaluation trial (PACE) evaluated the efficacy and safety of ponatinib at a starting dose of 45 mg once a day in 449 patients with CML-CP (n = 270) or Ph+ ALL resistant/intolerant to dasatinib or nilotinib, or with the BCR-ABL1 T315I mutation [38]. The efficacy and safety of the drug was evaluated in severely pretreated CML-CP patients (93% of them received ≥2TKI, 57% ≥3TKI) with a median follow up of 56.8 months. Among the evaluable patients, 40% and 24% achieved MMR and $MR^{4.5}$, respectively. The probability of maintaining major cytogenetic response (MCyR) for five years, which was obtained in 60% of patients, was estimated to be 82% among the responders. During the PACE study, a relatively high frequency of arterial occlusive events (AOEs) was noted, which resulted in the implementation of a drug dose reduction recommendation in October 2013. Despite a drug dose reduction of ≥90% in CML-CP patients with previously documented MCyR or MMR, the response remained after 40 months of follow-up [40]. A post hoc multivariate regression analysis of pooled data from three clinical trials on the use of ponatinib in patients with Ph^+ leukemia showed a 33% potential reduction in the risk of AOEs for each 15-mg/d decrease in the average ponatinib dose intensity [40]. To study this hypothesis, the phase II Optimizing Ponatinib Treatment in CP-CML (OPTIC) trial, exploring a response-based dose-reduction strategy, was designed and performed. The OPTIC trial included 283 CML-CP patients resistant to ≥2 prior TKI or BCR::ABL1 T315I mutation positive, with BCR::ABL1 [IS] transcript level >1%. The study participants were randomly allocated to ponatinib 45 mg/day, or 30 mg/day, or 15 mg/day. The final analysis of the study results confirmed that the absolute gain in efficacy was larger than the increase in AOEs, when therapy was started at a dose of 45 mg and followed by a reduction to 15 mg upon the achievement of a transcript level reduction of ≥1% $BCR\text{-}ABL1^{IS}$ [41].

Recently published data supports the use of ponatinib, rather than alternative 2G-TKIs, in the 3-line of treatment in CML-CP patients with 2G-TKI treatment failure (3-year PFS 83% vs. 59%, OS 87% vs. 83%) [42].

Data is scarce regarding the second-line treatment of CP-CML patients resistant and/or intolerant to prior TKI therapy with the 3G-TKI — ponatinib. Breccia et al. [43] collected the data of 29 patients in whom treatment with ponatinib allowed an improved molecular response in 85% of all patients and an $MR^{4.0}$ and $MR^{4.5}$ reduction of BCR::ABL1 copy numbers in 10 of the studied patients.

New concept of BCR-ABL1 tyrosine kinase inhibition

Despite evident progress in the treatment of CML-CP patients, there has long been a need for improvement in the therapy tolerance and efficacy in patients intolerant or resistant to adenosine triphosphate (ATP) competitive TKI (ATP-competitive inhibitors) BCR-ABL.

For this reason, novel methods of bypassing the ATP-competitive inhibitors resistance have been developed [39]. The first to appear in this new class was allosteric BCR-ABL1 TKI [asciminib (ABL001)] STAMP [44].

Under normal conditions, ABL1 activity is autoregulated by binding myristoylated N-terminus to the myristoyl pocket

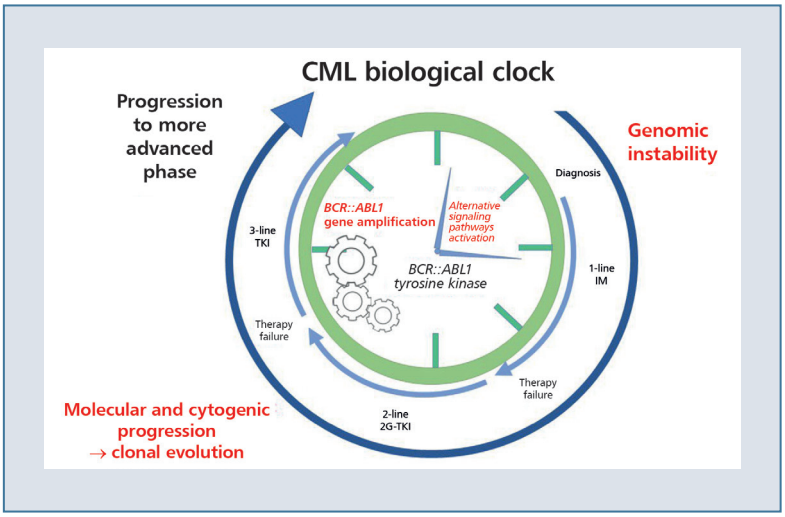


Figure 1. Unfavorable scenario of chronic myelogenous leukemia (CML) outcome due to multi-tyrosine kinase inhibitor (TKI) therapy failure. Imatinib resistance is associated with an increased risk of blastic transformation due to accumulation of genetic abnormalities detectable as additional cytogenetic changes and mutations in individual genes [37]. Another possible mechanism of disease clinical progression is associated with sequential use of TKI which may result in selection of TKI-resistant cells and disease clonal evolution [28]

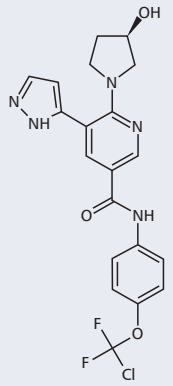
of the KD. In CML, c-ABL1 kinase is constitutively activated due to the loss of regulatory function with BCR::ABL1 fusion oncoprotein formation. The mechanism of action of asciminib includes binding to the myristoyl pocket of the ABL1 KD, induction of inactive conformational change, and inhibition of kinase activity [45, 46].

Asciminib was introduced after approval by the US Food and Drug Administration (FDA) into clinical practice in 2021 in CML patients after resistance and/or intolerance to two previous lines of treatment [47]. The detailed characteristics of asciminib are set out in Table I. Initially, asciminib has been evaluated in a phase I dose escalation study (10 to 200 mg once a day or twice a day) in severely pretreated CML patients (CP = 141, CP, accelerated phase = 9) with resistance to or unacceptable side effects from at least two previous ATP-competitive TKIs therapy, with promising results. Moreover, primary results of the phase I trial in patients with CML-CP or CML-acceleration phase, harboring the T315I BCR::ABL mutation and not in MMR at the screening, confirmed that asciminib administration at a dose of 200 mg twice a day resulted in durable molecular responses in both ponatinib-pre-treated and ponatinib-naïve cases (overall MMR rate by 96 weeks 32.1% and 66.7%, respectively) as well [53].

The pivotal trial evaluating asciminib vs. bosutinib efficacy and tolerability in adult patients with Ph+ CML-CP previously treated with at least two TKIs was the open-label, randomized, phase III ASCEMBL study [54]. The dose of asciminib was 40 mg twice a day. In the control arm, bosutinib daily dose was established at 500 mg once a day. Due to known bosutinib resistance, patients with T315I and/or V299L mutations at any time prior to study entry were excluded from the ASCEMBL trial. The MMR rate at 24 weeks was the primary endpoint of the study. The major secondary endpoints were MMR rate at 96 weeks and CCyR rate at 24 and 96 weeks. The initial evaluation after 24 weeks of follow-up showed a significantly higher MMR rate in asciminib vs. bosutinib arm (25.5% vs. 13.2%). The differences were even more pronounced at 96 weeks (37.6% vs. 15.8%). Also, differences in the CCyR rates obtained at 24 and 96 weeks were evident (40.8% vs. 24.2% and 39.8 vs. 16.1%). Another important study result was a higher probability of the $MR^{4.5}$ response obtained at 24 and 96 weeks in the asciminib compared to the bosutinib group (8.9% vs. 1.3% and 10.8% vs. 5.3%, respectively). The most frequent, at least grade 3, treatment emergent adverse events (TEAE) were thrombocytopenia, neutropenia, anemia, elevated pancreatic enzymes, and hypertension. At 96 weeks (median follow-up of 31.3 months), the treatment discontinuation rates due to drug-related adverse reactions were 7.7% vs. 23.6% in the asciminib and bosutinib arms, respectively [54]. The key results of the clinical trials designed to evaluate the efficacy and tolerability of asciminib in CML patients resistant/intolerant to ATP-competitive BCR-ABL tyrosine kinase inhibitors are set out in Table II.

A favorable asciminib response and tolerance profile was also confirmed in real-life analyses. Luna et al. [58] presented data concerning asciminib treatment efficacy and safety in ponatinib pre-treated (PPT, n = 19) and non-ponatinib pre-treated (non-PPT, n = 31) patients with resistance/intolerance to previous lines of TKI therapy. The

Table I. General characteristics of asciminib, an allosteric BCR-ABL tyrosine kinase inhibitor, specifically targeting ABL1 myristoyl pocket

Chemical structure		
IUAPC name	N-[4-[chloro(difluoro)methoxy]phenyl]-6-[(3R)-3-hydroxypyrrolidin-1-yl]-5-(1H-pyrazol-5-yl) pyridine-3-carboxamide	
Molecular formula	$C_{20}H_{18}ClF_2N_5O_3$	
Spectrum of inhibitory activity [43]	Myristoyl pocket of BCR-ABL1	
BCR-ABL1 tyrosine kinase inhibitory mode of action	On fusion of ABL1 to BCR, myristoylated N-terminal is lost and ABL1 kinase is activated. By allosterical binding of myristoyl site, asciminib mimics myristate and restores inhibition of BCR-ABL1 kinase activity [46, 47]	
	After binding to myristoyl pocket of ABL1 kinase domain, asciminib induces an inactive conformational change and inhibits kinase activity [45]	
Half-life time ($T_{1/2}$) [44, 48]	5.5 h (40 mg/day)	
	9 hours (200 mg twice a day)	
Resistant BCR-ABL1 mutants* [23, 44, 46, 49, 51]	**Detected in in vitro conditions**	**Emergence in clinical trials**
	A337V	G109D
	A344P	Y115N
	P465S	M244V
	F497F	V289I
		A337V/T
		E355G
		F359V
		E462K
		G463D/S
		P465S
		V468F
		S501R
		I502L
Oral dose per day	CP – 80 mg/d or 40 mg twice a day, in a case of T315I BCR::ABL1 mutation dosages up to 200 mg twice a day**	
Off-target inhibition [49]	Reversible inhibitor of CYP3A4/5, CYP2C8, CYP2C9, CYP2B6, inhibitor of BCRP, Pgp and weak inhibitor of OCT1	

**in vitro* and *in vivo*; ***not approved in T315I BCR::ABL1 mutation positive cases in Poland; IUAPC – International Union of Pure and Applied Chemistry; BCRP – breast cancer resistance protein; Pgp – glycoprotein P; OCT1 – organic cation transporter 1

Table II. Clinical trials designed to evaluate efficacy and tolerability of asciminib in chronic myeloid leukemia patients resistant/intolerant to ATP-competitive BCR-ABL1 tyrosine kinase inhibitors [48, 55–57]

Trial title (study identifier)	Study population/design	Main objective	Relevant data
A phase I, multi-center, open-label study of oral ABL001 in patients with chronic myelogenous leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) (NCT02081378)* (a dose-escalation study)	141 pts with CP and 9 pts with accelerated-phase CML who had resistance to or unacceptable side effects from at least two previous ATP-competitive tyrosine kinase inhibitors (TKIs)	The primary objective was to determine the MTD or the recommended dose (or both) of asciminib	Identification of the MTD, as well as assessing the safety, pharmacokinetics and efficacy of asciminib
ASC2ESCALATE: A phase II, multi-center, open-label, single-arm dose escalation study of asciminib monotherapy in 2nd line chronic phase chronic myelogenous leukemia (NCT05384587)* (a dose escalation study)	Adult pts (aged ≥18 years) with CML-CP without the T315I mutation who experienced resistance (*BCR::ABL1*^{IS} >1% with 6–12 months of 1L treatment or >10% with >12 months of 1st-line treatment) or intolerance (*BCR::ABL1*^{IS} >0.1%) with ≥6 months of treatment with 1 prior ATP-competitive TKI are eligible. All pts will initiate treatment with asciminib 80 mg once a day. For pts not achieving *BCR::ABL1*^{IS} <1% at 6 months, dose will be escalated to 200 mg once a day if pts do not have grade ≥3 toxicity or persistent grade 2 toxicity refractory to optimal management. In pts not achieving MMR at 12 months, either dose escalation from 80 to 200 mg once a day or from 200 mg once a day to 200 mg twice a day will occur or the pts will discontinue study treatment. Pts who achieve MMR at 12 months will continue asciminib at their current dose. Pts deriving clinical benefit from asciminib per investigator assessment may receive post-trial access	Percentage of participants who MMR (time frame: baseline up to 12 months) Secondary endpoints include: • MMR rates by 3, 6, 18, and 24 months • MR$^{4.5}$ (BCR::ABL1^{IS} ≤0.0032%) at 24 months • time to and duration of MMR • time to treatment failure; • and safety/tolerability	Ongoing trial (data not published yet)
A phase III, multi-center, open-label, randomized study of oral abl001 versus bosutinib in patients with chronic myelogenous leukemia in chronic phase (CML-CP), Previously treated with two or more tyrosine kinase inhibitors (ASCEMBL, NCT03106779)*	Pts with CML-CP previously treated with ≥2 TKIs randomized (2:1) to receive third-line asciminib 40 mg twice a day vs. bosutinib 500 mg once a day Randomization was stratified by MCyR status at baseline. Pts with documented treatment failure (specifically meeting the lack of efficacy criteria adapted from the 2013 ELN recommendations) while on bosutinib treatment were offered the option to switch to asciminib treatment within 96 weeks after the last pt was randomized to the study	Number of participants with MMR rate at 24 and 96 weeks	MMR rate: • at 24 weeks: 25.5% vs. 13.2% (bosutinib) • at 96 weeks: 37.6% vs. 15.8% (bosutinib)
A phase II, multi-center, open-label, randomized study of oral asciminib added to imatinib versus continued imatinib versus switch to nilotinib in patients with CML-CP who have been previously treated with Imatinib and have not achieved deep molecular response (ASC4MORE, NCT03578367)*	Pts aged ≥18 years, have CML-CP, and have been treated with 1st-line IM for ≥12 months. Study entry requires patients to be receiving IM 400 mg once a day at randomization, have *BCR-ABL1* transcript levels in the range of ≤1% to >0.01% on the IS, no prior achievement of MR^{4} (*BCR-ABL1*^{IS} ≤0.01%) confirmed by two consecutive tests, and no prior treatment failure	Molecular response (MR$^{4.5}$) rate between asciminib + IM and IM alone (time frame: at 48 weeks)	At week 96, 19.0%, 19.0%, 4.8%, and 9.5% of pts in the 40-mg asciminib add-on, 60-mg asciminib add-on n, IM, and NIL arms, respectively, were in MR$^{4.5}$

Table II (cont.). Clinical trials designed to evaluate efficacy and tolerability of asciminib in chronic myeloid leukemia patients resistant/intolerant to ATP-competitive BCR-ABL1 tyrosine kinase inhibitors [48, 55–57]

Trial title (study identifier)	Study population/design	Main objective	Relevant data
	The study evaluates the efficacy of asciminib in two different doses (40 mg or 60 mg) in combination with IM 400 mg vs. continued IM vs. switch to nilotinib, vs. asciminib 80 mg single agent in subjects with CML-CP who have been previously treated with IM 1st-line therapy for at least one year and have not achieved DMR. 84 eligible subjects were randomized 1:1:1:1 to receive asciminib 60 mg once a day as add–on therapy to IM 400 mg once a day, or 40 mg once a day as add–on therapy to IM 400 mg once a day, or to continue IM 400 mg once a day, or to switch to nilotinib 300 mg twice a day		Cumulative $MR^{4.5}$rates at week 96 were 28.6%, 28.6%, 9.5%, and 19.0%, respectively Despite longer median durations of exposure with asciminib add–on, fewer pts experienced adverse evenst leading to discontinuation with asciminib 40 mg (4.8%) and 60 mg (14.3%) add–on vs. switching to NIL (33.3%). Rates of discontinuation with asciminib add–on did not increase with longer follow up compared to the primary analysis

*https://clinicaltrials.gov/; ATP — adenosine triphosphate; ELN — European LeukiemiaNet; IM — imatinib; IS — International Scale; MMR — major molecular response; MTD — maximum tolerated dose; NIL — nilotinib; pts — patients; TKI — tyrosine kinase inhibitors

CCyR were obtained and maintained in 74% and 53% of patients, respectively. $MR^{4.5}$ was confirmed in 16% of the studied patients (10.5% in PPT vs. 19.4% in the non-PPT group). Grade 3–4 TEAE was observed in 22% of the non-PPT and 20% of PPT patients. Asciminib cross-intolerance was diagnosed in 20% of the ponatinib-exposed patients [58]. According to the available data, cross-toxicity does not appear to affect the occurrence of cardiovascular events, edema, abdominal pain, diarrhea or rash [59]. The most frequent adverse events associated with the administration of different TKIs and asciminib are set out in Figure 2.

Third-line CML-CP treatment dilemma

The final role of asciminib in the treatment strategy of CML patients remains to be established. It has been confirmed already that asciminib is an effective treatment option in CML-CP patients intolerant or resistant to ATP-competitive BCR-ABL1 tyrosine kinase inhibitors. This is mainly due to different inhibitory modes of action and good tolerability associated with limited off-target effects (*see* Tables I, II, Figure 2). A direct comparison of clinical asciminib and ponatinib efficacy in third-line settings is difficult. The OPTIC and the ASCEMBL studies differ in many aspects, especially in terms of the percentage of recruited patients with resistance to the prior TKI line therapy (97.3% vs. 61%), and the number of patients with and without T315I BCR::ABL1 mutation (23.7% vs. 0%) at study entry [54, 60]. Initial data suggests that asciminib and dose-modified ponatinib probably represent different therapeutic options which should be recommended in specific clinical situations in CML-CP patients. In a case of TKI 'pan-intolerance', asciminib would probably be the drug of choice, whereas a TKI pan-resistant patient with no evidence of optimal molecular response to previous TKIs might benefit from initial ponatinib therapy [47]. This is mainly due to different inhibitory modes of action and good tolerability associated with limited off-target effects (*see* Tables 1, 2, Figure 2).A still unanswered question is how to manage CML-CP patients non-optimally responding or resistant to the first-line TKI therapy or experiencing TEAE. Recent data suggests that asciminib may be used in the first-line setting or in combination with a 1G- or 2G-TKI. The latter strategy may enhance the rate of DMR obtained and the number of patients eligible for an attempt at TFR. Both ideas are now under vigorous investigation [asciminib in the first-line setting: CML13 study (ASCEND, ACTRN12620000851965) and ASC4 First trial ((NCT04971226); and asciminib to improve the DMR rate: ASC4MORE (NCT03578367) study] [57, 61, 62].

Summary

The introduction into clinical practice of a new category of BCR-ABL1 tyrosine kinase inhibitor specifically targeting

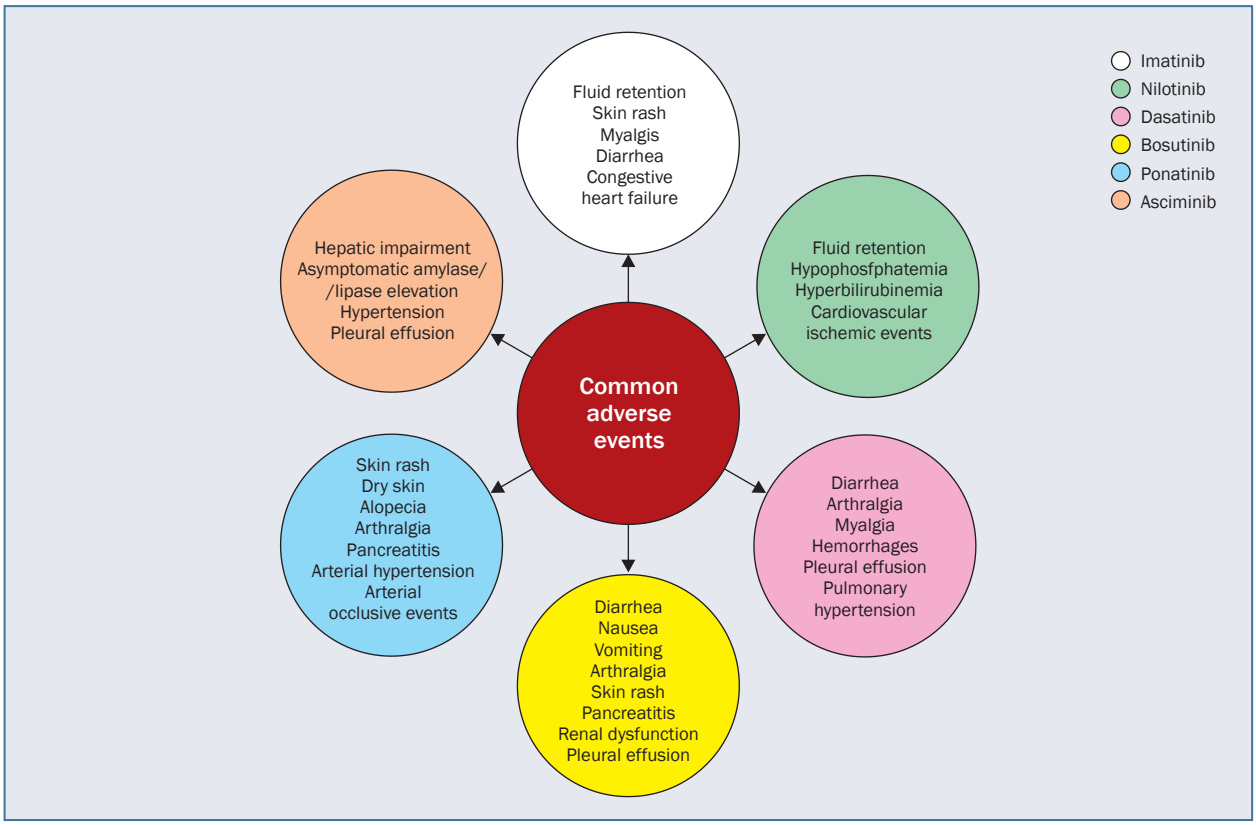


Figure 2. Common adverse events reported in chronic myelogenous leukemia patients treated with individual ATP-competitive BCR-ABL1 tyrosine kinase inhibitors and specifically targeting the ABL1 myristoyl pocket [64–71]. Common symptoms of intolerance: edema, muscle cramps, arthralgias, diarrhea/constipation, cytopenias

the myristoyl pocket of ABL tyrosine kinase changes the therapeutic approach in CML-CP patients not eligible to receive ATP-competitive inhibitors due to therapy failure or intolerance. Other possible applications of asciminib in CML patients include combined drug administration with ATP-binding TKIs. The applicability, tolerability and efficacy of such a therapeutic strategy is currently under investigation in clinical trials. Another potential practical benefit of using STAMP is the possibility of avoiding distant cardiovascular toxicity, increasingly reported in cases of long-term therapy with TKIs [63].

Article information and declarations

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Author contributions

Krzysztof Lewandowski is the author of the manuscript, including the tables and the figures.

Conflict of interest

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Supplementary material

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COVID-19 in patients with hematological malignancies

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Abstract

In most cases, COVID-19 is characterized by a mild clinical course. However, there are groups of patients at high risk of mortality and morbidity of COVID-19, including groups comprising older age (> 65 years), diabetes, hypertension, obesity, cancer, and hematological malignancies. Hematological patients are at high risk due to disease-related immune disorders and treatment-related factors. This review aims to summarize studies on COVID-19 in patients with the most common hematological neoplasms. We describe the fatality rate of COVID-19, the risk of severe disease, the efficacy and side effects of vaccines against COVID-19, and vaccine-drug interactions in chronic lymphocytic leukemia (CLL), multiple myeloma (MM), acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), diffuse large B cell lymphoma (DLBCL) as well as chronic myeloid leukemia (CML). We focus mainly on the use of mRNA vaccines, not other types of vaccines. Hematological patients are a priority group for vaccination against COVID-19, but serological response varies according to the type of hematological malignancy, with better responses in myeloid malignancies and poorer responses in CLL and lymphoma patients. Extended studies are needed to answer questions about a limited response to vaccines and the use of booster doses in CLL and patients treated with anti-CD38 therapy, BTKi therapy, anti-CD20 antibody or ruxolitinib therapy, as well as patients with non-Hodgkin lymphoma (NHL).

Keywords: hematological neoplasms, chronic lymphocytic leukemia (CLL), multiple myeloma (MM), Ph-chronic myeloproliferative disorders (CMD), chronic myeloid leukemia (CML), COVID-19 vaccines

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) expeditiously expanded from an epidemic outbreak in Wuhan, in the Hubei province of China in 2019, into a pandemic infecting more than 770 million individuals all over the world. SARS-CoV-2 invades host human cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor [1–3]. Specifically, SARS-CoV2 is firstly recognized by the toll-like receptors (TLRs) on host cells, which activates nuclear factor kappa B cells (NF-κB), which then activates the angiotensin-converting enzyme 2 (ACE2) receptors. After the activation of ACE2 receptors, the virus can enter cells and begin replication [4, 5]. Moreover, this process of entry initiates the so-called 'cytokine storm'. SARS-CoV-2 can trigger an immune response via pathogen-associated molecular patterns (PAMPs). The virus also causes the release of pro-inflammatory damage-associated molecular patterns (DAMPs) [4]. DAMPs cause the migration of immune cells which increases the release of pro-inflammatory cytokines such as interleukin 2 (IL-2), interleukin 7 (IL-7), interleukin 10 (IL-10), granulocyte colony-stimulating factor (G-CSF), and tumor necrosis factor (TNF) [5, 6] (Figure 1).

It is well documented that COVID-19 primarily manifests as a respiratory tract infection. However, emerging data indicates that it should be regarded as a systemic disease involving multiple systems, including the cardiovascular, respiratory, gastrointestinal, neurological, hematopoietic, and immune systems [1, 2, 7–9]. Patients can manifest

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with asymptomatic virus shedding or syndromes of varying severity [10, 11]. Symptoms can depend on the variant of the virus, but the most common are fever, cough, impairment of smell or taste, and dyspnea. It can also progress to persistent fever, respiratory failure, and even multi-organ failure [11].

Interestingly, there are risk groups that are more likely to come down with severe COVID-19. It has been shown that the older age group (> 65 years) is at high risk of severe SARS-CoV-2 infection, because of comorbidities e.g. diabetes, hypertension, obesity and cancer [12]. Furthermore, males are more critically ill compared to females [13]. The other group at high risk includes patients with cancer as well as hematological malignancies [14].

