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Autologous stem cell transplantation for adults with Philadelphia-negative acute lymphoblastic leukemia in first complete remission. A study by the Acute Leukemia Working Party of the EBMT

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Abstract

Background The role of autologous hematopoietic stem cell transplantation (AHSCT) in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia (Ph-ALL) remains controversial. The aim of this retrospective study was to analyze results of AHSCT and to identify prognostic factors.

Methods Overall, 700 patients transplanted in first complete remission between the years 1999-2020 were included. Median patient age was 31.9 years (68% male). B-cell precursor ALL (BCP-ALL) and T-cell precursor ALL (TCP-ALL) was diagnosed in 35% and 65%, respectively. Among 190 patients with available data, negative minimal residual disease (MRD) status was reported in 167 (88%) cases.

Results The probabilities of overall survival (OS) and leukemia-free survival (LFS) at 2 years were 67% and 56%; relapse incidence (RI) and non-relapse mortality (NRM) were 39% and 5%, respectively. TCP-ALL was associated with lower RI (41% vs. 56%, p=0.001), higher LFS (52% vs. 38%, p=0.002) and OS (58% vs 45%, p=0.001) at 5 years when compared to BCP-ALL. In the multivariate analysis, TCP-ALL and longer interval from diagnosis do AHSCT were associated with reduced risk of relapse (HR 0.7, p=0.006 and HR=0.95, p=0.018), better LFS (HR=0.76, p=0.02 and HR=0.95, p=0.01) and OS (HR=0.75, p=0.024 and HR=0.94, p=0.013, respectively). Increasing patient age was associated with higher NRM (HR=1.49, p<0.0001), worse LFS (HR=1.1, p=0.01) and OS (HR=1.17, p=0.0001).

Conclusions Autologous hematopoietic stem cell transplantation is relatively safe option of late treatment intensification in adults with Ph- ALL. It may be a valuable option especially in patients with TCP-ALL, however it should be proved in prospective clinical trials.

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Keywords Autologous stem cell transplantation, Philadelphia negative acute lymphoblastic leukemia, Complete remission

Background

The role of autologous hematopoietic stem cell transplantation (AHSCT) in adults with acute lymphoblastic leukemia (ALL) remains controversial. Based on the report from the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT), there is a considerable trend towards a decrease in the number of AHSCTs in ALL patients, especially among those with Philadelphia negative ALL (Ph- ALL) [1]. It can be explained by results of several prospective studies conducted mainly during the last decade of the 20th century. The Dutch-Belgian HOVON Group randomized patients according to availability of a matched sibling donor [2]. The authors showed improved leukemia-free survival (LFS) for those with a donor receiving allo-HSCT compared to non-donor recipients of AHSCT. Results of three prospective randomized trials and an individual patient data meta-analysis showed no advantage of AHSCT over conventional-dose chemotherapy, used as consolidation and maintenance [3–6]. Finally, the results of the MRC UKALL XII/ECOG E2993 trial revealed the superiority of chemotherapy over AHSCT used instead of consolidation in a standard-risk ALL population [7]. It should be stressed, however, that all prospective studies addressing the role of AHSCT in adults with ALL were performed before the era of routine assessment of minimal residual disease (MRD), and response at MRD level is now considered the most important prognostic factor [8]. Furthermore, as demonstrated by a retrospective analysis of the European Working Group for Adult ALL, MRD status strongly affects outcomes of AHSCT suggesting that the procedure should be restricted to patients in complete remission (CR) with MRD-negativity [9]. In a previous study we compared outcomes of AHSCT and allo-HSCT after reduced-intensity conditioning for ALL patients aged 55 years or older. No significant differences were observed between the study groups with regard to LFS, overall survival (OS) and relapse incidence (RI), while AHSCT was associated with a significantly reduced risk of non-relapse mortality (NRM) [10]. However, the population included both Ph- ALL and Philadelphia positive ALL (Ph+ ALL), while the treatment of these disease subtypes differs substantially. Reports on AHSCT in Ph+ ALL suggest marked improvement of outcomes in the era of tyrosine kinase inhibitors [11]. Results of AHSCT for Ph+ ALL appear comparable to allo-HSCT for patients treated in complete molecular remission [12, 13]. In contrast, data on the use of AHSCT for adults with Ph- ALL in the modern era are scarce. Moreover, there is no evidence for the difference in transplant outcomes after AHSCT between B-cell precursor (BCP)-ALL and T-cell precursor (TCP)-ALL. Therefore, the aim of our study was to analyze current results of AHSCT in this population and to identify prognostic factors.