Since the number of scientific publications about COVID-19 in patients with hematological malignancy is growing rapidly, the aim of this current paper was to examine the latest studies about the clinical characteristics of COVID-19 in patients with hematological neoplasms. We summarize the numerous findings, including data about fatality rate, the risk of acute disease, the efficacy of vaccines against COVID-19, and vaccine-drug interactions specifically in cohorts of patients with chronic lymphocytic leukemia (CLL), multiple myeloma (MM), acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), diffuse large B-cell lymphoma (DLBCL), as well as chronic myeloid leukemia (CML). Additionally, we share the results of clinical trials regarding the efficacy of vaccinations, drawing attention to the fact that the response varies depending on the specific disease (Table I).

Hematological malignancies as a high-risk group in COVID-19

Patients with hematological neoplasms, as immune-compromised people, are at high risk of severe COVID-19 [14]. This is due to immunosuppression, older age, and other comorbidities. Moreover, the specificity of the biology of hematological malignancy, dysfunctions of the immune system, and the type of therapy administered are all key factors that are conducive to the more frequent occurrence of COVID-19, or the development of severe COVID-19 [15]. Immune defects are diverse and include low number of functional B lymphocytes and antibody production, decreased percentage of CD4 lymphocytes, NK cells, impaired antigen presentation by a decrease in the number of dendritic cells, and an increase in the number of regulatory cells. Immune dysregulations depend on the type of disease [16]. Moreover, the treatment given to hematological patients, such as anti-CD20 antibodies, stem cell transplantation, and chimeric antigen receptor (CAR) T-cell therapies, very often impairs immunity [17, 18].

These factors have resulted in patients with hematological malignancies being particularly vulnerable to COVID-19 [18]. In these patients, mortality and morbidity are increased compared to healthy patients [19, 20].

The occurrence of severe COVID-19 in patients with hematological malignancies was observed in a large cohort of 3,801 patients with lymphoproliferative and myeloproliferative malignancies. Pagano et al. [20] showed severe COVID-19 in 63.8% (2,425/3,801) of the patients. Moreover, 73.1% (2,778/3,801) were hospitalized while 31.2% (1,185/3,801) died, of whom 58.1% (688/1,185) died due to COVID-19 infection, 14.6% (173/1,185) due to the hematological malignancy itself, and 13.1% (155/1,185) due to a combination of both. Increased COVID-19 mortality in hematological patients has also been proved. Yigenoglu et al. [17] observed a doubled mortality rate in 740 hematological patients compared to healthy controls (13.8% vs. 6.8%).

Interestingly, the highest mortality rate (58.9%) has been observed among patients receiving demethylating agents. In patients receiving CAR-T therapy, the mortality rate was also high at 47.6%. Patients undergoing autologous hematopoietic stem-cell (auto-HSCT) or allogenic hematopoietic stem-cell (allo-HSCT) transplantation had mortality rates of 27% and 24.8% respectively [20].

The development of COVID-19 vaccines decreased the risk of severe COVID-19. Therefore, vaccinations are recommended for this group of patients despite the fact that the vaccine response in these patients is weaker than in the healthy population [21, 22]. It has been proved that patients who receive two or more doses of COVID-19 vaccine have a reduced risk of COVID-19 [22–26]. Two weeks after the second dose of the BNT162b2 vaccine, 95% of the patients with solid tumors and 60% of those with hematological malignancies responded positively [27, 28]. The safety of mRNA vaccines in hematological patients has been shown to be comparable to that in healthy patients [19]. The most common adverse event was pain at the injection site, followed by fever and muscle soreness. Patients with hematological malignancies had lower median anti-S1 IgG antibody responses after two BNT162b2 vaccine doses than did healthy persons (median 6,961 (units) U/mL vs. 21,395 U/mL). Patients actively treated with BTKIs (0 U/mL) venetoclax (4 U/mL), or anti-CD20 antibody therapy (17 U/mL) showed poor antibody responses. New approaches to treating high-risk patients who are poor responders to vaccination are urgently required. However, patients receiving tyrosine kinase inhibitors (10,537 U/mL) or auto-HSCT (6,203 U/mL) or allo-HSCT (6,304 U/mL) did not differ from untreated patients with hematological malignancies [29]. Moreover, the breakthrough infection in this group of patients is increased, ranging from 11.0% for ALL to 17.2% for MM, with the risk being 4.5% in patients without neoplasms [30].

COVID-19 in chronic lymphocytic leukemia

It has been proved that patients with chronic lymphocytic leukemia (CLL) are at high risk of bacterial infections as well as severe COVID-19, partly due to their older age (median 69 years) and partly due to anti-leukemic treatment [31], [32]. Chatzikonstantinou et al. [31] analyzed a cohort of CLL patients, including almost 42% who had never received anti-CLL therapy, with the rest having been treated with at least one type of therapy. Most (c.56%) of the treated patients were administered with Bruton's tyrosine kinase (BTK) inhibitors (BTKi). Interestingly, almost 75% of CLL patients were admitted to hospital due to COVID-19 infection, and it was shown that 66.2% of patients had severe COVID-19. Nonetheless, the fatality rate among patients with severe COVID-19 was 38.4%. Additionally, patients without any treatment had a lower risk of death compared to those on therapy (33.6% vs. 52.3%). However, the researchers suggested that patients treated with the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib were less likely to be hospitalized. Moreover, they suggested that in patients with CLL and COVID-19, older age was related to a worse prognosis, with increased mortality. Untreated patients had a better chance of survival than did those on treatment or who had been recently treated.

Similarly, Mato et al. [33] confirmed that CLL patients are at high risk of COVID-19. They examined 198 CLL patients, of whom 45% (90/198) were on CLL therapy. The most common therapy was BTKi in monotherapy (60%, 54/90 patients) or in combination (21%, 19/90). The overall mortality rate was 33%. Interestingly, BTKi therapy was not a significant mortality factor.

Research by Roeker et al. [34] compared two cohorts of CLL patients to examine trends over time. They analyzed 374 patients (68%, 254/374 in the first group diagnosed from 17 February through 30 April 2020 and 32%, 120/374 diagnosed from 1 May 2020 through 1 February 2021 in the second group). Hospital admission was required for 75% of CLL patients and the mortality rate was 28%. Interestingly, a larger proportion of patients in the first group required Intensive Care Unit (ICU) admission (32% vs. 15%). It has been proved that BTKi therapy is irrelevant as a survival factor. Roeker et al. also proved that CLL patients are at high risk of severe COVID-19 and should be considered for administration of COVID-19 vaccines.

Many recent studies have evaluated the effectiveness of COVID-19 vaccinations, which are recommended for CLL patients as immunocompetent individuals who are in a high-risk group for severe disease. Furthermore, according to the recommendations of the Polish Society of Hematology and Transfusion Medicine, and the Polish Adult Leukemia Group-CLL, individuals diagnosed with CLL should receive vaccination promptly because they face a higher risk of hospitalization or mortality from severe COVID-19 compared to the general population [32]. Haydu et al. [35] analyzed humoral and cellular immunogenicity of SARS-CoV-2 vaccines in a group of 36 patients with CLL, including 83% (30/36) of patients not on therapy and 17% (6/36) on BTKi treatment. The majority of patients received mRNA vaccines (BNT162b2 or mRNA-1273) while the rest received an adenovirus-based vaccine (Ad26.COV2.S). The overall response after vaccination was 60% in those not on therapy, and 33% in those on BTKi therapy. In addition, in the untreated cohort, a 77% serological response after the mRNA vaccine was achieved compared to a 33% serological response after the adenovirus vaccine. 37% (11/30) of patients who had a negative response after the first dose of the vaccine received a second dose, and 55% (6/11) of them had a detectable response. In addition, it was proved that all patients had antibodies against wild-type SARS-CoV-2 and variants (alpha, beta, gamma, delta). Moreover, Haydu et al. suggested that novel vaccine strategies, including additional vaccine doses, may increase protection against SARS-CoV-2 infection.

Jimenez et al. [36] studied humoral and cellular immunogenicity one month after the second dose of the mRNA--1273 vaccine in CLL and MM patients. 76.3% of patients developed humoral immunity, and the cellular response rate was 79%. These results suggest that a significant difference between the humoral and cellular responses was observed in patients treated with anti-CD20 therapy (humoral response 17.5% vs. cellular response 71.1%). B-cell aplasia was present in these patients, while T-cell counts were maintained.

Experiments performed by Herishanu et al. [37] proved that the antibody response rate was 39.5% in 167 CLL patients after two doses of BNT162b2 mRNA vaccine. Furthermore, they observed that serological response in patients without treatment was significantly higher (58.7%) including patients off-therapy in remission (79.2%) compared to a group on therapy (16%). In general, 13% (21/167) of patients after the first dose, and 23% (39/167) of patients after the second dose, reported mild adverse effects e.g. weakness, headache and/or fever. In addition, there was no difference between patients on therapy compared to those off-therapy. Additionally, they carried out another study which observed patients with CLL after the administration of a third dose of BNT162b2 mRNA vaccine [38]. This proved that in 172 patients who failed to respond to the second dose of the vaccine, the antibody response rate was 23.8% after the third dose. As in the previous study, treatment status played a role in the serological response. Patients off-therapy had significantly higher (40.3%) response rates compared to those on therapy (12%). Interestingly, the response rate in patients receiving BTK inhibitors was 15.3% compared to 7.7% in patients treated with anti-CD20 antibodies. The most common adverse effect was pain at the injection site (54%).

Nonetheless, a different research study focused on 61 chronic lymphocytic leukemia (CLL) patients assessing their antibody response six months after receiving the second dose of the BNT162b2 mRNA vaccine [39]. Here, antibodies were still detectable in 90% (55/61) of patients. However, after six months, the antibody level had decreased significantly from 107.1 U/mL to 67.5 U/mL. It was shown that anti-CLL treatment played a role in serological response. 83% (5/6) of patients who were sero-negative were on therapy (BTKi or venetoclax plus obinutuzumab).

In another study, 500 CLL patients were examined after two doses of COVID-19 vaccine [40]. Antibody response was 67%; 41% received the BNT162b2 mRNA vaccine and 59% the ChAdOx1 (Oxford/AstraZeneca) vaccine. The use of different vaccine platforms did not influence antibody response. In addition, patients on BTKi therapy had a significantly lower response rate (33%). In addition, it has been proved that male gender (44% lower), BTKi therapy (80% lower), and the presence of IgA or IgM hypogammaglobulinemia (72% and 57% lower respectively) were factors that determined a lower immune response. Furthermore, neutralization of the delta variant was significantly lower (14%) compared to the Wuhan virus (62%).

Similar outcomes were presented by Bagacean at al. [41, 42]. 530 patients received mRNA vaccine (BNT162b2 or mRNA-1273). The response rate was 27% after the first dose and 52% after the second dose. The research proved that patients on therapy had a significantly lower immune response (22%) compared to treatment-naive persons (72%). All patients receiving venetoclax plus anti-CD20 mAbs and venetoclax plus BTKis did not respond after the second dose of the vaccine. Patients who did not seroconvert (18%, 95/530) after two doses of vaccine, received a third dose. In these patients, the response rate was 35%.

Furthermore, the reaction to mRNA vaccines against SARS-CoV-2 was examined in individuals with MM and CLL [43]. The authors assessed the humoral and T cell-mediated immunity following two doses of BNT162b2 or mRNA-1273 in short-term (2-5 weeks after the second dose) and long-term (12 weeks after vaccination) follow-ups in 62 CLL and 60 MM patients. Total anti-receptor binding domain (RBD) antibodies were detected in 22/60 (37%) MM patients before vaccination. This rate increased to 42/46 (91%) 2–5 weeks after the second dose, which remained stable with 44/47 (94%) positive patients 12 weeks after the second dose. Notably, they observed a tendency to higher frequencies of YLQ-specific CD8+ T cells a short time after the second dose compared to baseline (median: 0.18 vs. 0.11, $p < 0.06$), which might confirm the induction of specific CD8+ T cells after vaccination. In the CLL cohort, total antibody response was detectable in 13/62 (21%) of patients before vaccination. However, this increased to 18/40 (45%) 2–5 weeks after the second dose, with an additional increase to 30/42 (71%) 12 weeks after the second dose. However, in the CLL cohort, they did not find any differences between frequencies of YLQPRTFL-specific CD8+ T cells in either the short-term nor the long-term follow-up after the second dose compared to baseline samples.

Therefore, the authors suggested that specific CD8+ T cells against SARS-CoV-2 might be induced by vaccination, but do not correlate positively with serological responses.

COVID-19 in multiple myeloma

It has been shown that the risk of severe COVID-19 in multiple myeloma (MM) patients is significant. In a cohort of 617 MM patients, c. 34% died after a COVID-19 diagnosis [44]. In addition, the fatality rate in hospitalized patients increased from 31% to c.80% in patients with invasive ventilation. Furthermore, it was revealed that age represents another risk factor of COVID-19. The higher the age, the higher the probability of death. It was shown that 60-year-old patients have a c.31% probability of death, whereas in 80-year-old patients this is almost 50%. Interestingly, they proved that the time from diagnosis, and the number of prior types of treatment, are irrelevant as risk factors of COVID-19 disease.

Similarly, out of a group of 100 MM patients with COVID-19, 74% required hospital admission [45]. Among those hospitalized, 18% (13/74) needed mechanical ventilation, and 24% (18/74) unfortunately died. The laboratory findings in this multiple myeloma cohort revealed lymphopenia and elevated C-reactive protein, ferritin, D-dimer, and interleukin 6 (IL-6) levels. They found that the strongest risk factors for severe outcomes were similar to those in the general population i.e. hypertension and diabetes. However, the mortality rate was higher in the MM cohort compared to officially reported mortality rates.

One way to shield MM patients from severe COVID-19 or death caused by COVID-19 is vaccination. Researchers from all over the world have assessed immune responses after vaccination and their efficacy in MM. One of the first reports assessed the response to the first vaccination against SARS-CoV-2 in patients with MM. It was proved that 56% of patients (52/93) had anti-SARS-CoV-2 IgG in their blood after the first dose of the COVID-19 vaccine (BNT162b2 or mRNA-1273) [46]. Additionally, positive antibody results after the first vaccination, either IgG or total or both, were seen in 70% of patients (65/93). However, the total antibody assay provided a positive result in 30% (8/27) of patients with stable or progressive disease, and 48% (32/66) of patients under treatment. Therefore these authors suggested avoiding vaccination on a day when patients were receiving anti-myeloma therapy (except immunomodulatory agents) and that active disease might play a major role in attenuating the vaccine effect. However, in all cases where

the therapy cannot be postponed, the International Myeloma Society recommends vaccination.

An evaluation of the safety and antibody response was conducted following a two-dose SARS-CoV-2 messenger RNA vaccination in a group of 44 patients diagnosed with MM [47]. Half (22/44) of the patients received the BNT162b2 vaccine and the other half (22/44) received the mRNA-1273 vaccine. 93% (41/44) of patients had detectable antibody. Moreover, the three patients who had undetectable antibody (antibody titer < 0.79 U/mL) were treated with teclistamab and lenalidomide/ixazomib. Despite the limitation of the small size of cohort, the researchers stated that vaccination against SARS-CoV-2 is safe for patients with MM, and leads to high rates of seroconversion. Furthermore, increased anti-receptor binding domain (anti-RBD) antibody levels suggest that vaccination may indeed decrease COVID-19 morbidity and mortality in this population.

Currently, researchers are also exploring the impact of therapy on the efficacy of vaccines. Highly variable antibody responses to two doses of COVID-19 RNA vaccination were observed between MM patients during therapy and patients without therapy [44, 48]. The researchers tested 320 patients who received BNT162b2 or mRNA-1273 vaccinations and showed that patients who received therapy had a lower antibody level (70 U/mL) compared to patients without treatment (183 U/mL) [48]. Specifically, they observed that anti-CD38 and BCMA-targeted treatment is associated with lower antibody levels after vaccination. The negative effect of anti-CD38 therapy was also observed by Henriquez et al. [49]. They analyzed 72 MM patients: 66% (48/72) of them were on anti-CD38 treatment. They subsequently discovered lower IgG and similar IgA levels in patients on anti-CD38 treatment compared to other types of therapy. They also proved that BNT162b2 vaccine allowed patients to develop neutralizing antibodies (Nabs) against the alpha (51%) and delta (41%) COVID-19 variants. Although anti-CD38 therapy reduced the production of Nabs against the alpha variant compared to patients without treatment, there was no significant difference against the delta variant compared to other patients. The researchers suggested that impaired immune response to SARS-CoV-2 vaccine was favored by targeting nonmalignant B cells (e.g. anti-CD20 antibodies). Moreover, they suggested that impaired vaccine response in patients receiving anti-CD38 could have clinical implications that should be investigated prospectively.

Furthermore, two cohorts, each consisting of 35 patients, were examined [50]. The first group comprised individuals with both COVID-19 and MM, while the second group consisted of MM patients who had received the BNT162b2 vaccine. The researchers noted that patients on therapy in the first group had higher antibodies level (88%) compared to vaccinated patients (35.4%). On the other hand, patients without anti-myeloma treatment did not differ from the group of patients with COVID-19 in terms of their humoral response. Additionally, a highly significant difference in antibodies level was observed only in the vaccinated group. Patients without treatment had 91.7%, whereas those on therapy had 35.4%. Therefore, they suggested the administration of booster doses of vaccine to patients on therapy without prior COVID-19.

Another study confirmed that the response after either the BNT162b2 or the AZD1222 vaccine was dependent on vaccine-therapy interaction. It was proved that 53.5% (114/213) of MM patients developed measurable Nab after vaccination [51]. 20% (23/114) of patients were in remission, and 80% (91/114) were undergoing therapy. 50 days after vaccination, patients without anti-myeloma treatment reached a higher immune response (66%) compared to patients on belantamab mafodotin combinations (28.2%) or anti-CD38 combinations (48%). Furthermore, the antibodies level in the remaining types of treatment (62.8%) was similar to the antibodies level in patients without treatment (64.6%). Hence, patients during treatment should receive booster doses of vaccine.

COVID-19 in acute myeloid leukemia

A total of 108 patients with acute myeloid leukemia (AML) were analyzed to determine the clinical outcomes and assess the impact of therapeutic approaches during the COVID-19 infection [52]. 51.9% of patients had active leukemia and 70.4% were under any anti-leukemic treatment. It was shown that the main signs and symptoms of SARS-CoV-2 infection in AML patients include fever (75.0%), pneumonia (70.4%), cough (63.0%), dyspnea (51.9%), diarrhea (22.2%), nausea and/or vomiting (13.0%), rhinorrhea (13.9%), and headache (10.4%). Nevertheless, 38.9% of patients had severe outcome of the disease, while 3.7% of patients were asymptomatic. Therefore, 82.4% of patients received anti-SARS-CoV2 treatment: chloroquine or hydroxychloroquine (80.6%), lopinavir/ritonavir (50.2%), corticosteroids (37.0%), azithromycin (34.3%), tocilizumab (14.8%), plasma convalescent (2.8%), clinical trial medication (2.8%), remdesivir (1.9%), and/or anakinra (0.9%). Overall mortality was 43.5%. Higher mortality was observed in patients aged > 60 years (49.3%), male patients (56.1%), and those with active disease (60.4%) ($p = 0.036$, $p = 0.047$, $p = 0.014$). However, the researchers highlighted the protective effect of azithromycin ($p = 0.039$) and lopinavir/ritonavir ($p = 0.039$). They stated that AML patients are at a high risk of severe disease and increased mortality. It is recommended to delay therapy until SARS-CoV-2 is negative.

In research conducted by Marchesi et al. [53], 388 AML patients were examined. COVID-19 was severe in 41.2% and critical in 21.1% of patients. The mortality rate in patients with ongoing or recently treated AML was significantly higher compared to patients receiving treatment up to

three months or earlier before their diagnosis of COVID-19 ($p < 0.001$). Discontinuation of the chemotherapy which had been given within the month before the COVID-19 diagnosis was also associated with a higher mortality rate (80.9%). However, a significantly lower mortality rate was observed in patients whose chemotherapy was delayed (18.4%) compared to patients whose chemotherapy was not delayed (37.5%). Hence, it is suggested to delay AML treatment if possible to increase survival.

Recent studies have evaluated the effectiveness of COVID-19 vaccinations in AML patients. The antibody response to mRNA-1273 and BNT162b2 vaccines was evaluated in over 1,400 patients with hematological malignancies, including 34 with AML [54]. A positive antibody response was observed in 91.2% of AML patients.

Similar outcomes were observed in 46 AML patients [55]. In a cohort, 35 patients received the BNT162b2 vaccine and 11 patients the mRNA-1273 vaccine. The overall antibody response was 94.7%. Moreover, there was no significant difference between the antibody levels in healthy controls and AML patients in complete remission (CR) off therapy [1,079.0 (661.0–1,526.0) vs. 576.0 (158.3–1,708.8) U/mL, $p = 0.0885$]. However, AML patients receiving active treatment had lower antibody levels than those observed without treatment [92.2 (37.5–216.3) vs. 1,630.0 (806.0–2,454.0) U/mL, $p < 0.0001$]. Therefore, the researchers suggest that AML patients under observation without treatment in CR can be expected to have a vaccine effect comparable to that in healthy individuals.

COVID-19 in myelodysplastic syndrome

Myelodysplastic syndrome (MDS) is commonly associated with various infections e.g. COVID-19 which can lead to death [56, 57]. It has been proved that MDS patients have an increased mortality rate due to COVID-19 infection compared to the non-MDS population (42–50% vs. 29%) [53, 56–59]. High-risk MDS patients have the worst clinical outcome and the highest mortality rate, probably due to treatment with demethylating agents. Therefore, vaccination is recommended in this group of patients.

Recent studies have evaluated the effectiveness of COVID-19 vaccines in MDS [37, 60–63]. The antibody response after two doses of BNT162b2 vaccine was analyzed in MDS patients [60]. RBD-IgG antibodies were detected in 26/43 patients (60.5%) with MDS. However, Fattizzo et al. [61] observed increased antibody response in 45/46 (98%) low risk-MDS patients. Patients received either one dose of BNT162b2 or mRNA-1273. The researchers suggested that low risk-MDS patients have a seroconversion rate comparable to healthy individuals.

Experiments have revealed significantly reduced neutralization titers in MDS/AML patients following two or three doses of the BNT162b2 or mRNA-1273 vaccine, with geometric mean titer (GMT) of 1:139 against the homologous WA1/2020 strain compared to healthy controls (GMT) of 1:1,713 after second dose of vaccine [62]. Notably, in 11 patients who received a booster dose, WA1/2020 neutralizing antibodies were highly variable (GMT, 1:304), with 2/11 showing no neutralizing response and only 4/11 a strong response >1:500 GMT. Almost all patients with myeloid neoplasms showed minimal or no neutralizing antibodies against variants including omicron (92% of patients with <1:20 GMT against omicron) after two doses of vaccine. In addition, 63% of patients who received a booster dose showed significantly lower neutralization responses to all variants and no neutralization titer to omicron compared to healthy controls. Myeloid patients who received a booster dose showed increased antibody titers against omicron RBD, but lower than healthy adults (1,621 vs. 16,519 RBD IgG). Therefore, it is suggested to recommend booster doses to myeloid patients.

The efficacy of BNT162b2 and ChAdOx1 vaccinations was evaluated in a cohort of 38 patients diagnosed with MDS [37]. Antibody response after the second dose was 100% (15/15) in a BNT162b2 cohort and 76.2% (16/21) in a ChAdOx1 group. The researchers also evaluated T-cell response. The SARS-CoV-2 specific IFNg T-cell responses against the δ variant were present in 95% (20/21) of healthy adults, MDS ChAdOx1 70.6% (12/17), and MDS BNT162b2 71.4% (10/14). Notably, both serological and T-cell response was observed in 95% (20/21) of healthy adults, 71.4% (10/14) MDS BNT162b2, and 52.9% (9/17) MDS ChAdOx1. Therefore, BNT162b2 mRNA vaccine is recommended to increase both serological and T-cell response.

Recent studies have evaluated the effectiveness of antiviral drugs [63]. Research was conducted to assess the efficacy of molnupiravir (MOL), one of the first oral antiviral drugs to show significant benefits in reducing COVID-19 hospitalizations and deaths in healthy populations [64]. MOL was prescribed to patients with recent onset of symptoms (≤5 days), who did not require oxygen supplementation or hospitalization, and who were at high risk of disease progression to more severe COVID-19. They observed 59 MDS/AML patients and showed that only 20% of patients required hospitalization during MOL therapy. Nevertheless, they observed that mortality rate and hospitalization among hematological patients were still higher compared to a healthy population in terms of MOL therapy.

COVID-19 in diffuse large B-cell lymphoma

Recent studies confirmed that lymphoproliferative disorders e.g. non-Hodgkin lymphoma (NHL) are associated with a higher risk of COVID-19 infection [20, 39]. It has been proved that NHL patients have an increased mortality rate (31.8%) due to COVID-19 prior to vaccination. Therefore,

recent studies have evaluated antibody and mortality rates following vaccination in NHL patients.

A low neutralizing antibody (Nab) response has been observed in NHL patients after the first dose of the BNT162b2 and AZD1222 vaccines [65]. The study included six NHL patients vaccinated with BNT162b2 and two vaccinated with AZD1222. After the first dose of the vaccine, on day 22 post vaccination patients had lower Nab levels compared to controls (17% vs. 32%). Despite the low response, this suggests a booster dose in NHL patients, particularly those with a suboptimal response.

Perry et al. [66] analyzed the effect of anti-lymphoma therapy on the effectiveness of two doses of BNT162b2 vaccination in 149 B-NHL patients, including 69 diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma (PMBL). 28 patients (19%) were treatment-naïve, 55 (37%) were being actively treated with rituximab/obinutuzumab (R/Obi) (monotherapy or in combination), and 66 (44%) were last treated with R/Obi >6 months prior to vaccination. Antibody response was achieved in 73/149 (49%) B-NHL patients. However, a significantly lower antibody response (7.9%) was observed in patients treated with anti-CD20 Abs within six months prior to vaccination. Nevertheless, treatment-naïve patients and patients who completed therapy >6 months prior to vaccination had significantly higher seropositivity rates than actively treated patients (89.3%, 66.7% vs. 7.9% respectively). Thus the researchers stated that a longer time from exposure to anti-CD20 Abs is associated with higher seropositivity following BNT162b2 vaccination.

Antibody response was studied in 56 patients with Burkitt's lymphoma (BL), DLBCL and PMBL combined following BNT162b2, mRNA-1273 or Ad26.COV2-S vaccine [67]. 51% (28/55) of patients seroconverted after the first dose of vaccine, although in those who received an additional dose the seroconversion rate was 100% (10/10). Hence, booster doses are recommended.

Moreover, humoral response following booster BNT162b2 vaccination was evaluated in patients with B-cell malignancies by Terpos et al. [68], who observed 54 NHL patients and found that one month after the third dose, Nabs levels were very high in all healthy participants (median 97.5%), while in the NHL group half of the patients had Nabs levels below 20%. In addition, there were 32 patients (59.3%), with Nabs levels less than 30% and only 35.3% of patients with Nab ≥50% after the third dose. Terpos et al. observed that anticancer treatment is related to lower Nabs levels. Rituximab-treated NHL patients did not increase Nabs (16% before the third dose vs. 19% one month after the third dose) compared to NHL patients not treated with rituximab who experienced a statistically significant increase in Nabs (71.4% after the third dose vs. 44% before the third dose). Therefore, the researchers suggested to delay therapy, if possible.

Another study identified seroconversion rates after the third dose of BNT162b2 vaccine was evaluated in 44 patients with B-cell non-Hodgkin lymphoma (B-NHL), including 16 with DLBCL, who had not responded to two previous doses [69]. The overall seroconversion rate was 29.5% (13/44). However, in patients previously treated with anti-CD20 moAb who had completed treatment six months or more prior to the booster dose, the seroconversion rate was significantly higher at 47.8% (11/23) compared to 10.5% (2/19) of patients treated with anti-CD20 moAb within the six months prior to the booster (p = 0.019). Notably, 50% (8/16) of DLBCL patients were serologically positive after booster vaccination compared to 17.9% (5/28) of patients with another B-NHL (p = 0.025). The authors recommend booster doses of BNT162b2 vaccine for those patients who fail to seroconvert following two doses of vaccine.

COVID-19 in chronic myeloid leukemia

Research demonstrated that the rate of COVID-19 infection among chronic myeloid leukemia (CML) patients in Italy was exceptionally low one year into the pandemic [70]. In a cohort of 8,665 CML patients, they recorded 217 SARS-CoV-2-positive patients (2.5%). 21 patients (9.6%) required hospitalization, whereas 18 (8.2%) required respiratory assistance, eight (3.6%) were admitted to an ICU, while 170 (78%) were merely quarantined. Moreover, 12 patients died due to COVID-19, with a mortality rate of 5.5% in a COVID-19 positive cohort and 0.13% in the whole cohort of CML patients. The authors stated that the mortality rate in CML appears lower compared to other hematological malignancies, and that most patients were completely asymptomatic. They also highlighted the potential positive role of tyrosine kinase inhibitor (TKi) therapy in decreasing COVID-19 occurrence and mortality.

The outcome of COVID-19 was analyzed in 551 patients with CML receiving TKi [71]. 346 (65%) of them received imatinib, 102 (19%) dasatinib, 59 (11%) nilotinib, and 44 (8%) other types of TKi therapy. All 530 were in the CP stage. 81 (15%) had a complete hematological response (CHR), 52 (10%) a complete cytogenetic response (CCyR), and 387 (73%) a major molecular response (MMR). Five patients (0.9%) were diagnosed with COVID-19. The researchers observed that 1/21 patients receiving a third generation TKI (ponatinib and HQP1351) developed COVID-19 versus 3/346 patients receiving imatinib versus 0/162 patients receiving second generation TKIs (p = 0.096). They suggested that persons receiving TKI therapy may have a higher likelihood of developing COVID-19 than the general population, although the absolute case numbers are very low and clinical features are as normal.

Ali et al. [72] identified SARS-CoV-2 omicron variant infection in patients with CML. 11 patients had a mild disease. They suggested that infection with the omicron

variant usually results in mild disease not requiring hospitalization in patients with CML.

Many studies have evaluated the effectiveness of COVID-19 vaccinations, which are recommended for CML patients as immunocompetent individuals who are in a high-risk group for severe disease. Factors associated with negative antibody response after COVID-19 vaccination were analyzed in patients with hematological diseases [73]. Vaccination was performed with BNT162b2, mRNA-1273, ChADOx1, or a combination. Notably, in a cohort of CML patients, 100/101 (99%) had a positive vaccine response. Hence, the authors suggested that patients with CML were significantly less likely to have a negative response in univariate analysis. These patients were on TKI treatment or in treatment-free remission.

Humoral responses after a second anti-SARS-CoV-2 vaccine dose were studied in 54 patients with CML treated with TKi [74]. Approximately 21 days after the first dose of either BNT162b2 or ChAdOx1, 48/50 CML patients (96%) and 25/26 healthy persons (96%) had seroconverted. However, seropositivity declined c.50 days after the first dose in CML patients (31/39, 79.5%), but not in healthy persons (25/27, 92.6%). Then, c.21 days after the second dose, 51/52 patients (98%) and 29/29 healthy persons (100%) were seropositive, a finding that persisted up to c. 50 days after the second dose of vaccination.

The authors stated that patients with CML on TKI are able to develop an antibody response against SARS-CoV-2 that is not significantly different from that seen in healthy persons, and that persists for at least three months after the second dose of vaccine.

Similarly, humoral and poly-functional T-cell responses were analyzed in patients with CML after a single dose of BNT162b2 mRNA vaccine [75]. In a cohort of 16 patients, a positive anti-S IgG ELISA response was seen in 87.5% (14/16). Nonetheless, T-cell response was seen in 93.3% (14/15) of evaluable patients. A polyfunctional cytokine response in either $CD4^+$ or $CD8^+$ T cells was seen in 80% (12/15) of patients, with a poly-functional $CD4^+$ response (with expression of IFN-γ, TNF-α or IL-2) in 60% (9/15) and a poly-functional $CD8^+$ T-cell response in 40% (6/15) Notably, the only patient not showing a T-cell response was after allo-HSCT and was taking ponatinib. Therefore, the researchers showed that a single dose of BNT162b2 vaccine demonstrated the immunogenicity in most patients with CML with both humoral and poly-functional T-cell responses compared to patients with lymphoid malignancies.

Despite the large number of studies on vaccine response, little is known about the safety of vaccination in CML patients. Therefore, 335 CML patients were recruited who were vaccinated against SARS-CoV-2 with CoronaVac (164), BBIBP-CorV (91), ZF2001 (5), and others (75) [76]. A total of 19.1% (64/335) respondents reported adverse events (AEs) after vaccination. The most common (11%, 37/335) AE was pain at injection site. However, fatigue (3%, 10/335), sleepiness (2%, 7/335) and flu-like symptoms (2%, 7/335) were regarded as systemic AEs. Moreover, the AEs of vaccination were not significantly associated with vaccine brand or TKI type. Hence, the researchers suggested that the SARS-CoV-2 vaccines described in the study are safe for CP-CML patients.

Although patients with CML exhibit a higher rate of seroconversion compared to individuals with other hematological malignancies, they are still at risk of developing breakthrough infections. 287 fully vaccinated (BNT162b2, mRNA-1273 or Ad26.COV2.S) patients with CML were recruited, and the researchers observed that those patients had the highest risk for breakthrough infections (17.4%) among the seven hematological malignancy types compared to the healthy population (4.5%) [30]. Additionally, the authors suggested that breakthrough infections in hematological patients were associated with significant clinical outcomes, including hospitalizations and mortality.

COVID-19 treatment in hematological patients

Treatment of COVID-19 in patients with hematological malignancies depends on the stage of the disease, the patient's condition, and the type of anti-cancer treatment used. Prior to vaccination for mild symptoms of COVID-19 such as fever, cough and muscle aches, patients were advised to continue to isolate at home and to follow hygiene and social distancing guidelines. For more severe symptoms, such as shortness of breath and low blood oxygen levels, hospitalization was required [77].

Patients with hematological malignancies with an inadequate response to vaccination required other protective measures to prevent or minimize the risk of breakthrough infections, including antiviral therapy such as remdesivir, and anti-inflammatory drugs such as corticosteroids, to reduce inflammation caused by COVID-19, including ventilation, oxygen, monoclonal antibody therapy, immunomodulators or convalescent plasma [78–81].

The effectiveness of convalescent plasma (CP) was assessed in 3,596 patients, demonstrating its positive impact on the clinical outcomes of COVID-19 treatment. Notably, the early administration of CP was shown to reduce the duration of hospitalization (overall 13 vs. 12 days $p \leq 0.001$) [81].

The 2021 European Conference on Infections in Leukemia (ECIL 9) recommended in unvaccinated patients at risk of severe COVID-19 or COVID-19 progression, pre-exposure prophylaxis with long-acting anti-SARS-CoV-2 monoclonal antibodies (bamlanivimab/etesevimab, casirivimab-imdevimab, sotrovimab) [22]. In patients with mild COVID-19, molnupiravir or remdesivir or nirmatrelvir + ritonavir or monoclonal antibody were recommended. Nirmatrelvir/

/ritonavir has been shown to reduce the number of hospitalizations or deaths by 89% compared to a placebo in high-risk patients treated within three days of onset of COVID-19-related symptoms [82]. Remdesivir showed a similar reduction in hospitalizations and deaths of 87% in non-hospitalized patients, including a small group of 23 (4.1%) patients with impaired immune system [83]. During a clinical trial, molnupiravir showed a relative 30% reduction in the risk of hospitalization or death [84]. Hence, it has been recommended to use in hematological patients who do not require supplemental oxygen.

In patients with moderate or severe COVID-19, remdesivir and dexamethasone have been recommended. Dexamethasone was recommended in patients who required oxygen therapy and who had increased inflammatory markers. During a clinical trial, 6 mg daily for 10 days of dexamethasone showed a 3% reduction in mortality in patients on oxygen therapy [85]. Nevertheless, some potentially therapeutic agents have not shown a benefit in COVID-19 patients, including azithromycin, hydroxychloroquine, lopinavir-ritonavir, and convalescent plasma [86].

The results of early treatment of SARS-CoV-2 infection were evaluated in 328 hematological patients treated with monoclonal antibodies (MABs) (n = 120, 37%; sotrovimab, n = 73) or antivirals (n = 208, 63%; nirmatrelvir/ritonavir, n = 116, remdesivir n = 59, molnupiravir n = 33) [87]. Univariate and multivariate analysis confirmed a higher risk of failure and longer virus shedding in patients treated with MABs compared to those treated with antivirals.

Despite the existence of many forms of anti-COVID-19 therapy, vaccination is still the most effective in terms of reducing mortality and morbidity [87].

Conclusions

Patients with hematological malignancies are at high risk of severe COVID-19 due to disease-related, as well as treatment-related, immunosuppression, older age, and other comorbidities [88]. Treatment of COVID-19 in patients with hematological malignancies includes antiviral therapy, anti-inflammatory drugs, monoclonal antibody therapy, and/ /or immunomodulators. Treatment depends on the stage of the disease, the patient's condition, and the type of anti-cancer treatment used [78–80]. Infection prevention methods are recommended, although serological response following vaccination varies according to the hematological malignancy subtype, with better responses seen in CML, AML, and low risk MDS, while poorer responses have been seen in patients with CLL and lymphoma patients [20, 89, 90]. Hematological patients have a decreased likelihood of developing antibody response compared not only to the healthy population but also to patients with solid tumors [91]. Furthermore, patients actively treated with BTKis, CAR-T, ruxolitinib, venetoclax, anti-CD20 or anti-CD38 antibody treatments seem to experience a significant reduction in their ability to mount an effective immune response to vaccination. This could potentially leave them vulnerable to SARS-CoV-2 infection without adequate protection [29].

Therefore, a new approach is urgently needed to treat high-risk patients who respond poorly to vaccines and develop only limited protection from the infection. This group of patients requires other protective measures to prevent or minimize the risk of breakthrough infections including antiviral therapy such as remdesivir and anti-inflammatory drugs such as corticosteroids to reduce inflammation, as well as monoclonal antibody therapy or immunomodulatory drugs [78–80]. Importantly, patients with a history of SCT, COVID-19, CML, CMPDs, TKi, infection prior to vaccination, or no active treatment during vaccination, have been associated with increased seroconversion [18]. It has been proved that patients with myeloid malignancies have a seroconversion rate comparable to that of the healthy population after the mRNA-1273 or BNT162b2 vaccine. Moreover, the American Society of Transplantation and Cellular Therapy has advised that COVID-19 vaccines should be offered to patients three months or later following SCT and CAR-T therapy [89, 92].

Our research focused mainly on the use of mRNA vaccines including mRNA-1273 or BNT162b2, and therefore additional studies characterizing other vaccine platforms are required due to potentially different seroconversion. There is still limited data about the evaluation of the T-cell response, and hence further studies are recommended to assess T-cell responses post-vaccination and to estimate the effects of SARS-CoV-2 booster doses to make recommendations for COVID-19 vaccination in patients with hematological malignancies [91].

There is a need for more extended studies that will shed light on the causes behind the absence of a response to vaccines, how patients who have developed an antibody response can sustain it over time, and the use of booster doses in non-responders, particularly in the case of CLL patients who are actively receiving treatment at the time of vaccination and have a recent history of using anti-CD20 monoclonal antibodies.

Toll-like receptors (TLRs) detect the presence of SARS--CoV-2. Subsequently, downstream transcription factors like IRFs are stimulated, leading to generation of interferon type I (IFN-I) and excessive inflammation. In response to SARS-CoV-2 infection, immune system becomes activated, leading to engagement of various immune cells. Simultaneously, NF-κB is activated, prompting synthesis of pro-inflammatory cytokines known as 'cytokine storm'. These pro-inflammatory cytokines further trigger JAK-STAT or NF-κB signaling pathways by binding to their receptors on immune cells, resulting in increased expression of pro-inflammatory genes and eventually leading to multiorgan failure or death [6, 95–98].

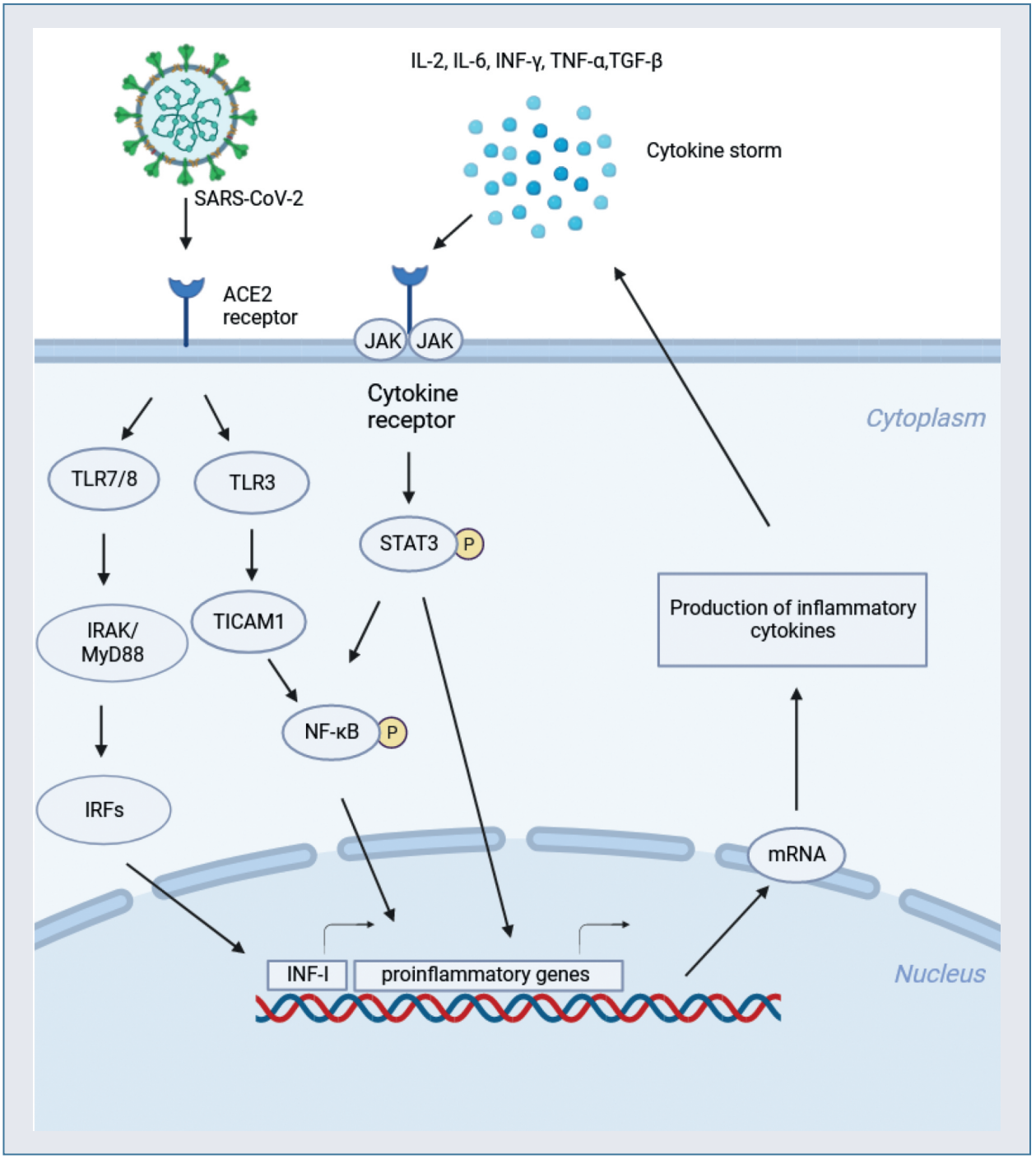

Figure 1. Signaling pathways responsible for triggering a cytokine storm in individuals infected with COVID-19 [64, 93–95]. Created with BioRender.com; LR — Toll-like receptors; ACE2 — angiotensin converting enzyme-2; IL — interleukin; IFN — interferon; JAK — Janus kinase; STAT3 — signal transducer and activator of transcription protein 3; NF-κB — nuclear factor kappa B; TICAM1 — TIR domain containing adaptor molecule 1; IRAK/MyD88 — myeloid differentiation primary response 88; IRFs — interferon regulatory factors; TNF-α — tumor necrosis factor α; TGF-β — transforming growth factor β

Table I. Efficacy of different COVID-19 vaccines in patients with hematological malignancies with lower response risk factor

Vaccine	N	Doses	Type of neoplasm	Median age	Overall response	Risk factors of lower response	Control group	Adverse events	Study
BNT162b2 (n = 48) ChAdOx1 (n = 45)	93	1	MM	65 (positive) 70 (negative)	56% (anti-SARS-CoV-2 IgG) 70% (total antibody)	1. Therapy at time of vaccination 2. Stable disease or progressive disease	Not reported	Not reported	Bird et al. [46]
BNT162b2 (n = 22) mRNA-1273 (n = 22)	44	1, 2	MM	64	93% (on therapy) 94% (not on therapy)	Not reported	Not reported	Pain at injection site, fatigue, headache	Greenberg et al. [47]
BNT162b2 (n = 221) mRNA-1273 (n = 87) Unknown (n = 12)	320	1, 2	MM	68	84.2% (219/260) 18.8% (60/320) had COVID-19 prior to immunization, hence were excluded	1. Anti-CD38 therapy 2. BCMA-targeted therapy	67 healthcare workers	Not reported	Oekelen et al. [48]
BNT162b2 (n = 72)	72	1, 2, 3 (only patients on anti-CD38 therapy)	MM	69.86	44% (1 month after D1) 85% (3 months after D1) 51% and 41% response against alpha and delta variants, respectively	1. Anti-CD38 therapy	23 healthy volunteers	Not reported	Henriquez et al. [49]
BNT162b2 (n = 215) ChAdOx1 (n = 61)	213	1, 2 (BNT162b2) 1 (ChAdOx1)	MM	74	62.8% Nab titers ≥30% 57.3% Nab titers ≥50% 4 weeks after D2 of BNT162b2 vaccine or 7 weeks after D1 of ChAdOx1	1. Anti-CD38 therapy 2. Belantamab-mafodotin combination	226 healthy controls	Pain at injection site, erythema and/or swelling after ChAdOx1, fatigue, fever, muscle pain, headache after BNT162b2	Terpos et al. [51]
BNT162b2 (n = 35) (35 vaccinated and other 35 with COVID-19 without vaccine)	70	1, 2	MM	65	87.6% Nab for COVID-19 positive 58.7% for vaccinated patients	1. Active anti-myeloma treatment only among vaccinated patients	35 matched fully vaccinated patients	Not reported	Gavriatopoulou et al. [50]
BNT162b2 (n = 35) mRNA-1273 (n = 11)	46	1	AML	67.5	94.7%	1. Active anti-myeloma treatment	43 healthy controls	Not reported	Mori et al. [55]

Table I (cont.). Efficacy of different COVID-19 vaccines in patients with hematological malignancies with lower response risk factor

Vaccine	N	Doses	Type of neoplasm	Median age	Overall response	Risk factors of lower response	Control group	Adverse events	Study
BNT162b2 (n = 149) B-NHL including 69 DLBCL patients)	149	1, 2	DLBCL	64	49% overall response 7.9% patients treated with anti-CD20 Abs within 6 months prior to vaccination	1. Anti-CD20 Abs within 6 months prior to vaccination	65 healthy controls	Pain at injection site, tiredness, muscle pain	Perry et al. [66]
BNT162b2 (n = 16) ChAdOx1 (n = 22)	38	1, 2	MDS	67.5	Humoral response 100% BNT162b2 76.2% ChAdOx1 T-cell response BNT162b2 71.4% ChAdOx1 70.6% Both responses 71.4% BNT162b2 52.9% ChAdOx1	Not reported	30 healthcare workers	Not reported	Abdul-Jawad et al. [37]
BNT162b2 mRNA-1273 Ad26.COV2.S	36	1, 2	CLL	62	60% not on therapy 72% treatment naïve 33% in patients on BTKi therapy	1. BTKi therapy 2. Adenovirus vaccine	Not reported	Not reported	Haydu et al. [35]
BNT162b2	167	1, 2	CLL	71	39.5%	1. On CLL therapy 2. BTK inhibitors and venetoclax ± anti-CD20 antibody	52 healthy controls	Pain at injection site, local erythema or swelling	Herishanu et al. [99]
BNT162b2	172	3	CLL	72.1	23.8%	1. On CLL therapy 2. BTK inhibitors and venetoclax ± anti-CD20 antibody	Not reported	Pain at injection site, local erythema, swelling, fatigue	Herishanu et al. [38]
BNT162b2	61	1, 2	CLL	69.4	90.2% Six months after D2	1. Active CLL treatment	39 healthy controls	Not reported	Herishanu et al. [100]

Table I (cont.). Efficacy of different COVID-19 vaccines in patients with hematological malignancies with lower response risk factor

Vaccine	N	Doses	Type of neoplasm	Median age	Overall response	Risk factors of lower response	Control group	Adverse events	Study
BNT162b2 (n = 204) ChAdOx1 (n = 296)	500	1, 2	CLL	67	67%	1. BTKi therapy 2. Male gender 3. IgA or IgM hypogammaglobulinemia	93 healthy donor controls	Not reported	Parry et al. [40]
BNT162b2 (n = 377) mRNA-1273 (n = 76) Unknown (n = 77)	530	1, 2, 3	CLL	71	27% after D1 52% after D2 35% after D3 in post-dose 2 seronegative patients	1. BTKi therapy 2. BTKI in combination with anti-CD20 monoclonal antibodies or venetoclax 3. Over 65 years	Not reported	Not reported	Bagacean et al. [41]
BNT162b2 ChAdOx1	50	1, 2	CML	51.2	96% 21 days after D1 79.5% 50 days after D1 98% 21 days after D2	Not reported	31 healthy controls	Not reported	Claudiani et al. [74]
BNT162b2	43	1, 2	MDS	73.0	60.5%	Not reported	272 healthy controls	Pain at injection site, fatigue and headache	Rahav et al. [60]
BNT162b2, mRNA--1273, ChADOx1	101	1, 2	CML	64	99%	Patient who did not seroconvert received combined treatment with ruxolitinib and bosutinib	35 patients with autoimmune and benign diseases	Not reported	Rotterdam et al. [73]
BNT162b2, mRNA-1273	62	1, 2	CMPDs	71.9	57.7 % MF 91.7% PV or ET	Patients receiving ruxolitinib	Not reported	Not reported	Cattaneo et al. [101]

MM — multiple myeloma; CLL — chronic lymphocytic leukemia; B-NHL — B-cell non-Hodgkin lymphoma; DLBCL — diffuse large B-cell lymphoma; AML — acute myeloid leukemia; CML — chronic myeloid leukemia; N — number of patients; D1 — first dose of vaccine; D2 — second dose of vaccine; D3 — third dose of vaccine; BTKi — Bruton's tyrosine kinase inhibitor; BCMA — B-cell maturation antigen; anti-CD20 Abs — anti-CD20 antibodies; MF — myelofibrosis; PV — polycythemia vera; ET — essential thrombocythemia; NS — not significant $p \geq 0.05$

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Conflict of interests
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Supplementary material
None.

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REVIEW ARTICLE

VIA MEDICA

Treatment of resistant viral infections after allogeneic hematopoietic stem cell transplantation using virus-specific T cells

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Abstract

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is widely used in the treatment of malignant and non-malignant diseases. Patients treated with allo-HSCT receive immunosuppression, which lowers the organism's immune response. This leaves a significant period during which the host is seriously deficient in T cell immunity. Viral infections are therefore one of the major causes of morbidity and mortality in these patients. Available prophylactic and preventive antiviral pharmacotherapies are often insufficient or limited due to toxicity, ineffectiveness, or the development of drug resistance, and additionally do not provide long-term protection or immunological memory.

A current extension of virostatic agents is the transplantation of antiviral immunity through adoptive transfer of virus-specific T cells (VSTs) against ADV, CMV, or EBV. Antigen-specific adoptive immunotherapy holds promise in selectively targeting and eradicating host cells by identifying particular antigens, such as those associated with specific viral infections and cancers. The successful application of adoptive transfer of antigen-specific effector immune cells has been demonstrated in the treatment of opportunistic viral infections following HSCT. VSTs exhibit significant potential as a valuable addition to current treatments for viral reactivation and disease, showing robust and enduring response rates with a manageable side effect profile.

Keywords: cell therapy, allogeneic stem cell transplantation, viral infections, lymphocytes T, virus-specific T cells

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Introduction

Hematopoietic stem cell transplantation (HSCT) is an important strategy for the treatment of malignant diseases (mainly leukemias and lymphomas) and non-malignant diseases (primary immunodeficiencies, metabolic diseases). However, achieving the desired outcome can be hampered by a wide range of transplant-related complications, including viral infections, which are a leading cause of morbidity and mortality in transplant patients [1].

There are many factors influencing the risk of infectious complications after HSCT and factors related to impaired reconstitution of the immune system after treatment. In the classical approach, the most important are neutropenia occurring immediately after the preparatory treatment (conditioning), functional and quantitative cellular disorders, as well as humoral disorders of the immune system related to delayed immune reconstitution during treatment, and graft-versus-host disease (GvHD) in recipients after allo-HSCT or in the course of other

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immunological complications occurring after transplantation [2, 3].

About one third of deaths caused by infections are caused by viruses, mainly human cytomegalovirus (CMV), Epstein-Barr virus (EBV) or human adenovirus (AdV) [4, 5]. After HSCT, the latent virus may reactivate and manifest itself as post-transplant lymphoproliferative disease (PTLD) [6, 7]. Frequently, local reactivations tend to resolve on their own, whereas systemic infections, particularly when a risk factor weakens T-cell protection, lead to significant morbidity and mortality [5, 8].