Methods

Study design and data collection

Data to this retrospective analysis was provided by the registry of the ALWP of the EBMT. The EBMT include more than 600 centres, mainly in Europe, which report all consecutive stem cell transplantations and follow-up once a year. All patients reported to the registry have provided informed consent for the use of their personal data for research purposes. Data collected in a central database are subject to quality control including cross-checking with the national registries and on-site control visits. The study was approved by the ALWP of the EBMT institutional review board and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Criteria for selection

We enrolled all patients from the EBMT registry who met the following inclusion criteria: 1) diagnosis of Ph- ALL, both BCP-ALL and TCP-ALL, 2) age $\geq$ 18 years 3) first AHSCT in first CR (CR1) between 1999 and 2020. Transplantations from both peripheral blood and bone marrow as a source of stem cells were allowed.

Statistical analysis

The study endpoints were LFS, OS, RI and NRM. OS was defined as time to death from any cause. LFS was defined as survival with no evidence of relapse or progression. NRM was defined as death from any cause without previous relapse or progression [14]. All events were measured from the time of transplantation. Median, minimum, and maximum values were used for quantitative data; frequencies, and percentages for categorical data [14]. Patients, disease and treatment characteristics were compared between BCP- and TCP-ALL patients. The continuous data were compared using the Mann-Whitney or Kruskal-Wallis test, while the categorical data were compared with the chi-squared or Fisher's exact test. Kaplan-Meier estimate was used to calculate the probabilities

of OS and LFS. The probabilities of RI and NRM were estimated using cumulative incidence curves. Univariate analyses were performed with the log-rank test for LFS and OS. The Gray's test was used to compare cumulative incidence estimates. Multivariate analysis was performed using a Cox proportional-hazards model which included variables differing significantly ($p< 0.05$) between the groups, factors known to be associated with outcomes plus a centre frailty effect to take into account the heterogeneity across centres. All tests were two-sided with a type I error rate fixed at 0.05 [14]. Statistical analyses were performed with SPSS 25.0 (IBM Corp., Armonk, NY, USA) and R 4.2.3 (R Core Team (2023). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Results

Patients and transplant procedure characteristics

In total, 700 patients met the inclusion criteria, 247 (35.3%) patients with BCP-ALL and 453 (64.7%) patients with TCP-ALL. The median follow-up was 129 and 79 months, respectively in the BCP- and TCP-ALL group ($p= 0.002$). The median year of transplantation was 2005 in both groups. Among 190 patients with available data, negative MRD status at AHSCT was reported in 167 (87.9%) cases. The patients diagnosed with BCP-ALL were older than those with TCP-ALL (40.9 years vs. 31.9 years, $p< 0.001$). There were more female patients in the BCP-ALL than in the TCP-ALL group (42.9% vs. 25.4%, $p< 0.001$). Karnofsky score below 90 was observed more frequently in BCP-ALL patients (35.4% vs. 17.8%, $p< 0.001$). There were no differences between BCP- and TCP-ALL group in relation to the median WBC count (88 x 10^9/L vs. 96.5 x 10^9/L, $p= 0.092$) and karyotype at diagnosis (normal karyotype was observed in 51.6% vs. 59.9%, respectively, $p= 0.1$). The median time from diagnosis to AHSCT and MRD status at transplantation did not differ between studied groups (6.5 vs. 6.6 months and positive MRD in 14.6% vs. 10.2%, respectively in the BCP- and TCP-ALL group, $p= 0.21$ and $p= 0.35$, respectively). The main stem cells source used for transplantation was peripheral blood in both studied groups (92.7% vs. 93.1%, respectively in BCP- and TCP-ALL patients, $p= 0.83$). Chemotherapy-based conditioning was used in 60.3% and 54.5% of patients, respectively in BCP- and TCP-ALL group ($p= 0.14$). Graft failure was observed in 1 (0.4%) BCP-ALL patient and in 8 (1.8%) TCP-ALL patients ($p= 0.13$). The patients and transplant characteristics of BCP- and TCP-ALL group is shown in Table 1.