Despite the fact that pharmacological therapies are available for the treatment of viral infections, many of them are, unfortunately, ineffective. This is sometimes due to drug resistance and sometimes to the need to withhold treatment due to drug-related toxicity. Furthermore, long-term treatment is expensive.

For all of these reasons, virus-specific T cells (VSTs), which are mainly cytotoxic T lymphocytes (CTLs), are increasingly being explored as a treatment option for refractory viral infections in transplant patients [1].

Complications after allo-HSCT and conventional treatment

Bacterial infections occur with a similar frequency after allo-HSCT and auto-HSCT transplantation, while fungal and viral infections occur much more often after allo-HSCT, which is due to the possibility of profound immunological disorders after allo-HSCT, related to HLA incompatibilities between the donor and recipient, the immunosuppressive therapy used, and the possible presence of GvHD [9].

CIBMTR (Center for International Blood and Marrow Transplant Research) registry data shows that among the causes of HSCT failure, infections account for 12% of deaths after HSCT from matched family donors, for 17% of deaths after HSCT from unrelated donors, and for 8% of deaths after auto-HSCT. American data shows that infections after allo-HSCT occur in 82% of children, but in only 21% of children with solid tumors and lymphomas after auto-HSCT, and in 49% of children with acute leukemias, again after auto-HSCT [9–11].

As a result, patients after allo-HSCT often experience reactivation of latent viruses, mainly herpes viruses, most often CMV and EBV, which constitute a significant clinical problem after allo-HSCT requiring the use of pre-emptive or targeted therapy. There is also frequent infection and reactivation of the BKV polyoma virus, which causes the development of hemorrhagic cystitis.

The clinical picture of latent virus infections is related to their direct effect, causing the development of a disease typical for a given virus (i.e. most often with CMV — pneumonia, liver, brain, gastrointestinal tract, and bone marrow failure; with EBV — PTLD, and lymphoproliferative syndrome; with VZV — herpes zoster; and with HHV6 — encephalitis). There is also an indirect effect related to the negative impact on the immune system contributing to the development of subsequent infections, including other viruses and fungal infections.

Undoubtedly, antiviral treatment has a harmful effect on the immune system and the function of the regenerating bone marrow. A common complication of viral infection and antiviral treatment is secondary bone marrow failure, which affects the functioning of the entire body and has an unfavorable effect on the transplant procedure. In other words, viral infections can undermine the best efforts of the transplant center and the effect of hematopoietic cell transplantation and anticancer treatment [9].

CMV is defined as a beta herpes virus. In monocytes, CMV causes lifelong latency [12, 13]. Whether the CMV infections are acute or reactive, they can cause multisystem diseases (e.g. pneumonia, hepatitis and encephalitis). Antiviral drugs, including gancyclovir and foscarnet, or newer drugs such as maribavir, brincidofovir and letermovir, reduce the frequency of infections in transplant recipients. Unfortunately, they are expensive and often accompanied by toxicity and antiviral resistance [14–16]. For CMV IgG positive adult HSCT-recipients, letermovir is approved CMV prophylaxis. Acyclovir/valacyclovir is not sufficiently effective against CMV. Gancyclovir and foscarnet have been shown to be effective but toxic in HSCT recipients (Table I). Moreover, valgancyclovir is effective in solid organ transplantation but causes myelosuppression, and therefore its use is greatly limited in HSCT recipients [17].

In children, the situation differs but there is data available on its off-label use with positive impacts on allo-HCT outcomes due to its favorable safety profile and high efficacy in preventing CMV reactivation [18–20]. Preemptive therapy is considered the standard strategy for CMV prevention after allo-HSCT. Under this, patients are monitored weekly for CMV reactivation by PCR. Current recommendations for preventive therapy for allo-HSCT patients according to the European Conference on Infection in Leukemia include the use of letermovir which has grade AI (A = strongly recommended, I = based on a randomized trial) recommendations for CMV prophylaxis in adult allo-HCT recipients according to ECIL7, intravenous gancyclovir or foscarnet (first-line therapy), and valgancyclovir instead of intravenous gancyclovir or foscarnet (except for patients with severe GvHD of the gastrointestinal tract) [1, 17, 21]. The choice of drug has also been shown to depend on time after HSCT, risk of toxicity, and prior antiviral drug exposure.

EBV is known as a gamma herpes virus. EBV leads to B lymphocyte latency throughout life, and can cause fulminant infectious mononucleosis or lymphoproliferative disease in immunocompromised patients [22, 23]. The use of rituximab has reduced the incidence of PTLD. Unfortunately, the risk of primary immunodeficiency diseases (PID) in

Table I. Data on viral reactivation, viral disease, standard treatment and response rate in patients

Virus	Patients	Viremia [%]	Viral disease [%]	Treatment	Response rate [%]
AdV	Children	15–30	6–11	Cidofovir	60–80
	Adults	6–15	2	Brincidofovir	
CMV	Children	12–20	4	Gancyclovir	
	Adults	39	13	Foscarnet	70–80
				Valgancyclovir	
EBV	Children	11	1–7	Rituximab	60–70

AdV — human adenovirus; CMV — human cytomegalovirus; EBV — Epstein–Barr virus

patients still remains. Preventing EBV-PTLD mainly involves selecting a donor who is serologically compatible with the transplant recipient. The preventive use of antiviral drugs is not recommended for this indication. Individual studies have indicated the effectiveness of the anti-CD20 monoclonal antibody, rituximab, administered prophylactically after allo-HSCT in a group of patients with a high risk of developing PTLD. Currently, the most widely used drug in preemptive therapy is indeed rituximab, which prevents the development of full-blown PTLD in 89% of treated patients. The use of 1–2 doses of the drug is usually sufficient to reduce EBV viral load. This therapy is currently used in more than 80% of European transplant centers, which has significantly contributed to reducing the number of cases of confirmed PTLD [3].

Adenovirus is a non-enveloped DNA virus and is the main cause of respiratory and gastrointestinal diseases in immunocompromised patients. Cidofovir is active against adenoviruses, but its use is often limited due to its renal toxicity. In small studies, brincidofovir has demonstrated efficacy against adenoviruses and no significant renal toxicity, but has been associated with gastrointestinal toxicity [24, 25]. For preventive therapy of AdV infection, cidofovir is currently the recommended first-line drug. However, treatment outcomes are confounded by drug toxicity (Table I) [1].

BK virus is a polyomavirus associated with hemorrhagic cystitis and rare cases of pervasive multifocal leukoencephalopathy [26, 27]. Brincidovir is used for the prophylactic or preemptive treatment of BKV. Furthermore, it has been shown that second-generation ciprofloxacin (a fluoroquinolone) can prevent BK virus replication *in vitro* and lead to a reduction in BK virus spread after allo-HSCT [28].

Available prophylactic and preventive antiviral pharmacotherapies are often insufficient or limited by toxicity, ineffectiveness, and/or the development of drug resistance, and additionally they do not provide long-term protection or immunological memory [29]. T cell reconstitution is a key requirement for effective infection control after HSCT, given the central role of pathogen-specific T cells in infection surveillance. Therefore, strategies that accelerate pathogen-specific immunity and T cell regeneration may complement or replace available treatments [30].

Treatment of resistant viral infections after allo-HSCT

Conventional pharmacological products against viral infections have limited effectiveness and corresponding toxicity.

In 2022, the USA's FDA and the EU's EMA approved the medicinal product Ebvallo (tabelecleucel). This product is used for allogeneic T-cell immunotherapy specific for EBV, which targets and eliminates EBV-infected cells in an HLA (human leukocyte antigen)-restricted manner.

Another interesting method of treatment is an adoptive cell therapy of viral infections using infusions of VST, first suggested in 1990 [31]. Over more than three decades, hundreds of patients have been treated with lymphocytes with anti-viral activity, also referred to as CTL therapy [5].

Riddell and Greenberg administered only VSTs to their patient [31, 32]. They produced CMV-specific CD8+ T cells by *ex vivo* culture of the donor's PBMCs (peripheral blood mononuclear cells) in the presence of autologous CMV-infected fibroblasts. This was followed by clonal expansion and depletion of CD4+ T cells. They observed no significant side effects in any of the treated patients [31, 32].

Rooney et al. manufactured EBV-specific T cells for the treatment of PTLD by successively stimulating donor-derived PBMCs with irradiated autologous EBV-transformed B cell lines [5, 33, 34].

Interestingly, multiple VSTs have also been produced. The process was established by using direct isolation using a cytokine capture technique [35]. Khanna et al. presented a protocol in which multipathogen-specific T cells (expressing CD154) were isolated by magnetic cell separation [36]. The comparison of multi-VSTs isolated by CD137 expression or IFNγ production showed no significant differences in CD4+/CD8+ T cell functionality or frequency [37].

Clinical trials using CMV, EBV, and AdV-specific T cells for adoptive T cell transfer have demonstrated that T cell therapy is an attractive approach to restoring protective antiviral T cell immunity. Over nearly 30 years of adoptive T cell transfer, 74% of 246 patients responded to treatment, 85% responded to CMV-specific T-cell transfer, 62%

to EBV-specific T-cell transfer, and 74% to AdV-specific T-cell transfer. The dosage of VSTs depends on the risk of GvHD, the method of production, and the degree of HLA matching/mismatching. For *ex vivo* generated T cells, the recommended upper dose limit is 2.5×10^4/kg recipient CD3+ cell weight in HLA-mismatched/haploidentical donors, and 1×10^5/kg in HLA-matched donors [5].

The development of a manufacturing process for VST-cell products has overcome the difficulties associated with the transfer of adoptive T-cells. Nevertheless, regulatory obstacles, logistics, and the time-consuming selection techniques for producing VSTs, limit the broad application of this therapy. 'Off-the-shelf' VSTs are promising, but clinical efficacy has not yet been confirmed in placebo-controlled trials. Moreover, third-party T cells have demonstrated clinical benefits, but the explanation for *in vivo* persistence remains to be explored [38]. The phase III clinical trial TRACE (international and placebo-controlled) aims to create clinical data to enable adoptive transfer of VSTs to be incorporated into evidence-based treatment guidelines. It also aims to eventually make third-party T cells available as a standard treatment for refractory viral infections after HSCT [5].

Posoleucel (formerly known as ALVR105) is an off-the-shelf multi-VST product designed for administration to immunocompromised patients as a partially HLA-matched solution. It aims to treat or prevent viral infections or diseases caused by AdV, BKV, CMV and EBV. Posoleucel is designed to reinstate T cell immunity in patients experiencing a period of severe immune compromise between the conditioning and reconstitution phases of their immune systems. By acting as an immunological bridge, posoleucel has the potential to significantly decrease or prevent virus-associated morbidity and mortality, leading to notable improvements in patient outcomes. The transformative impact of posoleucel on the management of transplant patients was explored in a phase II open-label, proof-of-concept study involving 58 allogeneic HCT patients with treatment-refractory infections. In this study, 95% of patients treated with posoleucel exhibited a predefined clinical response, and the treatment was generally well-tolerated.

Additionally, a phase II multi-virus prevention trial showed that posoleucel resulted in a substantial reduction in the anticipated rate of clinically significant viral infections or diseases. By the week 14 primary endpoint, 88% of patients remained free of clinically significant infections caused by any of the six viruses targeted by posoleucel [39]. In their study, Pfeiffer et al. determined the feasibility and safety of posoleucel in allo-HCT recipients infected with one or more of these viruses. This open-label, single-arm trial, approved by the FDA and the Baylor College of Medicine institutional review board, included patients who had undergone allo-HSCT from any donor source starting from day 28 post-transplant [40].

An appealing feature of third-party off-the-shelf multi-VSTs is their swift availability, reducing potential delays in treating these often life-threatening viral infections. Out of 59 posoleucel VST lines, a suitable line was identified for 97% (58/60) of screened and eligible patients, allowing local patients to receive treatment within 48 hours. Clinical benefit was observed even when posoleucel was matched on a single HLA allele, although the majority of patients received lines matched at a median of two alleles. Posoleucel is derived from healthy, seropositive third-party donors rather than being sourced from autologous or HLA-matched HSCT donors.

The trial results indicate that posoleucel is a safe and effective therapy for severe viral infections following allogeneic HSCT. Its use could potentially reduce the morbidity and mortality associated with post-HSCT viral infections while avoiding the nephrotoxic and myelosuppressive side effects linked to conventional antiviral medications [40].

Adoptive T cell therapies targeting specific viruses are generally considered safe. However, in allogeneic products, there is a potential concern for GvHD, with reported incidences ranging from 5–16%, despite the viral specificity of the majority of cells [41]. Regardless of the cell source, occurrences of cytokine release syndrome and graft failure due to T cell-mediated inflammation are possible but have only been rarely reported [42, 43]. An unresolved issue revolves around the simultaneous use of immunosuppressive drugs, which can impact the expansion and function of infused T cells in the patient. Determining the optimal timing and composition of immunosuppression at the time of VST infusion remains an unanswered question [41].

VST production

VSTs are manufactured as patient-specific products, and the time required for procurement, production, and marketing approval testing precludes their use in acutely ill patients. Moreover, products must always comply with good manufacturing practices (GMP).

A possible solution to this limitation is the automated production of VSTs. Kim et al. and Kállay et al. [35, 44] have described a manufacturing process using an IFN-γ cytokine capture system (CCS) in a closed system. The process is based on the presentation of viral antigens on donor's lymphocytes. The presentation of the antigens is followed by magnetic separation of VST cells that responds to antigen stimulation with the expression of IFN-γ. The whole process uses a fully automated CliniMACS Prodigy® system from Miltenyi Biotec (Bergisch-Gladbach, Germany).

In terms of manageability, the VST manufacturing process using the IFN-γ CCS with CliniMACS Prodigy® is reliable. VST cells against one virus, and also multi-VSTs, can be manufactured in enough cell numbers for 100% of patients. The final cell product received from CliniMACS

Prodigy® is ready for infusion within two days. This shows a significant reduction in manufacturing time compared to *ex vivo* culture methods that took 2–12 weeks to complete [31, 45]. The fully automated CliniMACS Prodigy® system telescoped the time to completion to c.14 hours. This reduces infrastructure requirements and lightens the load on the GMP team. These manufacturing times are consistent with a study by Priesner et al. comparing CliniMACS Prodigy®-based manufacturing to CliniMACS Plus®-based manufacturing [46]. Using both methods to manufacture CMV-specific T cells from three healthy donors, they demonstrated that the recovery rate was comparable in both methods. However, the purity of the product was noticeably higher using CliniMACS Prodigy® (purity range on Prodigy® 79.2–96.4% vs. 19.2–81.1% on Plus®). A comparable preclinical study by Kim et al. extensively described the characteristics of five products of CMV-specific T cells from healthy donors' leukapheresis products [44].

Regarding the safety profile of VST treatment, no major safety concerns have been identified in previous studies evaluating the use of VST [31, 35, 47–50].

The production of VST cells, for each virus, is a time–consuming and expensive process. Therefore, intensive work is being carried out to establish protocols for producing multi-VSTs in a single step.

Conclusions

Despite the fact that some advances have been made in antiviral pharmacotherapy, the available products still show significant toxicity. Moreover, they are rarely able to control the virus without restoring T-cell immunity. New antiviral drugs (e.g. letermovir) have provided additional preventive measures, but the therapeutic options still remain limited. VSTs are promising in combating refractory viral infections in HSCT patients, whether it is treatment or prevention. Importantly, VST therapy has the potential to become a valuable clinical extension to the available treatments for viral infections, given its robust and durable response rates and tolerable side effect profile. In Poland, the decision is being taken to introduce VST therapy into the treatment of resistant viral infections in patients after allo-HSCT as part of a project financed by the Medical Research Agency (ALLOVISTA, project number 2020/ABM/01/00125).

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REVIEW ARTICLE

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Update on management of diffuse large B-cell lymphoma Richter's transformation

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Abstract

Richter's transformation (RT) is defined as the development of an aggressive lymphoma in 2–10% of patients with chronic lymphocytic leukemia (CLL). Despite significant advances in the last decade, there is currently no established standard of care for RT, making its management a significant challenge. Questions regarding patients' treatment management in the era of novel agents and targeted therapies have yet to be answered. Nevertheless, several retrospective studies and clinical trials have emphasized the use of novel targeted agents to address this problem. In this review, we provide a summary of potential therapeutic options for RT.

Keywords: chronic lymphocytic leukemia, treatment, Richter's transformation, immunochemotherapy

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Introduction

Richter's transformation (RT) is characterized by the development of aggressive lymphoma in patients previously or concurrently diagnosed with chronic lymphocytic leukemia/ /small lymphocytic lymphoma (CLL/SLL) [1, 2]. RT is a rare event, occurring in 2–10% of CLL patients with an annual transformation rate of 0.5–1% [3]. It is associated with clonal evolution and the transformation of the original CLL clone into diffuse large B-cell lymphoma (DLBCL) or, less frequently, to Hodgkin lymphoma (HL). The great majority of RT cases (90–95%) manifest as diffuse large B-cell lymphoma RT (DLBCL-RT), while Hodgkin lymphoma RT (HL-RT) accounts for 5–10% of cases [4]. Rare cases of Richter's transformation into lymphoid or myeloid leukemia have been reported, as well as transformation into very aggressive mature T-cell lymphoma [5, 6]. Despite similar clinical characteristics to those of DLBCL, the molecular profile of RT is distinct. RT is characterized in most cases by rapid disease onset and progression. Transformation develops due to the acquisition of multiple genetic defects that facilitate rapid proliferation, such as *TP53* aberrations, *NOTCH1*, *MYC*, and *CDKN2A*, and DNA damage response mutations [7]. An important feature of RT is the clonal relation to preexisting CLL. Clonality can be determined by comparison of the immunoglobulin heavy chain variable region (IGVH) gene by next-generation sequencing or Sanger sequencing. Nevertheless, widespread testing of the clonal relationship has been limited due to the methodological issues dependent on the accessibility of RT tissue material for molecular testing. About 80% of RT is clonally related, whereas c.20% of RT is clonally unrelated: such cases are considered as the coexistence of two diseases: CLL and DLBCL. Clonality significantly worsens the prognosis [8–10].

RT can occur at any point in the disease course of a patient with CLL, including in previously untreated patients under observation or even as the initial presentation of CLL. However, such cases are very rare, and the vast majority of RT occurs in patients either on active CLL treatment or who are progressing after previous treatment [11]. The median time from CLL diagnosis to transformation is 2–5 years [12–14]. A recent epidemiological study

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comparing the incidence of RT in the era of novel agents revealed that this disease has occurred approximately half as frequently since the advent of the widespread availability of BCL-2 inhibitors or Bruton's tyrosine kinase inhibitors (BTKi) [15].

Despite advances in understanding the molecular variations and the disease's pathogenesis, DLBCL-RT is characterized by a poor prognosis, refractoriness to treatment, and short median overall survival (OS) of less than 12 months [10, 16]. Heavily pretreated CLL patients developing RT in the contemporary era following a targeted inhibitor such as BTKi have potentially an even worse outlook, with a series of cases demonstrating an OS of only 3–4 months [17, 18]. Better prognoses may be observed only in cases of clonally unrelated DLBCL-RT, which is similar to DLBCL *de novo,* with median survival of c.5 years [8–10].

There is currently no established standard of care for DLBCL-RT, making it one of the most significant clinical unmet needs in non-Hodgkin lymphoma (NHL) treatment. Nevertheless, progress in the development of novel targeted therapies holds the potential to enhance outcomes in RT. This review concentrates on treatment options for DLBCL-RT.

Treatment

Immunochemotherapy

In most cases, the therapy of RT-DLBCL is based on treatment experience from the B-cell non-Hodgkin lymphoma setting, albeit with significantly poorer outcomes. The predominant approach involves immunochemotherapy such as rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) [19]. While this regimen achieves high response rates in *de novo* DLBCL, and even cures up to two in every three patients, patients with RT are rarely cured by immunochemotherapy [7, 20, 21]. R-CHOP was initially investigated prospectively in a phase II study in 15 patients, which reported an overall response rate (ORR) of 67% with a low complete response (CR) rate of only 7%. Responses were generally not durable, with a median progression-free survival (PFS) of only 10 months (Table I) [22]. Similar results were noted in a retrospective analysis by the Polish Adult Leukemia Study Group. In a cohort of 76 DLBCL-RT patients treated with R-CHOP-like protocols, an ORR of 42.3% and a CR of 32.9% were reported, with a median PFS of 16.9 months [12]. It is however most important to underscore that in this retrospective analysis, both PET-CT as well as CT, were used for response assessment, thus potentially introducing bias.

Intensification of immunochemotherapy to hyper-CVAD (fractionated cyclophosphamide, vincristine, liposomal daunorubicin, and dexamethasone with or without methotrexate), OFAR (oxaliplatin, fludarabine, cytarabine, and rituximab), dose-adjusted R-EPOCH (rituximab, etoposide, prednisolone, vincristine, and doxorubicin), or other intensive protocols may deliver improved responses. However, these have not proved durable and OS has remained <12 months in the studies published to date. Moreover, the significant toxicity of such intensive chemotherapy is an important limitation [23–26].

A novel potential therapeutic option worth mentioning is polatuzumab vedotin (monomethyl-auristatin E conjugated CD79b antibody), which showed improved PFS when combined with R-CHP compared to R-CHOP in previously untreated DLBCL patients [27]. There is an ongoing trial with polatuzumab vedotin in combination with dose-adjusted R-EPOCH in RT (NCT04679012) (Table II) [28].

Hematopoietic stem cell transplantation

For patients who achieve response after induction treatment, hematopoietic stem cell transplantation (HSCT) still has a role to play as a consolidation in selected patients with no significant comorbidities and who are transplant eligible. Published data that supports HSCT consolidation in RT has come predominantly from retrospective and single-center studies, while prospective data is limited. Remarkably, there have been no prospective studies comparing autologous HSCT (auto-HSCT) versus allogeneic HCT (allo-HSCT). However, given that patients with RT have concomitant CLL, only allo-HSCT can achieve durable remissions for CLL , and therefore it remains the preferred transplantation approach [11].

Tsimberidou et al. in 2006 was one of the first studies to report the outcomes of allo-HSCT and auto-HSCT in RT. Seventeen patients underwent allo-HSCT and three auto-HSCT. The estimated 3-year OS was 75% for patients who underwent allo-HSCT after achieving at least a PR, 27% for patients responding to induction therapy but not undergoing allo-HSCT, and 21% for patients with relapsed/refractory (R/R) DLBCL-RT who underwent allo- or auto-HSCT as salvage therapy (Table I) [29]. Furthermore, one large recent retrospective study on allo-HSCT in patients with RT (118 patients) also confirmed that the disease status at the time of HSCT significantly correlates with the outcomes. The 3-year PFS for patients with CR at the time of allo-HSCT was 66%, 43% for those with PR, and only 5% for patients with resistant RT. Interestingly, in this study, the 3-year PFS and OS results were superior in the group of auto-HSCT recipients (48% and 57%, respectively) compared to allo-HSCT recipients (43% and 52%, respectively). However, as the authors note, it is not possible to compare outcomes after auto-HSCT against outcomes after allo-HSCT because of the differences in cohort characteristics (e.g. more patients in CR, few patients receiving prior novel agents, and few with high-risk cytogenetics in the auto-HSCT cohort, including nearly half with missing cytogenetic data), as well as the potential biases in selecting one transplant approach over the other [30].

Table I. Treatment outcomes for Richter's transformation

Author	Treatment regimen	Study	Number of patients	ORR (with CR)	Median PFS (months)	Median OS (months)
Langerbeins et al. [22]	R-CHOP	Phase II study	15	ORR 67% (CR 7%)	10.0	21.0
Tsimberidou et al. [29]	Chemotherapy or chemoimmunotherapy with or without stem cell transplantation	Retrospective study	130 in total	ORR 39% (CR 12%)	7.0	8.0
Tam et al. [36]	Zanubrutinib, alone and in combination with tislelizumab	Phase I/II study	13	ORR 62% (CR 15%)	17.3	29.3
Wierda et al. [11, 28]	Pirtobrutinib	Phase I/II study	75	ORR 52% (CR 10%)	3.7	13.1
Davids et al. [39]	Venetoclax plus dose-adjusted R-EPOCH	Phase II study	20	ORR 62% (CR 50%)	10.1	19.6
Ding et al. [48]	Pembrolizumab	Phase II study	9	ORR 44% (CR 11%)	5.4	10.7
Jain N et al. [50]	Nivolumab combined with ibrutinib	Phase II study	24	ORR 42% (CR 34%)		13.0
Frustaci et al. [54]	Venetoclax, atezolizumab and obinutuzumab	Phase II study	28	ORR 67.9% (CR 28.6%)	16.2	31.6
Guieze et al. [65]	Blinatumomab	Phase II study	25	ORR 36% (CR 20%)	–	–
Kater et al. [67]	Epcoritamab	Phase I/II study	10	CR 50%	–	–

CR — complete remission; ORR — overall response rate; PFS — progression-free survival; OS — overall survival; R-CHOP — rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-EPOCH — rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin

Table II. Ongoing clinical trials for Richter's transformation (RT) treatment

Study	ClinicalTrials.gov Identifier	Investigated drugs
Phase II Study of Venetoclax in Combination With Dose-adjusted EPOCH-R or R-CHOP for Patients With Richter's Syndrome	NCT03054896	Venetoclax + EPOCH-R Venetoclax + R-CHOP
Trial of CHOP-R Therapy, With or Without Acalabrutinib, in Patients With Newly Diagnosed Richter's Syndrome (STELLAR)	NCT03899337	Acalabrutinib + R-CHOP R-CHOP
Study to Evaluate the Efficacy and Safety of Obinutuzumab, Ibrutinib, and Venetoclax in Patients With Richter's Syndrome	NCT04939363	Obinutuzumab + ibrutinib + venetoclax
Polatuzumab Vedotin in Combination With Chemotherapy in Subjects With Richter's Transformation	NCT04679012	Polatuzumab vedotin + EPOCH-R
Safety and Efficacy Study of Epcoritamab in Subjects With Relapsed/Refractory Chronic Lymphocytic Leukemia and Richter's Syndrome	NCT04623541	Epcoritamab + venetoclax Epcoritamab + lenalidomide Epcoritamab + R-CHOP
Duvelisib and Venetoclax in Relapsed or Refractory CLL or SLL or RS	NCT03534323	Duvelisib Venetoclax
Phase II Study of Glofitamab as Monotherapy or in Combination With Polatuzumab Vedotin or Atezolizumab in Richter's Transformation	NCT06043674	Glofitamab Glofitamab + polatuzumab vedotin Glofitamab + atezolizumab
R-EPOCH in Combination With Ibrutinib for Patients With Classical RT of CLL	NCT04992377	Ibrutinib + EPOCH-R

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Table II (cont.). Ongoing clinical trials for Richter's transformation (RT) treatment

Study	ClinicalTrials.gov Identifier	Investigated drugs
Atezolizumab, Obinutuzumab, and Venetoclax in Treating Patients With Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma, or Relapsed or Refractory Richter's Syndrome	NCT02846623	Atezolizumab Obinutuzumab Venetoclax
Ipilimumab, Ibrutinib, and Nivolumab for the Treatment of Chronic Lymphocytic Leukemia and Richter's Transformation	NCT04781855	Ibrutinib Ipilimumab Nivolumab
Copanlisib and Nivolumab in Treating Patients With Richter's Transformation or Transformed Indolent Non-Hodgkin Lymphoma	NCT03884998	Copanlisib Nivolumab
ObinutuzuMab AtezOlizumab and VenetocLax in RichTer transfOrmation	NCT04082897	Obinutuzumab Atezolizumab Venetoclax
Time-limited Triplet Combination of Pirtobrutinib, Venetoclax, and Obinutuzumab for Patients With Treatment-naïve Chronic Lymphocytic Leukemia (CLL) or Richter's Transformation (RT)	NCT05536349	Pirtobrutinib Obinutuzumab Venetoclax
Study of Zilovertamab Vedotin (MK-2140) as Monotherapy and in Combination in Participants With Aggressive and Indolent B-cell Malignancies (MK--2140-006)	NCT05458297	Zilovertamab vedotin Nemtabrutinib
Study of Brexucabtagene Autoleucel in Adults With Rare B-cell Malignancies	NCT05537766	Brexucabtagene autoleucel
(CHANT) Real World Study of Duvelisib in the Treatment of Non-Hodgkin's Lymphoma (NHL)	NCT05923502	Duvelisib
Lisocabtagene Maraleucel, Nivolumab and Ibrutinib for the Treatment of Richter's Transformation	NCT05672173	Ibrutinib Lisocabtagene maraleucel Nivolumab
Acalabrutinib, Venetoclax and Durvalumab for the Treatment of Richter's Transformation From Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma	NCT05388006	Acalabrutinib Durvalumab Venetoclax
Zanubrutinib and Lisocabtagene Maraleucel for the Treatment of Richter's Syndrome	NCT05873712	Lisocabtagene maraleucel Zanubrutinib
Phase I/II study evaluating safety and efficacy of palbociclib in combination with immunochemotherapy R-CHOP in patients with Richter's transformation (PALIMRI)		R-CHOP Palbocyclib

CLL — chronic lymphocytic leukemia; R-CHOP — rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-EPOCH — rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin

It is worth mentioning that HSCT as a consolidation therapy in RT has been available only to a selected group of younger, fit, and chemosensitive patients [31]. Only four of the 204 patients proceeded to allo-HSCT in one large single-institution publication of biopsy-proven RT, underlying the unmet need for effective induction therapies and the rarity of transplant-eligible RT patients [13]. A retrospective analysis by the European Group for Blood and Marrow Transplantation (EBMT) centers included 59 patients with RT (n = 34, auto-HSCT; n = 25, allo-HSCT). In 18 allo-HSCT recipients (72%), reduced-intensity conditioning (RIC) was used. The 3-year estimates of the probabilities of OS and relapse-free survival (RFS) and the cumulative incidences of relapse and non-relapse mortality were 36%, 27%, 47%, and 26% for allo-HSCT and 59%, 45%, 43%, and 12% for auto-HSCT. RIC was associated with superior RFS after allo-HSCT in multivariate analysis. In this study, again, the results for the auto-HSCT group appear better compared to the allo-HSCT group. Although autografted and allografted patients were comparable

with regards to sex, age, and time from RT diagnosis to transplantation, significantly more allografted patients had chemotherapy-resistant disease at transplantation, and had received more than two lines of chemotherapy since their diagnosis of CLL [32].

BTKi and BCL inhibitors

The limited efficacy obtained with conventional treatments for DLBCL-RT has prompted the investigation of novel therapies, including targeted inhibitors of Bruton's tyrosine kinase (BTKi) and BCL2. However, the outcomes of monotherapy treatment with novel agents have been reported in only small series and describe short PFS [31].

In a phase I study of venetoclax as monotherapy, a cohort of seven patients with RT was included. 3/7 (43%) achieved a response, suggesting some biological activity of the drug in this disease, although these responses were mostly relatively short-lived [33].

In a retrospective series of four RT patients treated with ibrutinib, three achieved a response, but median treatment duration was only 6.1 months [34]. Similar outcomes were observed with acalabrutinib. In a phase I/II study, a cohort of 25 patients was included. The overall response rate was 40% (8% CR), but the median PFS was short, reaching only 3.2 months [35]. More favorable results were reported with zanubrutinib in monotherapy. In a recently published study, 13 RT patients received zanubrutinib. The majority of them received CHOP/R-CHOP as their first-line treatment for RT. The ORR was 62%, and the median PFS and OS were favorable at 17.3 months and 29.3 months, respectively (Table I) [36].

Similar results may be observed in treatment with noncovalent BTK inhibitors such as pirtobrutinib and nemtabrutinib. In the phase I/II BRUIN study with pirtobrutinib in monotherapy, a cohort of 82 RT patients was included, with efficacy data available for 75 patients to date including 68 who had received prior RT treatment. The ORR was 52%, with a CR rate of 10%, an ORR of 47% in patients who received a prior covalent BTKi and an ORR of 50% in RT patients who had received prior RT-directed therapy. Median OS was 13.1 months, even though the patients were relatively heavily pretreated, with a median of four lines of previous CLL and two lines of RT therapy. Despite these encouraging response rates, the median PFS was short at 3.7 months (Table I) [11, 37]. The results for six RT patients treated with nemtabrutinib were reported in the BELLWAVE-001 study, with an encouraging ORR of 50% (three patients achieved a PR) [38].

Several studies have investigated the efficacy of novel agents in RT with a combination of standard immunochemotherapy, which is hypothesized to show more encouraging outcomes than single-agent efficacy. Promising results were achieved with venetoclax in combination with dose-adjusted R-EPOCH, albeit in a small, select cohort. In a group of 26 patients, 20 received venetoclax and immunochemotherapy. The ORR was 62% (50% CR), median PFS 10.1 months, and median OS 19.6 months (Table I). Eight patients successfully proceeded to allo-HSCT, while 11 remained on venetoclax monotherapy maintenance at the end of the study. It is noteworthy that although only two patients in this study received prior RT treatment, and the cohort comprised relatively young and fit patients (median age 63), 52% (14/26) had prior novel agent therapy for CLL [39]. These encouraging results have prompted an extension of the study with a total of 67 patients enrolled (NCT03054896) (Table II). Immunochemotherapy was de-intensified from dose-adjusted R-EPOCH to R-CHOP due to excess toxicity (cytopenias and infections). Forty patients received R-CHOP-venetoclax, and the initial results of the first 27 patients (presented at the ICML 2023) showed ORR of 68% and CR of 48% [40, 41].

A real-world analysis from the Mayo Clinic and MD Andreson has led to further validation that venetoclax has synergistic properties with R-CHOP. In 55 patients evaluated with RT, 10 received venetoclax in combination with R-CHOP (ORR of 60%, CR of 50%); 20 received venetoclax in combination with chemoimmunotherapy (ORR of 50%, CR of 40%); 20 received venetoclax in combination with a BTKi and anti-CD20 antibody (ORR of 40%, CR of 30%); three received venetoclax in combination with "varied-based regimens" (ORR/CR not reported); and two received venetoclax monotherapy (ORR/CR not reported) [40, 42, 43]. Venetoclax is now being investigated in a range of combination strategies in ongoing clinical trials (NCT05388006, NCT02846623, NCT04939363) (Table II).

Additionally, the ongoing first-line STELLAR trial is a randomized study exploring the combination of acalabrutinib and R-CHOP versus R-CHOP alone in RT. This is the first, and currently only, randomized clinical trial globally in RT [44, 40].

Phosphoinositide 3-kinase inhibition

The treatment of RT is currently being investigated with another class of targeted agents: phosphoinositide 3-kinase inhibitors (PI3Kis). Limited data is available for PI3Kis as monotherapy. Idelalisib was tested in four patients with ibrutinib-resistant RT and demonstrated a 75% ORR, but with a response duration of only 6.4 months [45]. The combination of duvelisib plus venetoclax is now being tested in an ongoing phase I/II trial for relapsed and refractory CLL (R/R CLL) and RT [46]. The rationale for this combination is based on preclinical data demonstrating that PI3K enhances the dependence of CLL cells on BCL-2 for their survival [47]. Eight RT patients have been evaluated with this combination, and four responded to the treatment, with two achieving CR. Two patients underwent cellular therapy (allo-HSCT and chimeric antigen receptor T-cell) [46].

PD-1 blockade

The evidence of programmed death-1 (PD-1) expression and its ligands in the tumor microenvironment are promising biomarkers to select RT patients for PD-1 blockade. In nine RT cases, pembrolizumab, a humanized PD–1––blocking antibody, exhibited selective efficacy. In heavily pretreated RT patients, most of whom had received prior anthracycline-containing chemotherapy and/or ibrutinib, pembrolizumab was associated with an ORR of 44% and an OS of 10.7 months (Table I). Clinically durable responses were observed in RT patients who experienced progression after prior ibrutinib. It is worth mentioning that pembrolizumab demonstrated clinical activity in patients with RT, while no clear activity was observed for patients with relapsed CLL. Subsequently, some patients who responded to the treatment developed thrombocytopenia as a result of progressive CLL. Thrombocytopenia improved with the addition of a PI3K inhibitor (idelalisib), suggesting combination therapy to treat the underlying CLL. Another important observation resulting from this investigation was that PD-1/PD-L1 expression was associated with earlier ibrutinib treatment [48]. However, in the KEYNOTE-170 study, in 23 patients treated with pembrolizumab, the ORR was 13% with a median OS of 3.8 months and a median PFS of 1.6 months. Moreover, two of the three patients who responded had classical Hodgkin lymphoma histology, rather than DLBCL. It is difficult to compare the differing results between these two studies since the latter did not report prognostic RT variables, nor did it report PD-1 expression [42, 49].

More favorable outcomes have been achieved when checkpoint inhibitors were combined with other targeted agents to enhance the antitumor effect and additionally control the underlying CLL clone. Jain et al. investigated a combination of ibrutinib and nivolumab in patients with RT and CLL. In a group of 24 RT patients, ORR was 42%, with 34% CR. The median OS was 13 months, with an even higher rate of 24.1 months in patients treatment-naïve for RT (Table I) [50]. In the CLL-RT1 trial, a combination of zanubrutinib and a PD-1 inhibitor (tislelizumab) is being investigated. In preliminary results of seven patients, three have achieved a response (one CR and two PR) with a median PFS and OS of 2.9 months and 15.4 months, respectively. The group consists of 52 patients and the final results are eagerly awaited [51]. Copanlisib plus nivolumab has been investigated in a phase I study, showing an acceptable toxicity profile with an ORR of 29% and a CR of 14% [52]. Another investigational strategy including the combination of pembrolizumab, umbralisib (a PI3Ki) and ublituximab (a type I CD20 antibody) has shown promising initial results, with an ORR of 50% in four relapsed/refractory RT patients with ongoing remissions of 7+ months [42, 53].

Impressive results were recently reported in the MOLTO trial evaluating the activity and safety of a combination of atezolizumab (humanized monoclonal antibody blocking PD-L1), venetoclax and obinutuzumab in untreated DLBCL--RT. Twenty-eight patients were enrolled and the observed ORR was 67.9%, with a 28.6% CR rate. After a median follow-up of 11.6 months, 57.9% of patients are in continuous remission (eight on active therapy, two received allo-HSCT, and one discontinued therapy due to secondary myelodysplastic syndrome), and in six cases remission has been for ≥24 months. Median PFS was 16.2 months, and median OS was 31.6 months (Table I) [54]. There is also an ongoing trial with durvalumab (humanized monoclonal antibody blocking PD-L1), acalabrutinib and venetoclax (NCT05388006) (Table II).

CAR-T therapy

The promising results of chimeric antigen receptor T-cell (CAR-T) therapy in *de novo* DLBCL have prompted studies in RT. However, there is a lack of prospective data on the utility of CAR-T in RT specifically. One of the first small studies suggested a lack of response to CAR T-cell therapy or a non-sustained response in the context of RT [55, 56].

However, in a single-center phase II trial in Israel, 4/6 patients with DLBCL-RT achieved CR. At a median follow-up of 5.5 months, all patients were alive, and two underwent allo-HSCT [57].

A recent study by Kittai et al. reviewed nine high-risk RT patients with a median of four previous lines of treatment. Eight patients received a bridging therapy before axicabtagene ciloleucel (axi-cel) infusion: seven were treated with BTKis and the eighth with rituximab, dexamethasone, cytarabine, and oxaliplatin (R-DHAX). One patient received no bridging therapy. 55.6% of patients achieved CR, and three had PR. At a median follow-up of 6 months, only one patient had progressed, while all the others showed durable responses [58]. Moreover, ibrutinib has been shown to potentially address the immune dysfunction observed in CLL patients. This suggests that BTKis could improve CAR-T cell expansion and enhance its effector function in CLL patients [28, 59, 60]. In comparison, one recent multicenter analysis identified 55 patients who received anti-CD19 CAR-T infusion, mostly axi-cel, of whom c.45% achieved CR, although the OS was only 8.5 months [61]. Some prospective trials are ongoing to evaluate CAR-T's efficacy in RT patients. The ongoing ZUMA-25 trial investigates the role of brexucabtagene-autoleucel (brexu-cel) in relapsed and refractory rare B-cell malignancies (NCT05537766). Lisocabtagene-maraleucel (liso-cel) is being studied in combination with either zanubrutinib (NCT05873712) or with nivolumab and ibrutinib (NCT05672173) (Table II) [28].

Interestingly, one trial featured a novel CAR T-cell construct, ARI-0001 (CART19 product), given to five patients with RT. Four patients responded to the treatment; however, minimal residual disease (MRD) negativity was achieved in

all patients, both in peripheral blood and bone marrow, even those with a PR or stable disease in the lymph nodes. So far in this study, neurotoxicity has not been observed [62].

Another potential alternative therapeutic strategy is the use of chimeric antigen receptor-NK cells (CAR-NK). Initial results for CAR-NK treatment indicate lower toxicity and fewer complications compared to CAR-T treatment. Liu et al. conducted a phase I/II trial using anti-CD19 CAR-NK derived from cord blood, which was administered to 11 heavily pretreated patients with NHL (n = 6) and CLL/RT (n = 5, one patient with RT) (median of four prior lines of therapy). There were no reported cases of cytokine release syndrome or neurotoxicity. Three patients with CLL achieved CR, and one had remission of the RT component (but persistent CLL). At a median follow-up of 13.8 months, two of the three responding CLL patients required additional CLL therapy, as did the RT patient [63].

Bispecific antibodies

Bispecific T-cell–engaging antibodies (BITes) simultaneously bind to antigens on tumor cells and CD3 subunits on T cells. This simultaneous binding brings tumor cells close to effector T cells, followed by T-cell activation, degranulation and tumor cell elimination [64]. To date, four BITes have been analyzed for clinical efficacy in RT: blinatumomab (CD19/CD3 BITes), glofitamab, epcoritamab and mosunetuzumab (CD20/CD3 BITes). Early data seems promising. In the BLINART trial, blinatumomab was proven to induce a significant CR rate in patients with RT. 39 patients initiated treatment with R-CHOP. After two initial cycles, those patients who did not achieve CR assessed in PET-CT (25/39 patients) went on a course of blinatumomab. ORR was achieved in 46% of patients, and CR in 36% (Table I) [65].

Glofitamab has exhibited favorable activity with frequent and durable CRs and a predictable and manageable safety profile in patients with refractory DLBCL. A phase I study included 10 patients with DLBCL-RT. Six were evaluated for efficacy assessment: 3/6 achieved CR, and 2/6 achieved PR [66].

Similarly, epcoritamab has demonstrated its efficacy in initial results. In the ongoing EPCORE CLL-1 study (NCT04623541), RT patients treated with a maximum one prior line of RT therapy were enrolled. 6/10 patients responded and 50% (5/10) achieved CR (Tables I, II) [67].

In very recently published results of a phase I/II study, mosunetuzumab in monotherapy demonstrated efficacy in 20 patients with relapsed and refractory RT. Patients were treated with at least one line of prior therapy; the median number of treatment lines was 2.5, and 45% had received prior treatment with a BTKi. ORR was 40%, with 20% CR. Two of the patients had CR ongoing for ≥20 months at the data cut-off, and the other two patients had received a subsequent stem-cell transplant [68].

ROR1-targeting antibody-drug conjugate

The receptor tyrosine kinase-like orphan receptor 1 (ROR1) is a transmembrane oncofetal protein present on the surface of CLL and RT cells, as well as other hematological malignancies, and has recently been investigated as a target of ROR1-antibodies [11, 69, 70]. One potential advantage of this target is that it is not expressed on other hematopoietic cells, including B cells, thus having the potential to be less immunosuppressive [11]. The WAVELINE-001 study investigated the role of zilovertamab vedotin (MK-2140), which is an antibody-drug conjugate comprising a humanized IgG1 monoclonal antibody and the antimicrotubule cytotoxic agent monomethyl auristatin E (MMAE), in patients with relapsed/refractory NHLs. Recently reported results included seven patients with RT, four of whom responded, with a median duration of response of 2.8 months [71].

Richter treatment algorithm

Recent advancements in the treatment of lymphoid malignancies can also be applied to RT. Upon diagnosis, evaluating patient fitness and comorbidities is crucial to determine whether a patient can tolerate R-CHOP or dose-adjusted EPOCH-R and be considered for allo-HSCT. Currently, based on clinical trials and retrospective analyses, such an approach holds the potential for a cure, or may enable longer OS as the sole immunochemotherapy administration. It should be noted that the role of auto-HSCT in RT treatment diminishes, as it does not allow control of the underlying CLL clone. Nevertheless, only c.10% of RT cases can be treated with such a curative approach. Both prospective and retrospective analyses have indicated that R-CHOP and dose-adjusted EPOCH-R regimens can be well-tolerated and combined with venetoclax to increase the likelihood of achieving deep remission. However, it must be emphasized that the addition of venetoclax is used in an off-label setting in this indication. Furthermore, clinical trials assessing such combinations have predominantly involved younger RT patients, and regimens incorporating venetoclax appear to have yielded the most favorable responses among reported treatment approaches. Treating older patients with RT remains a clinical challenge, as these regimens can be excessively toxic and poorly tolerated.

Clinical trials evaluating combinations of BTK inhibitors with immunochemotherapy or other targeted agents are currently underway, with results eagerly anticipated. However, it is important to underscore that the widespread use of BTK inhibitors in CLL treatment may potentially reduce the effectiveness of such combinations. The alternative use of covalent or non-covalent BTK inhibitors, depending on the patient's treatment history, is likely to carry significant clinical implications when selecting appropriate agents for combinations. Given these considerations, clinical trials investigating the tolerability and effectiveness of compounds

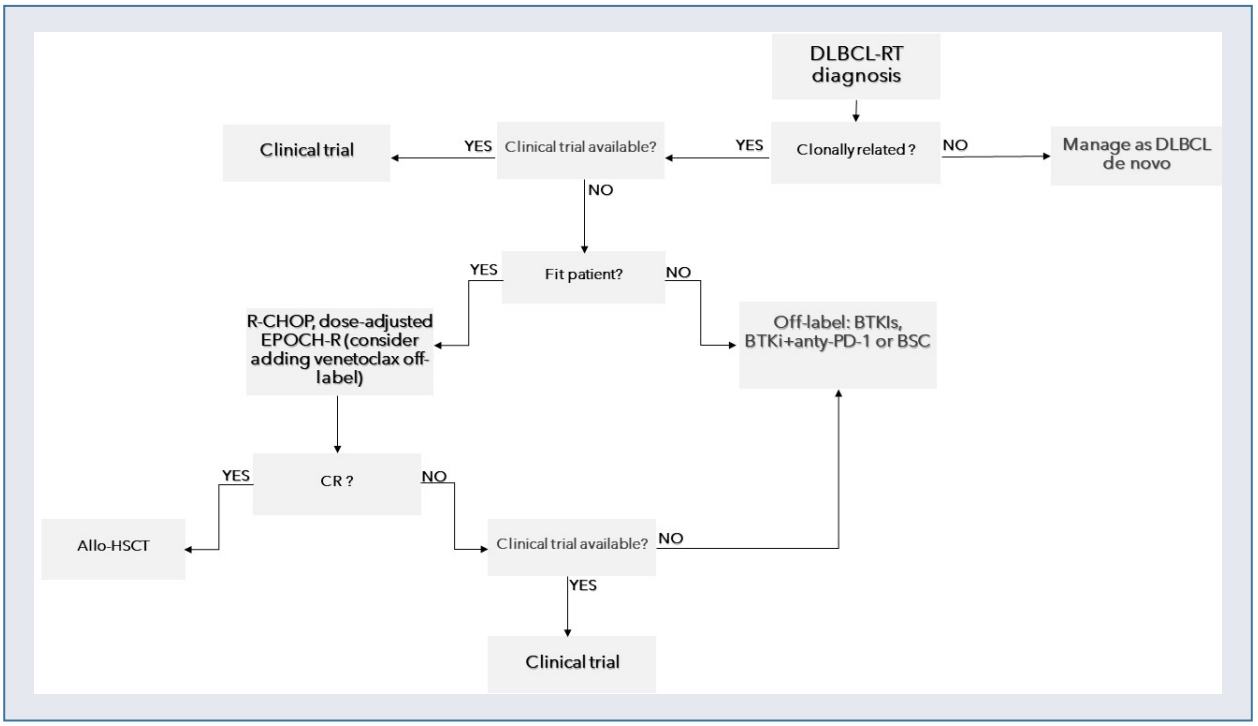

Figure 1. Richter treatment algorithm; allo-HSCT — allogeneic hematopoietic stem cell transplantation; anti-PD-1 — anti-programmed death-1; BSC — blood stem cell; BTKI — Bruton's tyrosine kinase inhibitors; CR — complete remission; DLBCL — diffuse large B-cell lymphoma; R-CHOP — rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-EPOCH — rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; RT — Richter's transformation

not extensively used for CLL treatment may identify novel and effective combinations. The blockade of the PD-1/PD-1L axis by atezolizumab, nivolumab, or pembrolizumab appears promising for specific patients. Inhibition of proliferation using cyclin-dependent kinase inhibitors (CDK) has demonstrated efficacy in experimental settings, and the first human trial combining a CDK4/6 inhibitor with R-CHOP is underway (Table II). As previously mentioned, ROR1 may also represent a novel target for RT, and a clinical trial with zilovertamab vedotin is currently underway.

For older patients, treatment with less toxic regimens in clinical trials, such as PD-1/PD-L1 axis inhibitors, bispecific antibodies, CAR-T, or non-chemotherapy-based combinations, appears to hold promise, as demonstrated by recently published clinical trials. Therefore, this specific patient group should be prioritized for clinical trial allocation whenever possible. The RT treatment algorithm is presented in Figure 1.

Conclusions

Despite significant advances in recent years, DLBCL-RT continues to pose challenges in terms of treatment. Current management strategies still utilize historical treatment approaches with immunochemotherapy, with the potential incorporation of novel agents through participation in clinical trials. However, tight eligibility criteria for clinical trials and a relative lack of available RT-specific trials are, for many patients, insurmountable obstacles.

For patients who are fit, allo-HSCT represents the only proven modality that can provide highly durable remission, with outcomes associated with the depth of response entering the transplant [11]. However, it should be emphasized that due to the clinical context, allo-HSCT can only be performed in 10–15% of patients diagnosed with RT [13, 72].

Many of the ongoing studies are single-arm, with some relying on retrospective data. Prospective studies often have limited sample sizes, and there have been no reported randomized controlled trials yet. Encouraging results observed in small patient cohorts may be influenced by factors such as the absence of clonal correlation evidence between CLL and DLBCL clones, leading to cases that may not truly represent Richter's transformation.

Despite all these challenges, broader advances in targeted therapeutics within the field of hematology are beginning to impact the management of RT. Promising targets include the inhibition of BTK, BCL2, and the PD1-PD-L1 axis, as well as T-cell–activating/engaging therapies. Many of these treatments, along with their combinations, demonstrate good tolerability and acceptable toxicity profiles. However, despite such promising developments, no

specific agents have yet been licensed or reimbursed for RT in the United States or Europe [40].

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ORIGINAL RESEARCH ARTICLE

VIA MEDICA

Eltrombopag and high-dose dexamethasone as first-line treatment in children with newly diagnosed primary immune thrombocytopenia

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Abstract

Introduction: Novel treatment strategies for newly diagnosed immune thrombocytopenia (ndITP) pediatric patients are required.

Material and methods: The aim of this study was to analyze the safety and efficacy of eltrombopag and dexamethasone when used as the first-line treatment in children with ndITP. Inclusion criteria: age 5–18 years, and ndITP with bleeding manifestation. Treatment course: 28 days of eltrombopag with oral dexamethasone in three repeated courses.

Results: A complete response was achieved in 90% of patients after the first week of treatment, and in all patients after the end of the treatment course. Durable and sustained platelet response was observed in 90% of patients after 12 months of follow-up.

Conclusions: Our finding support safety and efficacy of eltrombopag and dexamethasone as combined first-line therapy of ndITP in children.

Keywords: eltrombopag, dexamethasone, children, immune thrombocytopenia

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Introduction

Primary immune thrombocytopenia (ITP) is one of the most common hematological disorders in childhood. Due to the duration of the disease, ITP can be qualified as newly diagnosed (ndITP), which defines all cases at diagnosis, or persistent ITP (pITP) — lasting 3–12 months from diagnosis, or chronic ITP (cITP) lasting for more than 12 months. ITP is usually a self-limiting and mild disease, without life-threatening bleeding episodes or the need for hospitalization or treatment intervention [1, 2]. Although most children with ndITP achieve remission spontaneously, others require therapy for minor or moderate bleedings and improvements in their health related quality of life [3, 4]. The first-line treatment for ndITP includes corticosteroids, intravenous immunoglobulin, and anti-D globulin [1, 3, 5].

However, 10–20% of children with ITP do not respond to the recommended first-line therapies, going on to develop pITP or cITP. In addition, some patients become steroid-dependent or refractory, and this leads to adverse events and challenges in logistical and economic terms [4].

In recent years, several treatment modalities such as mycophenolate mofetil, rituximab and thrombopoietin

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receptor agonists have been explored for cITP pediatric patients, with the aim of establishing a durable platelet response and minimizing the bleeding risk or splenectomy qualification [6–17]. Even so, there remains a gap in the availability of novel treatment strategies for ndITP patients which may result in durable platelet response.

PINES is an ongoing phase III prospective randomized trial of eltrombopag's use in the management of ndITP in children [4]. Moreover, there has been convincing data from adult cohort studies suggesting that early aggressive and combined treatment protocols may be a good first-line therapeutic strategy for ndITP, resulting in sustained response rates [18, 19].