Outcomes in the whole study population

The probabilities of OS, LFS, RI and NRM for the whole population at 2-, 5- and 10-year follow-up are shown in Table 2 and Fig. 1. In total, 292 (41.7%) patients died during the follow-up. The most frequent causes of death were original disease (65.8%) and infections (12.6%).

In the univariate analysis, TCP-ALL was associated with lower RI (41.1% vs. 56.1%, $p= 0.001$) and higher LFS (51.7% vs. 37.5%, $p= 0.002$) and OS (58.3% vs. 45.1%, $p= 0.001$) at 5 years when compared to BCP-ALL (Fig. 2). Older patient age (> 32 years) was associated with increased NRM (9.4% vs. 4.5%, $p= 0.006$) and decreased LFS (41.9% vs. 50.8%, $p= 0.019$) and OS (47.6% vs 58.9%. $p= 0.001$). Higher NRM was also observed in patients after chemotherapy-based conditioning when compared to those transplanted after TBI (8.8% vs. 4.5%, $p= 0.047$). The univariate analysis for the whole population is shown in Table 3. In the multivariate analysis, patients with TCP-ALL had lower risk of relapse (HR 0.7, 95% CI 0.54–0.9, $p= 0.006$), better LFS (HR 0.76, 95% CI 0.61–0.96, $p= 0.023$) and OS (HR 0.75, 95% CI 0.58–0.96, $p= 0.024$) when compared to BCP-ALL patients. Older patient age (per 10 years) was associated with higher NRM (HR 1.49, 95% CI 1.23–1.79, $p< 0.001$), lower LFS (HR 1.1, 95% CI 1.02–1.19, $p= 0.01$) and OS (HR 1.17, 95% CI 1.08–1.28, $p< 0.001$). Longer time from diagnosis to AHSCT (per month) was associated with lower risk of relapse (HR 0.95, 95% CI 0.9–0.99, $p= 0.018$), better LFS (HR 0.95, 95% CI 0.91–0.99, $p= 0.01$) and OS (HR 0.94, 95% CI 0.9–0.99, $p= 0.013$). The multivariate analysis was shown in Table 4.

Outcomes in the BCP-ALL patients

In the group of BCP-ALL patients, 5-year OS was worse in patients older than 32 years (39.6% vs. 53.6%, $p= 0.031$). There were no significant differences in transplant outcomes between patients treated with chemotherapy- and TBI-based conditioning. There was a trend towards better LFS in patients transplanted between 1999 - 2009 than in the period of 2010 - 2020 (40.4% vs. 25.4%, $p= 0.08$). Patients transplanted at least 6 months from diagnosis tended to have better 5-year OS than those transplanted before that time (52.6% vs. 39.2%, $p= 0.08$). The univariate analysis in the BCP-ALL patients was shown in Table 5.

Outcomes in the TCP-ALL patients

In the group of TCP-ALL patients, older age (above 32 years) was associated with higher NRM (9,7% vs. 5.3%, $p= 0.017$) and a tendency towards worse 5-year OS (54.4% vs 61.4%, $p= 0.053$) when compared to younger patients. Patients treated with chemotherapy-based conditioning before AHSCT had higher NRM (10.3%