The aim of our study was to analyze the safety and efficacy of the use of eltrombopag and high-dose dexamethasone as the first-line treatment in children with ndITP.

Material and methods

Study design

Based on prior results from an adult study [18], we designed and performed an open-label, single-arm, observational, single-center study in pediatric patients with newly diagnosed ITP. Eligible patients were aged 5–18 years, with bleeding manifestation of ndITP scored according to the Buchanan bleeding scale [20, 21].

The study was conducted in accordance with the Declaration of Helsinki. The local Bioethical Committee approved the study, and all patients' legal caregivers gave written consent before enrollment (KB 695/2019).

The treatment course consisted of 50 mg of eltrombopag given orally from the day of ITP diagnosis for 28 days, and oral dexamethasone 28 mg/m^2/day, divided into three doses (maximum 40 mg/day), given as four-day courses, repeated three times alongside the eltrombopag ongoing therapy on days 1–4, 15–18, and 29–32. If the platelet count exceeded ≥400 × 10^9/L, eltrombopag was stopped.

Response assessment

Complete blood count assessment was performed at baseline, on days 7, 14, 32 and 46, and every three months until the end of the 12-month observation period.

Quality of response to the applied treatment was defined according to the International Consensus Guidelines: complete response (CR) was defined as platelet count ≥100 × 10^9/L and absence of bleeding; response (R) was defined as platelet count ≥30 × 10^9/L and at least a 2-fold increase in the baseline count and absence of bleeding; and no response (NR) was defined as platelet count ≤30 × 10^9/L or less than a 2-fold increase of baseline platelet count or bleeding. The duration of response was measured from the achievement of CR or R to the loss of CR or R [2].

Statistical analysis

Descriptive analysis was performed, with median and range values. Response and complete response rates at each timepoint were provided with 95% confidence intervals (95% CI). Duration of the response included the entire period of the follow up with any responses achieved (CR or R).

Results

A total of 10 children were enrolled in the study between February 2020 and January 2022. All patients met the criterion of newly diagnosed primary immune thrombocytopenia. Of the 10 patients, six were boys, and four were girls (Table I). Median age at the start of the combined eltrombopag/dexamethasone treatment protocol was 9.5 years (range 6–16). At the beginning of treatment, median platelet count was 7 × 10^9/L (range 1–30 × 10^9/L). The median follow-up was 23 months (range 14–37).

After the first week of eltrombopag/dexamethasone therapy, median platelet count was 315 × 10^9/L. Response was observed in 90% of patients, and 80% of patients achieved CR. In two patients, eltrombopag was stopped due to the platelet count being ≥400 × 10^9/L, and no relapse was noted. At the end of the therapy protocol (day 32), CR was observed in all patients. A long-term duration of response was obtained in all patients after six months, and in 90% of patients after 12 months, of follow-up (Figure 1). One patient relapsed 12 months after the initial eltrombopag/dexamethasone treatment, and received intravenous immunoglobulin rescue.

No serious adverse effects were observed during the study.

Discussion

It has been proven that thrombopoietin receptor agonists (TPO-RAs) are one of the most effective alternative treatment options for patients with cITP [22–24]. Several studies have so far confirmed the safety and efficacy of TPO-RAs in pediatric patients, with special regard to orally administered eltrombopag in cITP [7, 13, 14]. Although there has been no data regarding eltrombopag use in newly diagnosed ITP patients, we can expect that with its mechanism of action i.e. stimulating the proliferation and maturation of megakaryocytes due to interactions with thrombopoietin receptor, eltrombopag use may result in significant platelet count increase [25]. Eltrombopag, indirectly increasing T-regulator cell activity, may play a significant role in modulating the natural history of ITP.

It is known from other studies that both newly diagnosed and chronic patients can achieve remission with high-dose dexamethasone courses (HDD). HDD can be effective in about 45% of pediatric severe cITP patients [8].

Table I. Patient characteristics and treatment results

Patient	Age/sex	Bleeding score	Baseline PLT	D7/PLT	D14	D32	3 months	6 months	12 months	Follow-up/ months
1	9/M	2	7	325	CR	CR	CR	CR	CR	37
2	14/M	3	30	261	NR	CR	R	R	R	36
3	15/F	2	12	191	R	CR	R	R	R	26
4	6/M	2	8	323	NR	CR	CR	CR	CR	26
5	16/M	2	2	372	CR	CR	CR	CR	CR	23
6	11/M	1	12	308	R	CR	CR	CR	NR	26
7	8/M	2	3	10	R	CR	CR	CR	CR	21
8	6/F	2	7	661	CR	CR	CR	CR	CR	20
9	14/F	2	2	86	NR	CR	NR	CR	CR	19
10	10/F	1	1	859	CR	CR	CR	CR	CR	14

M – male; F – female; PLT – number of platelets; CR – complete response; R – response; NR – no response; D7 – day 7; D14 – day 14; D32 – day 32

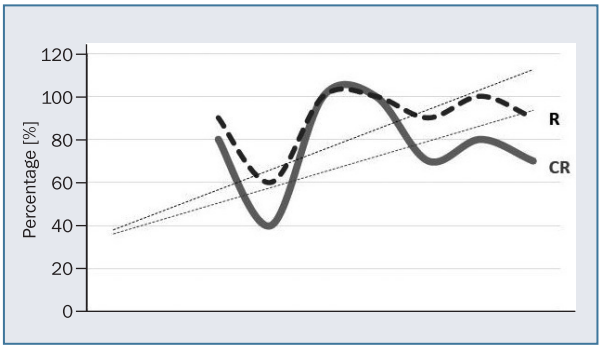

Figure 1. Time-dependent response (R) to eltrombopag/dexamethasone combined therapy; CR – complete response

Other authors have concluded that HDD courses may be preferable in terms of bringing about rapid platelet count increases, but not in terms of improved durable platelet count responses, compared to standard-dose prednisone [26].

Conclusions

Our study confirms that combined eltrombopag/HDD therapy may lead to a quick initial response in newly diagnosed ITP pediatric patients. We found that early escalated therapy determined high CR rates as well as sustained and long-lasting remissions. In all patients, an early escalated and short course of eltrombopag/HDD therapy was well tolerated and safe during the observation period. Response duration and response quality were satisfactory, and, moreover, constantly rising. Almost all of the evaluated patients presented durable response with sustained platelet response after a single course of combined treatment within their first episode of ITP.

Our data supports the safety and efficacy of eltrombopag and high-dose dexamethasone as first-line therapy for newly diagnosed ITP in children.

Article information and declarations

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Authors contributions

MRP, MW – design of study; MRP, DK – provision of clinical data; MRP – writing manuscript, editing manuscript; all authors – analysis of clinical data, critical revision and final approval.

Conflict of interests

MRP and MW received lecture fees from, and participated in meetings organized by, Novartis.

Data availability statement

All data underlying the results is available as part of the article, and no additional source data is required.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki. The local Bioethical Committee approved the study and all patients' legal caregivers gave written consent before enrollment (KB 695/2019).

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Supplementary material

None.

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ORIGINAL RESEARCH ARTICLE

VIA MEDICA

Evaluation of colonization and infection profile in allogeneic hematopoietic stem cell transplantation recipients

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Abstract

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

Material and methods: We conducted a single-center retrospective analysis of colonization and infection epidemiology in 44 patients who underwent matched related donor (MRD) allo-HSCT between 2012 and 2022.

Results: Colonization was observed in 84.1% of patients before allo-HSCT. The most common location was the anus, colonized in 55.4% of patients, mostly by *Klebsiella pneumoniae* ESBL(+) — 28.6%. Multi-drug resistant bacteria (MDR) accounted for 50.7% of positive colonization cultures before allo-HSCT.

In the post-transplantation period (i.e. up to 100 days after allo-HSCT), infections occurred in 86.4% of patients. Bacteremia was observed in 47.7% of patients, mostly caused by methicillin-resistant coagulase-negative *Staphylococcus epidermidis* — 39.4%. Infection of the skin and soft tissue near the central line was found in 27.3% of patients, urinary tract infections in 56.8%, and gastrointestinal infections in 38.6%. Fungal infections were reported in 31.8%. MDR pathogens accounted for 58.1% of all infecting pathogens. The most common resistance was extended-spectrum beta-lactamase (ESBL), accounting for 50.8% of all MDR strains. Viral reactivations were detected in 29.5% of patients.

59.5% of colonized patients developed an infection with the pathogen responsible for their previous colonization. Infections with such pathogens were significantly more frequent in colonized patients than with *de novo* pathogens ($p = 0.04$).

Conclusions: The results of the presented study highlight the role of colonization assessment as a tool to identify patients at high risk of developing post-transplant infections, guiding the possibility of efficient targeted antibiotic therapy.

Keywords: hematopoietic stem cell transplantation, infections, bacteremia

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Introduction

A key action of allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the ability to replace the recipient's abnormal immune and hematopoietic cells with long-term repopulation of cells from a healthy donor. In 2021, the European Society for Blood and Marrow Transplantation (EBMT) reported c.47, 400 HSCTs [1].

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Allo-HSCT was performed in 19,806 of these patients (42%) and its main indications were myeloid malignancies (58%), lymphoid malignancies (28%), and non-malignant disorders (13%) [1].

Allo-HSCT is still associated with a high risk of treatment-related mortality (TRM), which is mainly caused by infection, toxicity, and graft-versus-host disease (GvHD) [2]. However, according to the Center for International Blood and Marrow Transplant Research (CIBMTR), the 100-day TRM in acute myeloid leukemia (AML) patients transplanted using myeloablative conditioning (MAC) regimens decreased from 15% to 6% in matched related donors (MRD), and from 37% to 14% in matched unrelated donors (MUD) [3]. Furthermore, several studies have reported a significant decrease in TRM over time, which is explained as being the result of less toxic conditioning, more accurate HLA matching, advances in the prevention and treatment of GvHD, and more effective infection prophylaxis and treatment [4].

Nevertheless, infection-related mortality (IRM) remains a major challenge associated with the HSCT procedure, particularly when using alternative donors. The emergence of multidrug-resistant pathogens has become a global threat connected with life-threatening opportunistic infections causing an increased risk of both early and late IRM [5]. The CIBMTR estimates that in MRD, HSCTs infections are responsible for 19% and 17% of deaths in the early and late post-transplantation periods, respectively, whereas in haploidentical HSCTs, IRM is 28% and 17%, respectively. In MUD, HSCT infections account for 22% of early deaths, and 16% of late ones [6].

More than half of IRM is associated with an unspecified etiology. Of the known factors, IRM of bacterial origin accounts for c.35%, fungal — 25–30%, viral — 20–30%, parasitic — 3–5%, and infections of mixed origin — 12% [5].

The most important predictors determining the occurrence of infections after allo-HSCT are the patient's pre-transplant colonization, and the microbial epidemiology of the transplant center. In addition, other factors are also crucial for infection development such as the severity of treatment-induced neutropenia (<7 vs. >7 days, absolute neutrophil count (ANC) <0.5 G/L duration), older age, mucositis associated with chemotherapy toxicity, donor-recipient virological status (CMV, EBV), the type of cancer, the type of conditioning (myeloablative vs. non-myeloablative), the type of donor (i.e. related, unrelated, alternative) as well as the occurrence of GvHD [2, 7–9].

Material and methods

We performed a retrospective, single-center analysis to assess the colonization with pathogenic microorganisms and the profile of its changes after MRD HSCT. In addition, we analyzed the incidence of infections up to 100 days after MRD allo-HSCT, and the effectiveness of the prophylaxis used.

Table I. Allogeneic hematopoietic stem cell transplantation indications

Diagnosis	N [%]	Conditioning regimen in a particular diagnosis	N [%]
AML	23 (52.3)	Flu/Bu 4	8 (34.8)
		BuCy 2	7 (30.4)
		TBI/Cy	3 (13.1)
		Flu/Bu 2	2 (8.8)
		Flu/Bu 4 + ATG	1 (4.3)
		Flu/Bu 2 + ATG	1 (4.3)
		Cy/ATG	1 (4.3)
ALL	8 (18.1)	TBI/Cy + ATG	5 (62.5)
		BuCy 2	2 (25)
		Cy/ATG	1 (12.5)
AA	4 (9.1)	Cy/ATG	4 (100)
MDS	2 (4.5)	Treo/Flu/ATG	1 (50)
		Treo/Cy	1 (50)
T-PLL	2 (4.5)	Flu/Bu 4	2 (100)
CML	1 (2.3)	Flu/Bu 4	1 (100)
aCML	1 (2.3)	Flu/Bu 4	1 (100)
HL	1 (2.3)	Flu/Bu 2	1 (100)
MPAL	1 (2.3)	BuCy 2	1 (100)
T-LBL	1 (2.3)	TBI/Cy	1 (100)

AML — acute myeloid leukemia; ALL — acute lymphoblastic leukemia; AA — aplastic anemia; MDS — myelodysplastic syndrome; T-PLL — T-cell prolymphocytic leukemia; CML — chronic myeloid leukemia; aCML — atypical chronic myeloid leukemia; HL — Hodgkin lymphoma; MPAL — mixed phenotype acute leukemia; T-LBL — T-cell lymphoblastic lymphoma; Bu — busulfan; Cy — cyclophosphamide; Flu — fludarabine; TBI — total body irradiation; ATG — anti-thymocyte globulin

All 44 patients, 17 of whom were men (39%), and 27 women (61%), with a median age of 45 years (range: 18–68) underwent allo-HSCT transplantation between January 2012 and December 2022 in the Department of Hematology of the Medical University of Lodz, Poland. Indications for allo-HSCT procedure are set out in Table I. Allo-HSCT was performed in accordance with current EBMT recommendations [10].

A central vascular catheter was implanted in all patients before the chemotherapy prior to the transplantation procedure. Microbiological cultures of urine and material collected in the form of swabs from the throat, nasal cavity, and anal area were performed on each patient in the pre-transplant period, and additionally at weekly intervals after the allo-HSCT procedure. The results of these tests were used to determine the colonization. Each patient gave informed consent for access to his or her clinical data. This study has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

According to the guidelines of the European Conference on Infections in Leukemia (ECIL) and the EBMT, prophylactic antibacterial treatment (ciprofloxacin) was administered to all patients from the start of chemotherapy until ANC >0.5 G/L was reached. Antiviral (acyclovir), antifungal (fluconazole), and pneumocystosis (cotrimoxazole) prophylaxis was administered until six months after allo-HSCT, or until the end of immunosuppression if this was a longer period.

Moreover, environmental prophylaxis was administered to all patients, which was associated with increased restriction of aseptic and antiseptic regimens in the Marrow Transplant Unit. This prophylaxis included the use of air-conditioned isolation rooms with high-efficiency particulate arresting (HEPA) air, no contact with visitors, an appropriate diet with thermal treatment and strict personal hygiene, and sterilization of clothes and bedsheets. The median duration of hospitalization for patients undergoing allo-HSCT at our center was 47 days (range 31–74).

Bacteremia was defined as a positive microbiological culture from a single or, in the case of gram-positive infections, two consecutive, blood cultures taken from a febrile patient.

In a case of fever in patients with no clinically overt sign of infection, nopathogen colonization nor any prior infection with a resistant pathogen, one of two empiric treatment options was used: a cephalosporin with activity against *Pseudomonas* (cefepime or ceftazidime) or piperacillin with tazobactam. For patients with a complicated clinical course of infection, carbapenem was administered in combination with a glycopeptide/oxazolidine or a beta-lactam antibiotic with activity against *Pseudomonas* along with an aminoglycoside in combination with a glycopeptide/oxazolidine. If the patient was not colonized, carbapenem was administered along with an aminoglycoside and glycopeptide/oxazolidine [11].

The presence of colonization with a resistant pathogen was the reason for implementing targeted antibiotic therapy. Recommendations were modified according to the results of microbiological cultures and imaging studies, and treatment was continued for at least 72 hours after the fever and other signs of infection had resolved, and until the presence of ANC >0.5 G/L for two consecutive days. However, in patients with fever >72–96 hours despite the introduction of broad-spectrum antibiotic therapy, empirical antifungal therapy with an amphotericin B lipid complex or caspofungin was used [11].

Statistical analysis was performed using multivariate tables and the Chi^2 test with Yates's correction to compare qualitative parameters. For quantitative variables, such as the number of days of hospitalization, fever, and antibiotic therapy, we performed a normality check of the distribution using the Shapiro–Wilk test. For comparisons of variables without a normal distribution, we used the Mann–Whitney U test with correction for continuity and the Kruskal–Wallis test for comparisons of more than two groups. We looked for differences between groups using post-hoc tests. We assessed patient survival through the Kaplan–Meier method and compared using the log-rank test. We created univariate and multivariate survival analysis models using the Cox proportional hazards method. In all analyses, we used P-values with a significance level of 0.05. In the survival analysis, the confidence interval was 95%.

Results

Analysis of patients who underwent MRD allo-HSCT

Evaluation of colonization in pre-transplant period

Colonization with any pathogen before allo-HSCT was found in 84.1% (37/44) of patients, and in 54.5% (24/44) of them the place undergoing colonization analysis was colonized by more than one pathogen. The total number of sites colonized by at least one pathogen was 56. The anal region was most frequently colonized by at least one pathogen [55.4% (31/56) of all colonized sites], followed by the urinary tract 30.3% (17/56), nasal cavity 8.9% (5/56), and then the throat 5.4% (3/56).

The analyzed group demonstrated 49 positive cultures in the anal region and the most common strain was *Klebsiella pneumoniae* ESBL (+) 28.6% (14/49). Of the 20 positive urinary tract cultures, *Enterococcus spp.* was detected most often — in 35% (7/20). Five positive nasal cultures were confirmed — three with methicillin-sensitive *Staphylococcus aureus* (MSSA), and one each with *Klebsiella pneumoniae* ESBL (+) and *Streptococcus pneumoniae*. Three positive tests from the throat were obtained — *Escherichia coli* ESBL (+), *Klebsiella pneumoniae* ESBL (+), and *Enterococcus faecium*.

The total number of pathogens responsible for colonization was 77 (73 positive bacterial cultures and four positive fungal cultures). Among bacterial cultures, 50.7% (37/73) were caused by MDR strains. The most common type of resistance was ESBL, accounting for 81.1% (30/37) of all resistance types (Table II).

Evaluation of colonization in post-transplant period

In 27% (10/37) of patients colonized before allo-HSCT, there was a change in the result of the weekly post-transplant colonization assessment. In 16.2% (6/37) of patients, there was an eradication of the originally colonizing pathogen. In 10.8% (4/37) of patients, colonization from the urinary tract was eradicated, and the following pathogens were erased: *Escherichia coli* ESBL (+), *Klebsiella pneumoniae*, and *Enterococcus spp*. In 5.4% (2/37) of patients, disappearance of colonization from the nasal cavity with *Streptococcus pneumoniae* and *Staphylococcus*

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

Location of colonization	Etiology of colonization	Positive colonization culture, n [%]
Anal area		49 (100)
	Klebsiella pneumoniae ESBL (+)	14 (28.6)
	Escherichia coli ESBL (+)	8 (16.3)
	Enterococcus faecium	7 (14.3)
	Enterococcus faecalis	7 (14.3)
	Enterococcus faecium GRE	3 (6.1)
	Escherichia coli ESBL (–)	3 (6.1)
	Enterobacter cloacae ESBL (+)	2 (4)
	Candida albicans	2 (4)
	Candida krusei	1 (2.1)
	Candida glabrata	1 (2.1)
	Staphylococcus haemolitycus	1 (2.1)
Urinary tract		20 (100)
	Enterococcus spp.	7 (35)
	Coagulase-negative staphylococci	5 (25)
	Escherichia coli ESBL (+)	3 (15)
	Enterobacteriaceae	1 (5)
	Escherichia coli ESBL (–)	1 (5)
	Klebsiella pneumoniae ESBL (+)	1 (5)
	Streptococcus agalactiae	1 (5)
	Serratia marcescens	1 (5)
Nasal cavity		5 (100)
	Staphylococcus aureus MSSA	3 (60)
	Klebsiella pneumoniae ESBL (+)	1 (20)
	Streptococus pneumoniae	1 (20)
Pharynx		3 (100)
	Klebsiella penumoniae ESBL (+)	1 (33.3)
	Enterococcus faecium	1 (33.3)
	Escherichia coli ESBL (+)	1 (33.3)

*In 15 (34.1%) patients before allogeneic HSCT, the location was colonized by > 1 pathogen; ESBL — extended-spectrum beta-lactamases; GRE — glycopeptide-resistant enterococci; MSSA — methicillin-sensitive *Staphylococcus aureus*

aureus MSSA was observed. On the other hand, three patients had a change in Gram-negative bacteria in the evaluation of colonization from the anus. The first of these patients had a change from *Escherichia coli* to *Klebsiella pneumoniae*, the second from *Klebsiella pneumoniae* to *Escherichia coli* ESBL (+), and the third from *Enterobacter cloacae* to *Escherichia coli*. In one case, a new pharyngeal colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) was detected. Among patients who were not colonized before allo-HSCT, we did not observe the appearance of bacterial colonies during the routine evaluation of colonization after allo-HSCT.

Infection evaluation

Post-transplantation infections occurred up to 100 days after allo-HSCT in 86.4% (38/44) of patients. Among patients with fever, of which the median duration was four days, microbiologically documented infections were found in 71.1% (27/38) of patients, fever of unknown origin (FUO) in 26.3% (10/38), and only clinically documented infection

Table III. Location and etiology of infections caused by colonizing pathogen

Number of patients colonized before allo-HSCT				N = 37
Number of patients with at least one infection with colonizing pathogen [%]				22/37 (59.5%)
Etiology	Location of colonization		Location of infection	Number of infections with a pathogen detected in colonization
Escherichia coli ESBL (+)	Anus	→	Urinary tract	8
	Anus	→	Vascular bed	2
	Anus	→	Gastrointestinal tract	1
Enterococcus faecium	Anus	→	Urinary tract	7
	Anus	→	Vascular bed	1
Klebsiella pneumoniae ESBL (+)	Anus	→	Urinary tract	2
	Anus	→	Vascular bed	1
	Anus	→	Gastrointestinal tract	1
	Urinary tract	→	Urinary tract	1
	Urinary tract	→	Vascular bed	1
Staphylococcus epidermidis MRCSNE	Urinary tract	→	Vascular bed	2
	Anus	→	Urinary tract	1
Enterococcus faecalis	Anus	→	Vascular bed	1
	Anus	→	Urinary tract	1
Candida krusei	Anus	→	Urinary tract	1

allo-HSCT — allogeneic hematopoietic stem cell transplantation; ESBL — extended-spectrum beta-lactamases; MRCNSE — methicillin-resistant coagulase-negative *Staphylococcus epidermidis*

in 2.6% (1/38). Mucositis occurred in 93.2% (41/44) of patients, whereas pneumonia occurred in 9.1% (4/44) of patients.

The total number of pathogens responsible for infections was 138 (105 positive bacterial cultures, 16 positive fungal cultures, and 17 viral infections). On average, there were 3.1 infection factors per patient (138 infections in 44 patients).

Bacterial infections

There were 105 microbiologically confirmed positive bacterial cultures detected up to 100 days after allo-HSCT. Gram-positive infections predominated, accounting for 76.2% (80/105) of all bacterial infections in this group. MDR pathogens were observed in 58.1% (61/105). ESBL was the most common type of resistance, making up 50.8% (31/61).

59.5% (22/37) of colonized patients developed a total of 31 infections with the pathogen responsible for their previous colonization. Infections with such pathogens were significantly more frequent in colonized patients than with *de novo* pathogens ($p = 0.04$). It is worth underscoring the frequent occurrence of bacteremia caused by pathogens that were detected in the colonization of the anal area before allo-HSCT. More detailed information on infections with the pathogen that was previously found in colonization is set out in Table III.

Bacteremia occurred in 47.7% (21/44) of allo-HSCT patients, of which central line-associated bloodstream infections (CLABSI) were noted in 27.3% (12/44) of patients. Bacteremia accounted for 25.8% (8/31) of all infections identified with a pathogen that had been detected previously in colonization. In 20.5% (9/44) of patients, cultures showed more than one pathogen responsible for the blood infection. In total, 33 positive blood cultures were noted. MRCNSE, which accounted for 39.4% (13/33) of etiological factors, was most frequently isolated.

The skin and soft tissue in the region of the central vascular catheter were infected in 27.3% (12/44) of patients. There were 13 positive cultures, and the main etiological agent was MRCNSE, accounting for 38.5% (5/13) of pathogens infecting this area.

Urinary tract infections occurred in 56.8% (25/44) of patients, and the most common etiological factor was *Escherichia coli* ESBL (+), responsible for 25.9% (7/27) of positive cultures in this area.

Positive stool cultures were observed in 38.6% (17/44) of patients. Infection with *Clostridioides difficile* occurred in 15.9% (7/44) of patients (Table IV).

Fungal infections

Fungal infections occurred in 31.8% (14/44) of patients up to 100 days after allo-HSCT. Sixteen positive cultures

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

Location of infection	Type of infection	Etiology of infection	Positive cultures [%]
Gastrointestinal tract			48 (100)
	Gram-positive bacteria	*Enterococcus faecium*	8 (16.7)
		Clostridioides difficile	7 (14.5)
	Gram-negative bacteria	*Klebsiella pneumoniae* ESBL (+)	9 (18.8)
		Escherichia coli ESBL (+)	7 (14.5)
		Escherichia coli ESBL (–)	3 (6.3)
	Fungi	*Candida albicans*	6 (12.5)
		Candida glabrata	5 (10.4)
		Candida krusei	3 (6.3)
Bacteremia			33 (100)
	Gram-positive bacteria	*Staphylococcus epidermidis* MRCNSE	13 (39.4)
		Enterococcus faecium	3 (9.1)
		Staphylococcus hominis MRCNS	2 (6.2)
		Staphylococcus haemolyticus	2 (6.2)
		Staphylococcus spp. MLS_B (+)	1 (3)
		Staphylococcus epidermidis MSCNS	1 (3)
		Streptococcus miti	1 (3)
		Enterococcus faecalis	1 (3)
		Actinomyces naeslundii	1 (3)
		Corynebacterium jeikeium	1 (3)
		Granulicatella adiacens	1 (3)
	Gram-negative bacteria	*Escherichia coli* ESBL (+)	3 (9.1)
		Escherichia coli ESBL (–)	1 (3)
		Klebsiella pneumoniae ESBL (+)	1 (3)
		Pseudomonas aeruginosa	1 (3)
Urinary tract			27 (100)
	Gram-positive bacteria	*Enterococcus faecium*	3 (11.1)
		Enterococcus spp.	2 (7.4)
		Enterococcus faecalis	1 (3.7)
		Enterococcus faecalis HLGR	1 (3.7)
		Enterococcus raffinosus	1 (3.7)
	Gram-negative bacteria	*Escherichia coli* ESBL (+)	7 (26)
		Escherichia coli ESBL (–)	5 (18.5)
		Klebsiella pneumoniae ESBL (+)	5 (18.5)
	Fungi	*Candida krusei*	2 (7.4)
Skin and soft-tissue of the central line area			13 (100)
	Gram-positive bacteria	*Staphylococcus epidermidis* MRCNSE	5 (38.4)
		Staphylococcus epidermidis MSCNS	2 (15.4)
		Staphylococcus hominis MRCNS	2 (15.4)
		Enterococcus spp.	2 (15.4)
		Staphylococcus aureus MSSA	2 (15.4)

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

were observed. Of these 16, 87.5% (14/16) affected the gastrointestinal tract and 12.5% (2/16) were observed in the urinary tract. The most common etiology of fungal infections was *Candida albicans* 37.5% (6/16), whereas 62.5% (10/16) of fungal infections were associated with resistant strains [*C. krusei* 31.3% (5/16); *C. glabrata* 31.3% (5/16)] (Table IV).

Microbiologically confirmed viral reactivation

Viral reactivation was reported in 29.5% (13/44) of initially seropositive patients during the first 100 days after allo-HSCT. In 6.8% (3/44) of patients, more than one virus was reactivated. CMV reactivation was observed in 22.7% (10/44), EBV in 13.6% (6/44), and HSV in 2.3% (1/44) of patients.

Treatment outcome

The median duration of empirical and targeted antibiotic therapy in patients after allo-HSCT was 24 (range 22–28) and 26 (range 20–34) days, respectively. We showed that patients colonized initially with at least one pathogen had significantly longer fever durations (mean: 4.18 days, SD: 2.96) compared to non-colonized patients (mean: 1.71 days, SD: 2.14) (p = 0.01). Colonization at three or more sites was associated with a longer duration of fever (p = 0.04).

The median overall survival (mOS) for all patients after allo-HSCT included in our study (n = 44) was 52.8 months (95% CI: range 19–56 months), and the median follow-up was 74 months. We found no differences in mOS between colonized patients and non-colonized patients (p = 0.33). For patients with MDR pathogen infection, mOS was 32 months (95% CI: 15–56 months), while mOS for patients without MDR infection was not reached (p = 0.352). The presence of CMV reactivation did not affect OS (p = 0.89), whereas patients with EBV reactivation showed almost halved 2-year survival compared to patients without EBV reactivation (33% vs. 61%), as well as worse mOS (15 months, 95% CI: 5–44 months vs 56 months, 95% CI: 21–56 months) (p = 0.03). Moreover, shorter mOS was observed in patients with candidiasis (30 months, 95% CI: 9–53) vs those without (56 months, 95% CI: 19–56), but the differential trend was marked after a longer follow-up and showed no statistical significance (p = 0.213).

In univariate survival analysis, the variables significantly affecting OS were the age of the patient at the time of allo-HSCT (older patients survived for a shorter time, HR: 1.04, 95% CI: 1.01–1.08, p = 0.01), EBV reactivation (HR: 2.70, 95% CI: 1.05–6.94, p = 0.03), and pneumonia (HR: 3.87, 95% CI: 1.41–10.64, p = 0.01). Hospitalization days demonstrated a tendency towards OS but did not show a statistical significance (HR: 1.06, 95% CI: 0.99–1.13, p = 0.08). In the multivariate regression model, the age of the patient at the time of allo-HSCT (HR: 1.06, 95% CI: 1.02–1.11, p = 0.01), as well as EBV reactivation (HR: 6.03, 95% CI: 1.96–18.54, p = 0.002) and the occurrence of pneumonia (HR: 4.01, 95% CI: 1.28–12.56, p = 0.02) proved to be independent factors significantly worsening OS.

Death occurred in 13.6% (6/44) of patients within 100 days after allo-HSCT. Four of these six patients died in the course of bacteremia and two of acute GvHD.

Discussion

We present a comprehensive analysis of the colonization of patients undergoing allo-HSCT and its impact on post-transplantation infectious complications. To the best of our knowledge, there has been no previous study in the literature analyzing the etiology and frequency of colonization of all sites, such as urine, throat, nasal cavity, and anal area, which were subject to standardized microbiological evaluation before allo-HSCT, and its influence on patient outcomes.

In our study, colonization before allo-HSCT with at least one pathogen was found in 84.1% of patients, while MDR bacteria accounted for half (50.7%) of all positive colonization cultures. The analysis conducted by Scheich et al. [12] in 264 patients who underwent allo-HSCT between 2006 and 2016 demonstrated that colonization of the anus, nasal cavity, and throat with multi-drug resistant flora occurred in 53.8% of patients, which is consistent with our observations. However, preliminary data from our team's prospective analysis from 2022 in 239 allo-HSCT recipients shows a decrease in the amount of MDR pathogens, which accounted for 29% of colonization cultures [13]. Another European study by Bilinski et al. [14] revealed MDR bacteria colonization after allo-HSCT in 31% of patients, although only gastrointestinal tract colonization was evaluated.

Infections are the most common and significant cause of stem cell transplant failure, as well as mortality, after allo-HSCT [6]. They are associated with a specific cascade of immune dysfunction, the reconstruction of which can take up to several years after the HSCT procedure. The regeneration of individual elements of the immune system proceeds with different dynamics, with innate immunity (neutrophils, monocytes, and natural killer cells) usually preceding adaptive immunity (T and B lymphocytes) [15–17].

We determined the number and type of infections involved in the post-transplantation period, which occurred in 86.4% of patients. Analysis conducted by Schuster et al. [18] on 431 patients undergoing allo-HSCT between 2006 and 2011 revealed the presence of infection in 93% of patients. The number of infections after allo-HSCT observed in our analysis is similar to the results received in other transplantation centers in Poland and worldwide, where, despite applied anti-infection prevention, infections occur frequently in 80–100% of patients [18–20].

We found the presence of bacteremia in 47.5% of patients, which is similar to other centers. Schuster et al. [18] noted bacteremia in 53% of patients after allo-HSCT. In the analysis conducted between 2008 and 2013 by Gjaerde et al. [21] on 460 patients undergoing allo-HSCT, bacteremia was observed in 34% and 17% of patients after MAC and reduced toxicity conditioning (RIC), respectively.

In our study, CLABSI was observed in 27.3% of patients after allo-HSCT. Mariggiò et al. [22] reported CLABSI in 32% of patients after allo-HSCT. The results obtained in our study are comparable to those presented by other researchers [22, 23].

Neutropenic fever (FN) complicates more than 80% of severe chemotherapy-induced neutropenia, and 50–60% of these patients go on to develop FUO, whereas microbiological detection of infection is possible in only 10–20% of patients, and clinically documented in 20–30% [24]. The mortality rate associated with FN is c.10%, but in cases of severe infection or septic shock, it can reach 50% [25]. Patients with profound neutropenia, defined as ANC less than 0.1 G/L, represent the group at highest risk. Bacteremia then occurs in 20% and can progress with septic shock and multiple organ failure [26].

There are two main sources of bacterial infections in the early phase before allo-HSCT. The endogenous flora of the gastrointestinal tract is mainly responsible for Gram-negative bacterial infections as a result of treatment-related mucosal damage. Secondly, exogenous nosocomial microorganisms, which are often associated with catheter-related infections, are predominantly Gram-positive bacteria. The incidence of Gram-positive bacterial infections has been increasing since the 1980s. However, Gram-negative bacterial infections are still associated with high mortality rates, and the incidence of infections with MDR strains has been increasing over the past decade [17, 27]. In our cohort, Gram-positive bacteria also predominated, accounting for 76.2% of all positive cultures from infected sites, and most often we observed coagulose-negative *Staphylococci*. Contrary to some other studies, Gram (–) bacteria constituted a minority in our center — 23.8% [28–30]. Meanwhile, an analysis by Girmenia et al. [31] of 1,118 patients after allo-HSCT assessed the cumulative incidence of pre-engraftment Gram (–) bacteremia to be 17.3% of patients and 13.2% as for Gram (+). Observations made by Mikulska et al. [28] in a 2004–2007 study of 132 patients undergoing allo-HSCT showed a decrease in the ratio of Gram (+)/Gram (–) bacteria in cultures from the vascular bed in subsequent years of the study — 68%/28% (2004) vs. 48%/48% (2007). However, in our center, there is still a trend of significant predominance of Gram (+) bacteremia over Gram (–) etiologies.

Over the last dozen or so years, the number of MDR infections has significantly increased, thus creating numerous problems for effective antibiotic therapy. In our study, MDR pathogens accounted for 58.1% of bacterial etiological factors after allo-HSCT. Our literature review did not find a multi-drug resistance analysis covering multiple locations of infection and different types of resistance simultaneously. Mikulska et al. [28] analyzed Gram-negative MDR bacteria, which constituted 35% of all Gram-negative infectious bacteria isolated in the vascular bed in patients after allo-HSCT. In a multicenter analysis, Averbuch et al. [32] evaluated the Gram-negative bacteria resistance of 414 recipients of allo-HSCT and 241 recipients of auto-HSCT between 2014 and 2015. The percentages of Gram-negative MDR rods were 44% and 20% for the allo-HSCT and auto-HSCT groups, respectively [32].

Invasive fungal infections are an important type of infection complication associated with the transplantation procedure. In our analysis, infection with at least one fungal pathogen occurred in 31.8% of patients after allo-HSCT, the most common pathogen being *Candida albicans*. A study conducted by Shi et al. [33] in 408 patients undergoing allo-HSCT detected the presence of fungal infection in 22.5% of analyzed patients. *Candida* was the most common pathogen for early fungal infection, and *Aspergillus* was the most frequent causative organism for late fungal infection.

Yeast, which causes an infection called candidiasis, enters the body by translocation through catheters or damaged intestinal mucosa, unlike mold, which enters the body by the inhalation of airborne spores. Due to the suppression of cellular immunity, phagocytosis of these pathogens by macrophages is impaired, allowing their reproduction [17, 34]. In our study, *Candida spp*. was responsible for 100% of all fungal pathogens, headed by *C. albicans* — 37.5%. An analysis by Kontoyiannis et al. [35], conducted on 16,200 patients after auto- and allo-HSCT between 2001 and 2006, showed that among invasive fungal infections, 43% were invasive aspergillosis and 28% were invasive candidosis. *C. glabrata* (33%) and *C. albicans* (20%) cultures predominated in the group of candidiasis [35].

According to scientific reports, the incidence of aspergillosis and infections caused by *Candida spp.*, and in particular by *C. albicans*, has decreased in recent years, due to widely conducted prophylactic and therapeutic activities, including the use of second-generation azoles [36].

On the other hand, intensive prophylaxis has contributed to an increase in the incidence of resistant strains such as *C. glabrata* or *C. krusei* [36–38]. In a study by Kontoyiannis et al. [35], *C. glabrata* and *C. krusei* accounted for 33% and 6%, respectively, among invasive candidiasis. It is worth noting that among allo-HSCT recipients of our study, 62.5% of fungal infections were associated with resistant strains [*C. krusei* 31.3% (5/16); *C. glabrata* 31.3% (5/16)].

Both our previous [39] and our current observations, as well as those of Hierlmeier et al. [40] and Pagano et al.

[41], show a disproportion between the incidence of fungal infections depending on the type of transplantation, in favor of allo-HCT.

Some of the most important causes of mortality and morbidity after allo-HSCT are related to viral reactivations. In our study, the reactivation of at least one viral agent in patients originally seropositive was reported in 29.5% of patients. An analysis of the first 100 days after allo-HSCT confirmed reactivation of CMV in 22.7%, EBV in 13.6%, and HSV in 2.3% of patients, respectively. A study including 65 patients undergoing allo-HSCT, performed by van Esser et al. [42], revealed that EBV reactivation occurred in 28% (day range: 2 + 107). However, Walker et al. [43] revealed CMV reactivation in 22% of 753 patients undergoing allo-HSCT (day range: 0 + 182). It is important to underscore that in our cohort the incidence of viral reactivation might be higher given the longer follow-up.

With regards to the total number of infectious pathogens detected in patients of our center in the post-transplantation period, there were on average 3.1 infectious factors per patient in the allo-HSCT group. Compared to an earlier analysis at our center, which looked at patients after auto-HSCT, this is twice as much for allo-HSCT compared to auto-HSCT (3.1 vs. 1.5) [39].

Colonization, mainly with MDR pathogens, contributes to an increased risk of infection and reduces the effectiveness of subsequent antibiotic therapy, thus posing a threat to the effective regeneration of the hematopoietic system. In our center, 59.5% of patients who appeared to be colonized before allo-HSCT could not avoid at least one infection with a colonizing pathogen. As far as infections with a pathogen detected in colonization are concerned, allo-HSCT recipients were most frequently affected by urinary tract infections with pathogens of previous anal colonization, mostly *Klebsiella pneumoniae* ESBL (+) and *Escherichia coli* ESBL (+). Moreover, recent studies have highlighted the importance of colonizing gut microbiota in the prognosis after allo-HSCT and the role of fecal microbiota transplantation as a potential therapeutic option in cases of microflora dysfunction, primary gastrointestinal colonization with MDR bacteria, or acute gastrointestinal GvHD [44, 45].

In our study, infections after allo-HSCT caused by pathogens that were detected in colonization before allo-HSCT were almost 10 times more common compared to an earlier analysis of auto-HSCT recipients at our center (59.5% vs. 6.4%) [39].

Conclusions

Despite the development of modern preventive strategies, and a better understanding of the mechanisms of immunosuppression, the problem of post-transplantation infections is still an unmet clinical challenge. Assessment of colonization and infections in the peri-transplant period should be carried out systematically. Such management allows optimal selection of prophylaxis and empirical therapy for neutropenic fever, and potentially translates into faster implementation of targeted therapy and improvement of infection outcomes.

Our study has demonstrated that infections with a colonizing pathogen can be observed after allo-HSCT. This is most likely due to a longer period of marrow aplasia, mechanical damage to mucosal barriers, more intensive immunosuppressive treatment, and frequent development of GvHD in allogeneic transplant recipients.

The results of the presented study highlight the role of colonization assessment as a tool for identifying patients at high risk of developing post-transplant infections, thus providing an opportunity for prompt targeted antibiotic therapy.

Article information and declarations

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Author contributions
All authors contributed to study conception and design. Material preparation, data collection and analysis performed by KK, PS, KS, MC, AS, OGI, AW and AP. First draft of manuscript was written by KK, and all authors commented on subsequent versions of manuscript. All authors read and approved final manuscript.

Conflict of interests
The authors declare no conflict of interests.

Data availability statement
The datasets generated during and/or analyzed during the current study are not publicly available due to the fact that individual privacy could be compromised, but are available from the corresponding author upon reasonable request.

Ethics statement
This study was performed in line with the principles of the Declaration of Helsinki. This research study was conducted retrospectively from data obtained for clinical purposes. Informed consent was obtained from all individual participants included in the study.

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Supplementary material

None.

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Allogeneic hematopoietic stem cell transplantation for acute lymphoblastic leukemia with accompanying hereditary hemorrhagic telangiectasia

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Introduction

Rendu–Osler–Weber disease also known as hereditary hemorrhagic telangiectasia (HHT) is a rare autosomal dominant disorder [1]. It is caused by mutations in the *ENG, ACVRL1* or *SMAD4* genes that result in impaired angiogenesis and vascular remodeling [2].

The Curaçao criteria used for diagnosis include spontaneous recurrent nosebleeds, multiple telangiectasias, visceral lesions including arterio-venous malformations (AVMs) and family history of the disease [3, 4]. Although life-threatening hemorrhages occur only rarely in these patients, the risk of severe bleeding increases with additional coagulopathies and hematological malignancies.

We present an unusual case report of a patient with HHT treated with allogeneic hematopoietic stem cell transplantation (allo-HSCT) for high-risk acute lymphoblastic leukemia (ALL).

Case report

In June 2021, a 42-year-old female with *BCR::ABL*p190 positive ALL underwent allo-HSCT in our center. She had been diagnosed with HHT seven years earlier based on the presence of gastrointestinal angiodysplasia, frequent epistaxis, and a positive family history.

Treatment of ALL was according to the Polish Adult Leukemia Group (PALG) ALL7 Ph (+) protocol with rituximab and a tyrosine kinase inhibitor (TKI) i.e. imatinib. Although the first cycle of therapy was well tolerated, complete hematological remission (CHR) was not achieved. As a reinduction therapy, a second generation TKI, dasatinib with dexamethasone was introduced. Seven weeks later, the patient achieved CHR with measurable residual disease (MRD) at 0.36% on flow cytometry (FC) and at 0.06% of *BCR::ABL*p190 IS. She continued dasatinib treatment until the transplantation procedure.

She proceeded to allo-HSCT from a 9/10 HLA-matched unrelated donor (HLA-A mismatch) with minor ABO incompatibility. The source of hematopoietic stem cells was peripheral blood. Total body irradiation of 12 Gy and 6 g of cyclophosphamide were administered as myeloablative conditioning. For graft-versus-host disease (GvHD) prophylaxis, the patient received cyclosporine with methotrexate and anti-thymocyte globulin (thymoglobulin). She developed severe epistaxis, while her conditioned-platelet (PLT) count dropped from 139 G/L on day –3 to 52 G/L on day –2. Antihemorrhagic drugs were administered (i.e. ethamsylate and tranexamic acid) but bleeding recurred on the following days. This required bilateral anterior nasal packing for the next three weeks, plus multiple red blood cells (RBC) as well as platelet (PLT) and plasma transfusions. On day +1 after transplantation, the patient complained of abdominal pain and blood-staine diarrhea. Abdominal computed tomography (CT) excluded gastrointestinal bleeding or tract perforation. In addition, an inflammatory infiltration of the left labia was observed, accompanied by an increase of C-reactive protein up to 159 mg/L (normal range 0–5). Despite the use of broad-spectrum antibiotics, antifungal and antiviral agents, inflammation progressed, leading to the formation of fistula and necrosis that required surgical treatment. *Pseudomonas aeruginosa* was isolated from the lesion,

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Table I. Disease status before and after allogeneic stem cell transplantation (allo-HSCT) including flow cytometry measurable residual disease (FC-MRD), *BCR::ABL*p190 transcript, and donor chimerism

Time to allo-HSCT	FC-MRD	*BCR::ABL*p190 IS [%]	Donor chimerism [%]
Before transplant	Positive	0.06	–
+ 28 days	Negative	0.025	90
+ 56 days	Negative	0.0025	94
+ 98 days	Negative	0.012	85
Cyclosporine discontinuation			
+ 5 months	Negative	0.073	81
At dasatinib commencement			
+ 6 months	Negative	0.003	100
+ 8.5 months	Negative	0.003	100
After dasatinib discontinuation			
+ 11 months	Negative	Undetectable	100
+ 14 months	Negative	0.004	100
+ 17 months	Negative	0.003	100
+ 20 months	Negative	Undetectable	99
+ 26 months	Negative	Undetectable	100

and targeted antibiotic therapy with colistin was implemented. In total, she received 16 units of RBC and 34 units of PLT transfusions. The patient's overall condition eventually started to improve alongside the normalization of inflammatory markers. She engrafted her neutrocytes and platelets on days +17 and +28 after transplantation, respectively.

Cytomegalovirus reactivation was detected on day +31 and successfully eradicated with valgancyclovir. She was discharged on day +38 after transplantation. Bone marrow biopsy at discharge showed CR with negative MRD-FC and *BCR::ABL*p190 transcript of 0.025% (Table I).

Due to the mixed donor chimerism, the dose of cyclosporin was gradually tapered off. On a follow-up visit two weeks later, she presented acute grade II cutaneous GvHD which was treated effectively with methylprednisolone. A repeated bone marrow biopsy confirmed CR with negative MRD, although donor chimerism had decreased alongside a *BCR::ABL*p190 increase. Dasatinib at a dose of 140 mg daily was initiated, and the treatment resulted in *BCR::ABL*p190 eradication. Dasatinib treatment was eventually stopped nine months after allo-HSCT due to gastrointestinal intolerance (i.e. intense nausea). Currently, 30 months after transplantation, the patient is free of TKIs, with full donor chimerism.

Discussion

In patients with HHT, gastrointestinal bleeding, epistaxis or pulmonary AVMs remain the most common cause of death [5]. Based on the genotype and location of vascular malformations, HHT may be classified as HHT1, HHT2, or juvenile polyposis HHT (JP-HHT). HHT1 is associated with a mutation in the *ENG* gene and poses the highest risk of the development of pulmonary, cerebral and gastrointestinal AVMs. In HHT2, which is caused by a mutation in the *ALK1* gene, hepatic AVMs are common. JP-HHT, with a mutation in the *SMAD4* gene, is characterized by the presence of colorectal hamartomatous polyps [6, 7]. Genetic diagnostics for HHT mutations are not routinely available in Poland. The diagnosis of the disease worldwide is made on the basis of the Curaçao criteria which refer to clinical symptoms.

Myeloablative conditioning rapidly reduces platelet count and impairs gastrointestinal mucosa which can may lead to coagulation disturbances with life-threatening bleeds. Moreover, it is important to remember that dasatinib can cause thrombocytopenia and hemorrhages as a side effect [8]. In a single previous case report, of a 23-year-old patient with Ph(+) ALL and accompanying JP-HHT, despite CR after induction chemotherapy and young age, the patient was not considered for allo-HSCT. Eventually, he relapsed and reinduction therapy with dasatinib was complicated by several episodes of gastrointestinal bleeding, which finally led to his death [9].

Patients suffering from HHT and an aggressive hematological malignancy require special attention. Physicians should be alert to any bleeding symptoms and should not hesitate to perform rapid imaging diagnostics where there is a suspicion of internal bleeding so as to undertake urgent treatment.

Proper management of bleeding can lead to clinical improvements in these high-risk patients, and eventually enable an effective therapy of the underlying hematological malignancy. Despite several life-threatening complications, allo-HSCT was successful in the described patient.

Article information and declarations

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Authors contributions
DH, SG — analysis of clinical data, literature search, original draft preparation. AS — supervision, original draft preparation, conceptualization. GH — supervision, writing review and editing.

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Authors declare that informed consent for publication was not obtained, as published data does not allow for patient identification.

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Multidrug rescue for pediatric refractory ITP complicated by intracranial bleeding

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Introduction

Immune thrombocytopenia, formerly known as idiopathic thrombocytopenic purpura (ITP), is the most common cause of low platelet count in children. As the previous name suggests, an ITP diagnosis follows the exclusion of other identifiable diseases and confirmation via successful therapy [1]. It is estimated that c.95% of children with ITP experience spontaneous remission or a positive response to initial treatments, while the majority of the remaining non-responders eventually achieve platelet normalization with second-line therapies [2, 3]. Newly diagnosed refractory ITP is rare among pediatric patients. Although there is no consensus definition for this condition in childhood, it is generally considered after a failure to achieve a response to two standard first-line treatments, i.e. intravenous immunoglobulin (IVIG) and steroids [2, 4]. It is becoming accepted that newly diagnosed refractory ITP requires intensive diagnostics and a rapid transition to second-line treatments [2, 5].

Case report

A 3-month-old male infant with no significant medical history was admitted to hospital due to a petechial rash and severe isolated thrombocytopenia. There was no family history of bleeding disorders or hematological diseases. A 5-day course of IVIG, with a total dose of 2 g/kg, was immediately started because of pronounced cutaneous bleeding signs and a positive test for occult fecal blood. On the second day of treatment, the intestinal bleeding became clinically overt, resulting in anemia and the need for packed red blood cell transfusions. The patient was also transfused multiple times with platelet concentrates without elevating the thrombocyte levels. Consequently, methylprednisolone at a dose of 2 mg/kg daily was added to the initial IVIG regimen. On the fourth day of treatment, romiplostim was initiated at a weekly dose of 10 μg/kg and steroid therapy was escalated to 4 mg/kg daily. The next day, the patient exhibited signs of neurological impairment, and a computed tomography (CT) scan revealed intracranial bleeding (see Figure 1).

Following transfer to the pediatric intensive care unit (PICU), the patient was put into deep sedation and administered emergency vincristine at a dose of 0.05 mg/kg. Additionally, he developed severe hypertension requiring treatment with a continuous urapidil infusion. The day after, eltrombopag was introduced to the therapy with a daily dose of 25 mg, and the methylprednisolone dose was increased to 10 mg/kg daily. On the eighth day, his thrombocyte level remained zero, even after receiving a platelet concentrate transfusion. Therefore, a first dose of rituximab was administered, and two days later a second course of IVIG was started.

In the meantime, significant diagnostic data was obtained, including negative results of genetic testing for Epstein–Barr virus (EBV) and cytomegalovirus (CMV), normal ADAMTS13 activity, and positive findings for antiplatelet antibodies of undetermined specificity at that stage. Bone marrow cytology was non-contributory. The patient's mother tested negative for antiplatelet antibodies, ruling out fetal and neonatal alloimmune thrombocytopenia [6]. A follow-up CT scan revealed minimal progression of the initial hemorrhagic lesion (see Figure 1).

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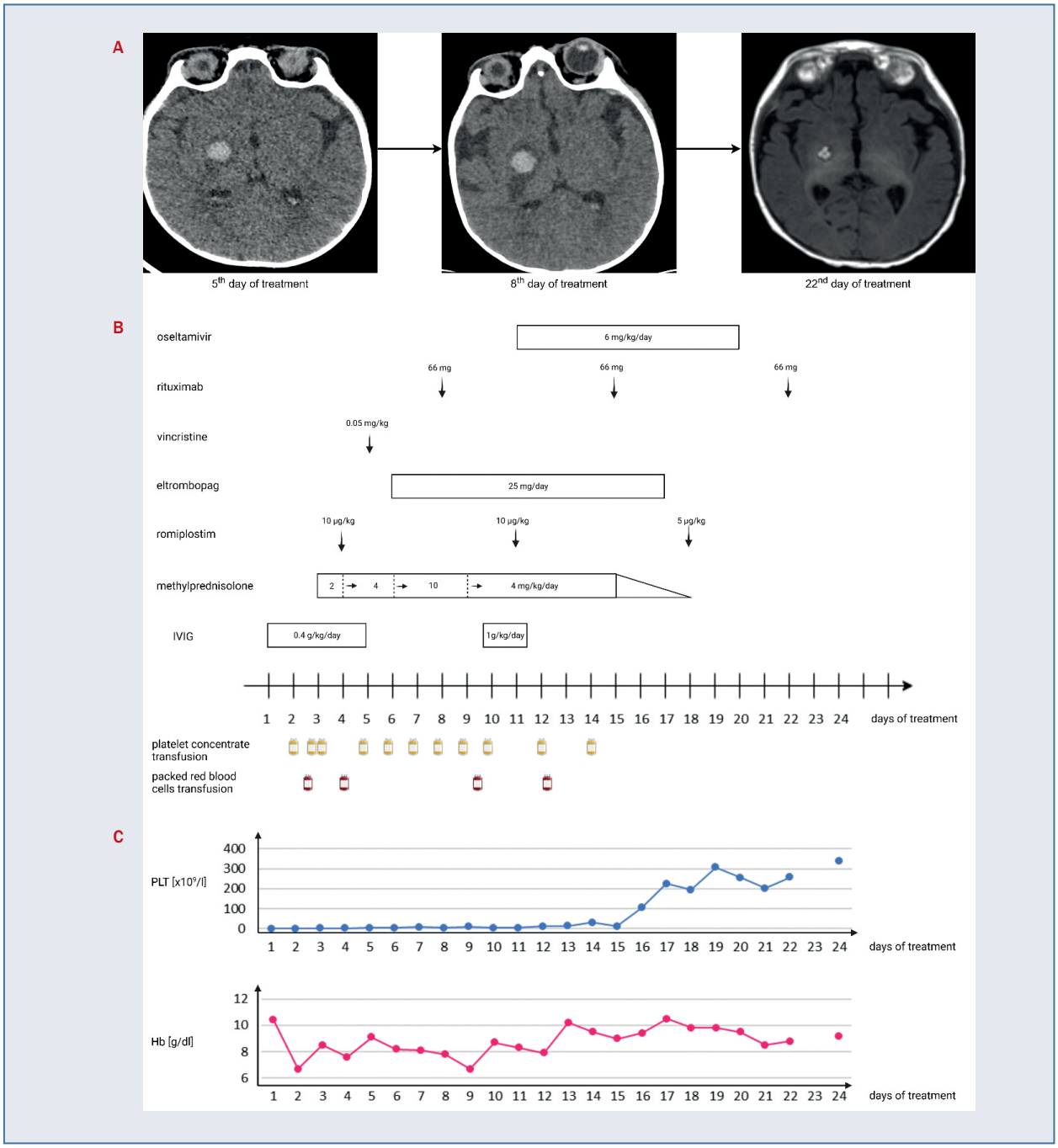

Figure 1A. Evolution of intracerebral hemorrhage on computed tomography and magnetic resonance neuroimaging; **B.** Therapeutic interventions with drug doses presented on time axis; **C.** Graphs depicting platelet levels (PLT) and hemoglobin concentration (Hb) during hospitalization; IVIG — intravenous immunoglobulin

On the 12th day of treatment, oseltamivir was added to the therapy due to persistently low platelet counts and the determination of anti-GPIIb/IIIa specificity in the previously detected antiplatelet antibodies. Some studies have suggested that anti-GPIIb/IIIa antibodies may induce desialylation, contributing to platelet death, which can be alleviated by neuraminidase inhibitors [7–9].

On the 14th day of treatment, the first significant increase in platelet levels was noted, and two days later the patient's thrombocyte count exceeded 100,000/µl. The therapies were gradually discontinued, as shown in Figure 1.

The patient's condition improved over time, leading to his transfer from the PICU to the hematology department

and eventual discharge after 26 days of hospitalization. The boy continued rituximab, receiving four doses in total, and four months after the onset of the disease remains in remission without further treatment. During that time, he has displayed notable advances in psychomotor development while under the care of a medical team comprising a pediatric hematologist, a neurologist, and a rehabilitation specialist. Nevertheless, further observation is necessary to monitor for potential long-term neurological sequelae.

Discussion

Although we cannot identify which specific treatment component had the most significant impact on the patient's remission, this case report supports the opinion that prompt initiation of second-line treatments in refractory ITP cases is justified [2, 4, 5]. It is highly probable that a combination of medications, which exhibit a cumulative effect, played a crucial role.

Recent research has suggested that combining steroids with rituximab or thrombopoietin receptor agonists may determine synergistic results, rather than just the sum of each drug's action [10]. Further studies are needed to assess the potential effect of oseltamivir in this context. It is noteworthy that most of the drugs used in this case were administered off-label. Despite the aggressive treatment approach and the rapid introduction of multiple agents with partially overlapping activities, no complications explicitly attributed to any drug used were observed.

We conclude that in the setting of primary refractory ITP, the potential benefits of early aggressive multimodal treatment far outweigh the possible adverse effects.

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Authors contributions
BU — conceptualization, writing of manuscript; OW, ES, MZ, MW — clinical data; DB — radiological imaging data; WM — supervision; SJ — conceptualization, writing and critical review of manuscript, supervision. All authors have read and agreed to the published version of the manuscript.

Conflict of interests
The authors declare no conflict of interests.

Ethics statement
Authors declare that informed consent for publication was not obtained, as published data does not allow for patient identification.

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Supplementary material
None.

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Postać, skład: Tabletka powlekana. Każda tabletka zawiera 21,62 mg chlorowodorku asciminibu, co odpowiada 20 mg asciminibu, lub 43,24 mg chlorowodorku asciminibu, co odpowiada 40 mg asciminibu. Każda tabletka zawiera 43 mg lub 86 mg laktozy jednowodnej. Pełny wykaz substancji pomocniczych, patrz ChPL. **Wskazania:** Lek Scemblix jest wskazany do stosowania w leczeniu dorosłych pacjentów z przewlekłą białaczką szpikową z chromosomem Philadelphia w fazie przewlekłej (Ph+ CML-CP), leczonych wcześniej dwoma lub więcej inhibitorami kinazy tyrozynowej (patrz ChPL). **Dawkowanie:** Leczenie powinno być rozpoczynane przez lekarza doświadczonego w rozpoznawaniu i leczeniu pacjentów z białaczką. Dawkowanie: Zalecana dawka wynosi 40 mg dwa razy na dobę w przybliżeniu co 12 godzin. *Pominięcie dawki:* Jeśli od czasu przyjęcia dawki minęło mniej niż 6 godzin, należy ją przyjąć, a kolejną dawkę należy zażyć zgodnie z planem. Jeśli od czasu przyjęcia dawki minęło więcej niż około 6 godzin, należy ją pominąć i przyjąć kolejną dawkę zgodnie z planem. *Czas trwania leczenia:* Leczenie asciminibem należy kontynuować tak długo, jak długo obserwuje się korzyści kliniczne lub do wystąpienia nieakceptowalnej toksyczności. *Dostosowanie dawki ze względu na działania niepożądane:* Dawka początkowa wynosi 40 mg dwa razy na dobę, natomiast dawka zmniejszona wynosi 20 mg dwa razy na dobę. Dawkę można modyfikować w zależności od indywidualnego bezpieczeństwa stosowania i tolerancji, zgodnie z informacjami podanymi w Tabeli 1. Leczenie asciminibem należy zakończyć i nie wznawiać u pacjentów nietolerujących dawki 20 mg dwa razy na dobę.

Tabela 1. Plan modyfikacji dawki asciminibu w ramach postępowania z działaniami niepożądanymi

Działania niepożądane	**Modyfikacja dawki**
Małopłytkowość i (lub) neutropenia	
ANC <1,0 x 10^9/l i (lub) PLT <50 x 10^9/l	Wstrzymać podawanie asciminibu do czasu, gdy ANC ≥1 x 10^9/l i (lub) PLT ≥50 x 10^9/l. Jeśli powrót do tych wartości nastąpi: • W ciągu 2 tygodni: wznowić leczenie od dawki początkowej. • Po ponad 2 tygodniach: wznowić leczenie w zmniejszonej dawce. W przypadku ponownej ciężkiej małopłytkowości i (lub) neutropenii, wstrzymać podawanie asciminibu do czasu powrotu do wartości ANC ≥1 x 10^9/l i PLT ≥50 x 10^9/l, następnie wznowić leczenie w zmniejszonej dawce.
Bezobjawowe zwiększenie aktywności amylazy i (lub) lipazy	
Zwiększenie >2,0 x GGN	Wstrzymać podawanie asciminibu do czasu powrotu do wartości <1,5 x GGN. • Jeśli to działanie niepożądane ustąpi: wznowić leczenie w zmniejszonej dawce. Jeśli zdarzenia wystąpią ponownie po podaniu zmniejszonej dawki, zakończyć leczenie i nie wznawiać. • Jeśli to działanie niepożądane nie ustąpi: zakończyć leczenie i nie wznawiać. Wykonać badania diagnostyczne w celu wykluczenia zapalenia trzustki.
Niehematologiczne działania niepożądane	
Działania niepożądane w stopniu 3. lub wyższym[1]	Wstrzymać podawanie asciminibu do czasu ustąpienia działań do stopnia 1. lub niższego. • Jeśli działania ustąpią: wznowić leczenie w zmniejszonej dawce. • Jeśli działania nie ustąpią: zakończyć leczenie i nie wznawiać.

ANC – (ang. *absolute neutrophil count*) bezwzględna liczba granulocytów obojętnochłonnych; PLT – płytki krwi; GGN – górna granica normy.
[1] Na podstawie powszechnych kryteriów terminologicznych dla zdarzeń niepożądanych opracowanych przez amerykański Narodowy Instytut Raka (ang. *National Cancer Institute Common Terminology Criteria for Adverse Events*, NCI CTCAE) w. 4.03.

Szczególne populacje pacjentów: Pacjenci w podeszłym wieku: Brak konieczności dostosowania dawki u pacjentów w wieku 65 lat lub starszych. *Zaburzenia czynności nerek:* Brak konieczności dostosowania dawki u pacjentów z łagodnymi, umiarkowanymi lub ciężkimi zaburzeniami czynności nerek (patrz ChPL). *Zaburzenia czynności wątroby:* Brak konieczności dostosowania dawki u pacjentów z łagodnymi, umiarkowanymi lub ciężkimi zaburzeniami czynności wątroby (patrz ChPL). *Dzieci i młodzież:* Nie określono bezpieczeństwa stosowania ani skuteczności leku Scemblix u dzieci i młodzieży w wieku poniżej 18 lat. Dane nie są dostępne. Sposób podawania: Lek Scemblix jest przeznaczony do podawania doustnego. Tabletki powlekane należy połykać w całości popijając szklanką wody i nie należy ich przełamywać, kruszyć ani żuć. Tabletki należy przyjmować doustnie bez pokarmu. Należy unikać spożywania pokarmu przez co najmniej 2 godziny przed i 1 godzinę po przyjęciu asciminibu (patrz ChPL). **Przeciwwskazania:** Nadwrażliwość na substancję czynną lub na którąkolwiek substancję pomocniczą wymienioną w ChPL. **Środki ostrożności/Ostrzeżenia:** Zahamowanie czynności szpiku: U pacjentów otrzymujących asciminib występowała małopłytkowość, neutropenia i niedokrwistość. Podczas leczenia asciminibem zgłaszano ciężką (stopień 3. lub 4. wg NCI CTCAE) małopłytkowość i neutropenię (patrz ChPL). Zahamowanie czynności szpiku było na ogół odwracalne i kontrolowane za pomocą czasowego wstrzymania leczenia. Badanie morfologiczne krwi należy wykonywać co dwa tygodnie przez pierwsze 3 miesiące leczenia, a następnie co miesiąc lub według wskazań klinicznych. Należy monitorować pacjentów w kierunku podmiotowych i przedmiotowych objawów zahamowania czynności szpiku. W zależności od nasilenia małopłytkowości i (lub) neutropenii, podawanie leku należy czasowo wstrzymać, zmniejszyć dawkę lub zakończyć leczenie i nie wznawiać, zgodnie z informacjami zamieszczonymi w tabeli 1 (patrz ChPL). Toksyczne działanie na trzustkę: U pacjentów otrzymujących asciminib występowało zapalenie trzustki i przebiegające bezobjawowo zwiększenie aktywności lipazy i amylazy w surowicy, w tym reakcje ciężkie (patrz ChPL). Aktywność lipazy i amylazy w surowicy należy sprawdzać co miesiąc podczas leczenia asciminibem lub w zależności od wskazań klinicznych. Należy kontrolować pacjentów pod kątem podmiotowych i przedmiotowych objawów toksycznego działania na trzustkę. U pacjentów z zapaleniem trzustki w wywiadzie monitorowanie powinno odbywać się częściej. Jeśli zwiększeniu aktywności lipazy i amylazy w surowicy towarzyszą objawy w jamie brzusznej, należy czasowo wstrzymać leczenie i rozważyć przeprowadzenie odpowiednich badań diagnostycznych, aby wykluczyć zapalenie trzustki (patrz ChPL). W zależności od nasilenia zwiększenia aktywności lipazy i amylazy w surowicy, podawanie leku należy czasowo wstrzymać, zmniejszyć dawkę lub zakończyć leczenie i nie wznawiać, zgodnie z informacjami zamieszczonymi w tabeli 1 (patrz ChPL). Wydłużenie odstępu QT: U pacjentów otrzymujących asciminib występowało wydłużenie odstępu QT (patrz ChPL). Zaleca się wykonanie badania elektrokardiograficznego przed rozpoczęciem leczenia asciminibem oraz monitorowanie w trakcie leczenia według wskazań klinicznych. Hipokaliemię i hipomagnezemię należy wyrównać przed podaniem asciminibu oraz kontrolować w trakcie leczenia według wskazań klinicznych. Należy zachować ostrożność podając asciminib jednocześnie z lekami, o których wiadomo, że zwiększają ryzyko wystąpienia częstoskurczu typu *torsades de pointes* (patrz ChPL). Nadciśnienie tętnicze: U pacjentów otrzymujących asciminib występowało nadciśnienie tętnicze, w tym ciężkie nadciśnienie tętnicze (patrz ChPL). W trakcie leczenia asciminibem należy regularnie kontrolować oraz leczyć nadciśnienie tętnicze i inne czynniki ryzyka sercowo-naczyniowego, wykorzystując standardowe leczenie. Reaktywacja wirusowego zapalenia wątroby typu B: Reaktywacja wirusa zapalenia wątroby typu B (HBV) występowała u pacjentów będących nosicielami tego wirusa po podaniu innych inhibitorów kinazy tyrozynowej (TKI) BCR::ABL1. Należy zbadać pacjentów pod kątem zakażenia HBV przed rozpoczęciem leczenia asciminibem. Nosiciele HBV, u których konieczne jest leczenie asciminibem należy kontrolować w kierunku podmiotowych i przedmiotowych objawów aktywnego zakażenia HBV przez cały czas trwania leczenia oraz przez kilkanaście miesięcy po zakończeniu leczenia. Laktoza: Lek nie powinien być stosowany u pacjentów z rzadko występującą dziedziczną nietolerancją galaktozy, brakiem laktazy lub zespołem złego wchłaniania glukozy-galaktozy. Sód: Lek zawiera mniej niż 1 mmol (23 mg) sodu na tabletkę powlekaną, to znaczy lek uznaje się za „wolny od sodu". **Działania niepożądane:** Podsumowanie profilu bezpieczeństwa: Do najczęstszych działań niepożądanych o dowolnym stopniu nasilenia (częstość występowania ≥20%) u pacjentów otrzymujących asciminib należały: bóle mięśniowo-szkieletowe (37,1%), zakażenia górnych dróg oddechowych (28,1%), małopłytkowość (27,5%), uczucie zmęczenia (27,2%), ból głowy (24,2%), ból stawów (21,6%), zwiększona aktywność enzymów trzustkowych (21,3%), ból brzucha (21,3%), biegunka (20,5%) i nudności (20,2%). Do najczęstszych działań niepożądanych stopnia ≥3. (częstość występowania ≥5%) u pacjentów otrzymujących asciminib należały: małopłytkowość (18,5%), neutropenia (15,7%), zwiększona aktywność enzymów trzustkowych (12,4%), nadciśnienie tętnicze (8,7%) i niedokrwistość (5,3%). Ciężkie działania niepożądane wystąpiły u 12,4% pacjentów otrzymujących asciminib. Do najczęstszych ciężkich działań niepożądanych (częstość występowania ≥1%) należały: wysięk opłucnowy (2,5%), zakażenia dolnych dróg oddechowych (2,2%), małopłytkowość (1,7%), gorączka (1,4%), zapalenie trzustki (1,1%), pozasercowy ból w klatce piersiowej (1,1%) i wymioty (1,1%). Wykaz działań niepożądanych: Ogólny profil bezpieczeństwa stosowania asciminibu oceniono u 356 pacjentów z Ph+ CML w fazie przewlekłej (CP) i w fazie akceleracji (AP) w badaniu rejestracyjnym III fazy A2301 (ASCEMBL) i w badaniu I fazy X2101. W badaniu ASCEMBL pacjenci otrzymywali asciminib w monoterapii w dawce 40 mg dwa razy na dobę. W badaniu X2101 pacjenci otrzymywali asciminib w monoterapii w dawkach z zakresu od 10 do 200 mg dwa razy na dobę oraz od 80 do 200 mg raz na dobę. Analiza danych zbiorczych wykazała, że mediana czasu trwania ekspozycji na asciminib wyniosła 116 tygodni (zakres: 0,1 do 342 tygodni). Działania niepożądane obserwowane w badaniach klinicznych wymieniono według klasyfikacji układów i narządów MedDRA. W każdej grupie układów i narządów działania niepożądane zostały wymienione według częstości ich występowania, poczynając od najczęstszych. W obrębie każdej grupy o określonej częstości występowania działania niepożądane są wymienione zgodnie ze zmniejszającym się nasileniem. Ponadto kategorie częstości dla każdego działania niepożądanego zostały podane zgodnie z następującą konwencją: bardzo często (≥1/10); często (≥1/100 to <1/10); niezbyt często (≥1/1 000 do <1/100); rzadko (≥1/10 000 do <1/1 000); bardzo rzadko (<1/10 000). ***Bardzo często:*** zakażenie górnych dróg oddechowych[1], małopłytkowość[3], neutropenia[4], niedokrwistość[5], dyslipidemia[6], ból głowy, zawroty głowy, nadciśnienie tętnicze[7], kaszel, zwiększona aktywność enzymów trzustkowych[8], wymioty, biegunka, nudności, ból brzucha[9], zwiększenie aktywności enzymów wątrobowych[11], wysypka[13], bóle mięśniowo-szkieletowe[14], ból stawów, uczucie zmęczenia[15], świąd. ***Często:*** zakażenie dolnych dróg oddechowych[2], grypa, zmniejszenie apetytu, hiperglikemia, suchość oka, niewyraźne widzenie, kotatania, wysięk opłucnowy, duszności, pozasercowy ból w klatce piersiowej, zapalenie trzustki[10], zwiększenie stężenie bilirubiny we krwi[12], pokrzywka, gorączka[16], obrzęk[17], zwiększenie aktywności fosfokinazy kreatynowej we krwi. ***Niebyt często:*** gorączka neutropeniczna, nadwrażliwość, wydłużenie odstępu QT w badaniu elektrokardiograficznym. Opis wybranych działań niepożądanych: *Zahamowanie czynności szpiku:* Małopłytkowość wystąpiła u 27,5% pacjentów otrzymujących asciminib, a działania w stopniu 3. i 4. Zgłoszono u odpowiednio 6,7% i 11,8% pacjentów. U pacjentów z małopłytkowością stopnia ≥3. Mediana czasu do pierwszego wystąpienia działań wyniosła 6 tygodni (zakres: 0,14 do 64 tygodni), a mediana czasu trwania dowolnego występującego działania wyniosła 1,71 tygodnia (95% CI, zakres: 1,43 do 2 tygodni). U 2% pacjentów otrzymujących asciminib zakończono i nie wznawiano leczenia asciminibem z powodu małopłytkowości, podczas gdy leczenie asciminibem zostało czasowo wstrzymane u 12,6% pacjentów z powodu działania niepożądanego. Neutropenia wystąpiła u 19,4% pacjentów otrzymujących asciminib, a działania w stopniu 3. i 4. Zgłoszono u odpowiednio 7,3% i 8,4% pacjentów. U pacjentów z neutropenią stopnia ≥3. mediana czasu do pierwszego wystąpienia działań wyniosła 6 tygodni (zakres: 0,14 do 180 tygodni), a mediana czasu trwania dowolnego występującego działania wyniosła 1,79 tygodnia (95% CI, zakres: 1,29 do 2 tygodni). U 1,1% pacjentów otrzymujących asciminib zakończono i nie wznawiano leczenia asciminibem z powodu neutropenii, podczas gdy leczenie asciminibem zostało czasowo wstrzymane u 9,6% pacjentów z powodu działania niepożądanego. Niedokrwistość wystąpiła u 12,9% pacjentów otrzymujących asciminib, a działania w stopniu 3. wystąpiły u 5,3% pacjentów. U pacjentów z niedokrwistością stopnia ≥3. mediana czasu do pierwszego wystąpienia działań wyniosła 30 tygodni (zakres: 0,4 do 207 tygodni), a mediana czasu trwania dowolnego występującego działania wyniosła 0,9 tygodnia (95% CI, zakres: 0,43 do 2,14 tygodnia). Leczenie asciminibem zostało czasowo wstrzymane u 0,6% pacjentów z powodu działania niepożądanego. *Toksyczne działanie na trzustkę:* Zapalenie trzustki wystąpiło u 2,5% pacjentów otrzymujących asciminib, a działania stopnia 3. Wystąpiły u 1,1% pacjentów. Wszystkie takie działania wystąpiły w badaniu I fazy (X2101). U 0,6% pacjentów otrzymujących asciminib leczenie asciminibem zakończono i nie wznawiano z powodu zapalenia trzustki, natomiast u 1,1% pacjentów leczenie asciminibem zostało czasowo wstrzymane z powodu działania niepożądanego. Bezobjawowe zwiększenie aktywności lipazy i amylazy w surowicy wystąpiło u 21,3% pacjentów otrzymujących asciminib, przy czym działania stopnia 3. i 4. wystąpiły u odpowiednio 10,1% i 2,2% pacjentów. Wśród pacjentów ze zwiększeniem aktywności enzymów trzustkowych u 2,2% pacjentów leczenie asciminibem zostało definitywnie zakończone z powodu działania niepożądanego. *Wydłużenie odstępu QT:* Wydłużenie odstępu QT obserwowane w badaniu elektrokardiograficznym wystąpiło u 0,8% pacjentów otrzymujących asciminib. W badaniu klinicznym ASCEMBL u jednego pacjenta wydłużenie odstępu QTcF przekroczyło 500 milisekund (ms) wraz z wydłużeniem QTcF względem wartości początkowej o ponad 60 ms, a u jednego pacjenta wystąpiło wydłużenie odstępu QTcF wraz z wydłużeniem QTcF względem wartości początkowej o ponad 60 ms. *Nadciśnienie tętnicze:* Nadciśnienie tętnicze wystąpiło u 18,5% pacjentów otrzymujących asciminib, a działania stopnia 3. i 4. zgłoszono odpowiednio u 8,4% i 0,3% pacjentów. U pacjentów z nadciśnieniem tętniczym w stopniu ≥3., mediana czasu do pierwszego wystąpienia działań wyniosła 14 tygodni (zakres: 0,1 do 156 tygodni). Leczenie asciminibem zostało czasowo wstrzymane u 0,8% pacjentów z powodu działania niepożądanego. *Nieprawidłowe wyniki w badaniach laboratoryjnych:* Zmniejszenie stężenia fosforanów wystąpiło jako nieprawidłowy wynik w badaniach laboratoryjnych u 17,9% (wszystkie stopnie) i 6,4% (stopień 3./4.) spośród 156 pacjentów otrzymujących asciminib w dawce 40 mg dwa razy na dobę. Zgłaszanie podejrzewanych działań niepożądanych: Po dopuszczeniu leku do obrotu istotne jest zgłaszanie podejrzewanych działań niepożądanych. Umożliwia to nieprzerwane monitorowanie stosunku korzyści do ryzyka stosowania leku. 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. **Pozwolenia Komisji Europejskiej na dopuszczenie do obrotu nr:** EU/1/22/1670/001-005. **Kategoria dostępności:** Rpz – Lek wydawany na receptę do zastrzeżonego stosowania. **Podmiot odpowiedzialny:** Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road Dublin 4, Irlandia. **Uwaga:** Przed przepisaniem leku należy zapoznać się z pełną informacją o leku. **Pełna informacja o leku jest dostępna w:** Novartis Poland Sp. z o. o., 02-674 Warszawa, ul. Marynarska 15, tel. +48 22 375 4 888. **Opracowano:** 07/2023

[1] Zakażenie górnych dróg oddechowych obejmuje: zakażenie górnych dróg oddechowych, zapalenie jamy nosowej i gardła, zapalenie gardła oraz zapalenie błony śluzowej nosa. [2] Zakażenia dolnych dróg oddechowych obejmują: zapalenie płuc, zapalenie oskrzeli oraz zapalenie tchawicy i oskrzeli. [3] Małopłytkowość obejmuje: małopłytkowość i zmniejszenie liczby płytek krwi. [4] Neutropenia obejmuje: neutropenię i zmniejszenie liczby granulocytów obojętnochłonnych. [5] Niedokrwistość obejmuje: niedokrwistość, zmniejszenie stężenia hemoglobiny i niedokrwistość normocytową. [6] Dyslipidemia obejmuje: hipertriglicerydemię, zwiększenie stężenia cholesterolu we krwi, hipercholesterolemię, zwiększenie stężenia trójglicerydów we krwi, hiperlipidemię i dyslipidemię. [7] Nadciśnienie tętnicze obejmuje: nadciśnienie tętnicze i wzrost ciśnienia tętniczego krwi. [8] Zwiększenie aktywności enzymów trzustkowych obejmuje: zwiększenie aktywności lipazy, zwiększenie aktywności amylazy i hiperlipazemię. [9] Ból brzucha obejmuje: ból brzucha i ból w górnej części jamy brzusznej. [10] Zapalenie trzustki obejmuje: zapalenie trzustki i ostre zapalenie trzustki. [11] Zwiększenie aktywności enzymów wątrobowych obejmuje: zwiększenie aktywności aminotransferaz alaninowej, zwiększenie aktywności aminotransferazy asparaginianowej, zwiększenie aktywności gamma-glutamylotranspeptydazy i zwiększenie aktywności aminotransferaz. [12] Zwiększenie stężenia bilirubiny we krwi obejmuje: zwiększenie stężenia bilirubiny we krwi, zwiększenie stężenia bilirubiny sprzężonej i hiperbilirubinemię. [13] Wysypka obejmuje: wysypkę i wysypkę grudkowo-plamistą. [14] Bóle mięśniowo-szkieletowe obejmują: ból w kończynie, ból pleców, ból mięśni, ból kości, ból mięśniowo-szkieletowy, ból karku, mięśniowo-szkieletowy ból w klatce piersiowej i dyskomfort mięśniowo-szkieletowy. [15] Uczucie zmęczenia obejmuje: uczucie zmęczenia i astenię. [16] Gorączka obejmuje: gorączkę i zwiększenie temperatury ciała. [17] Obrzęk obejmuje: obrzęk i obrzęk obwodowy.

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SCEMBLIX® (asciminib) jest wskazany w leczeniu dorosłych pacjentów z przewlekłą białaczką szpikową z chromosomem Philadelphia w fazie przewlekłej (Ph+ CML-CP), leczonych wcześniej dwoma lub więcej inhibitorami kinazy tyrozynowej[1]

1. SCEMBLIX® (asciminib) Charakterystyka Produktu Leczniczego, 07/2023

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SCEMBLIX®
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