Table 1 Patient and transplant-related characteristics of BCP- and TCP-ALL

	BCP-ALL (*n*=247)	TCP-ALL (*n*=453)	*P* value
Median follow-up (months) [95% CI]	129.3 [97.1–156]	79.4 [68.3–89.7]	0.002
Patient age (years; min-max)	40.9 (18.1–75.8)	31.9 (18.1–75.8)	< 0.001
Median year of AHSCT (IQR)	2005 (2002 - 2011)	2005 (2002 - 2011)	0.64
Median time from diagnosis to AHSCT (months; min-max)	6.5 (2.6–23.6)	6.6 (2.2–23.6)	0.21
Karnofsky performance status score:			
• < 90	40 (35.4%)	38 (17.8%)	< 0.001
• >= 90	73 (64.6%)	175 (82.2%)	
• missing	134	240	
MRD pre AHSCT:			
• MRD negative	70 (85.4%)	97 (89.8%)	0.35
• MRD positive	12 (14.6%)	11 (10.2%)	
• missing	165	345	
Median WBC at diagnosis (G/L; min-max)	88 (1–184)	96.5 (1–186)	0.092
Patient sex:			
• Male	141 (57.1%)	338 (74.6%)	< 0.001
• Female	106 (42.9%)	115 (25.4%)	
Cells source			
• BM	18 (7.3%)	31 (6.9%)	0.83
• PB	229 (92.7%)	421 (93.1%)	
• Missing	0	1	
Karyotype:			
• Normal	115 (51.6%)	103 (59.9%)	0.1
• Abnormal	108 (48.4%)	69 (40.1%)	
• Not done/Failed	24	281	
Conditioning:			
• TBI-based	98 (39.7%)	206 (45.5%)	0.14
• CT-based	149 (60.3%)	247 (54.5%)	
Dose of TBI (Gy)			
• 8–10	12 (12.9%)	16 (11.9%)	0.86
• 12	72 (77.4%)	103 (76.3%)	
• 13–14	9 (9.7%)	16 (11.9%)	
• Missing	154	318	
Engraftment:			
• Graft failure	1 (0.4%)	8 (1.8%)	0.13
• Engrafted	239 (99.6%)	442 (98.2%)	
• Missing	7	3	

AHSCT autologous hematopoietic stem cell transplantation, *ALL* acute lymphoblastic leukemia, *BCP-ALL* B-cell precursor ALL, *TCP-ALL* T-cell precursor ALL, *MRD* minimal residual disease, *WBC* white blood cell, *BM* bone marrow, *PB* peripheral blood, *TBI* total body irradiation, *CT* chemotherapy, *IQR* interquartile range, *min* minimum, *max* maximum, *CI* confidence interval

vs. 3.8%, p= 0.029) than those transplanted after TBI-based conditioning. No other differences in transplant outcomes were observed in relation to year of AHSCT (1999-2009 vs. 2010-2020), patients sex, Karnofsky score and time from diagnosis to AHSCT (Table 6).

Discussion

In this study we analyzed the results of AHSCT conducted in Ph- ALL patients between 1999 and 2020. We found that BCP-ALL, older age and short time from diagnosis to AHSCT are risk factors for poor transplant outcomes. To our best knowledge this is the first large multicenter study evaluating AHSCT in this subpopulation of ALL patients.

Table 2 Outcome probabilities for the whole population

	2 years	5 years	10 years
OS (95% CI)	66.8% (62.8 - 70.4)	53.3% (49 - 57.3)	48.7% (44.2 - 52.9)
LFS (95% CI)	56% (51.9 - 59.8)	46.3% (42.2 - 50.3)	42% (37.8 - 46.1)
RI (95% CI)	39.3% (35.4 - 43.1)	46.8% (42.7 - 50.7)	48.9% (44.7 - 53)
NRM (95% CI)	4.8% (3.3 - 6.6)	6.9% (5 - 9.2)	9.1% (6.8 - 11.8)

OS overall survival, *LFS* leukemia-free survival, *RI* relapse incidence, *NRM* non-relapse mortality, *CI* confidence interval

Data on AHSCT in Ph- ALL patients are very limited and no consensus regarding the role of AHSCT in this population has been achieved so far. According to recommendations of the American Society for Transplantation and Cellular Therapy, AHSCT is not recommended for Ph- ALL patients [15]. According to the EBMT guidelines, AHSCT is not considered a standard therapy but may be an option for patients with MRD-negative standard-risk ALL in CR1, not eligible for allo-HSCT [16, 17]. In the largest prospective MRC UKALL XII/ECOG E2993 Trial conducted between 1993 and 2006, patients with ALL having a matched sibling donor received an allo-HSCT, while those without such donors received either chemotherapy-based consolidation and maintenance or AHSCT (instead of consolidation) [7]. Allo-HSCT was found to be superior to other options in standard-risk patients in terms of OS. Moreover, among patients randomized to chemotherapy or AHSCT,

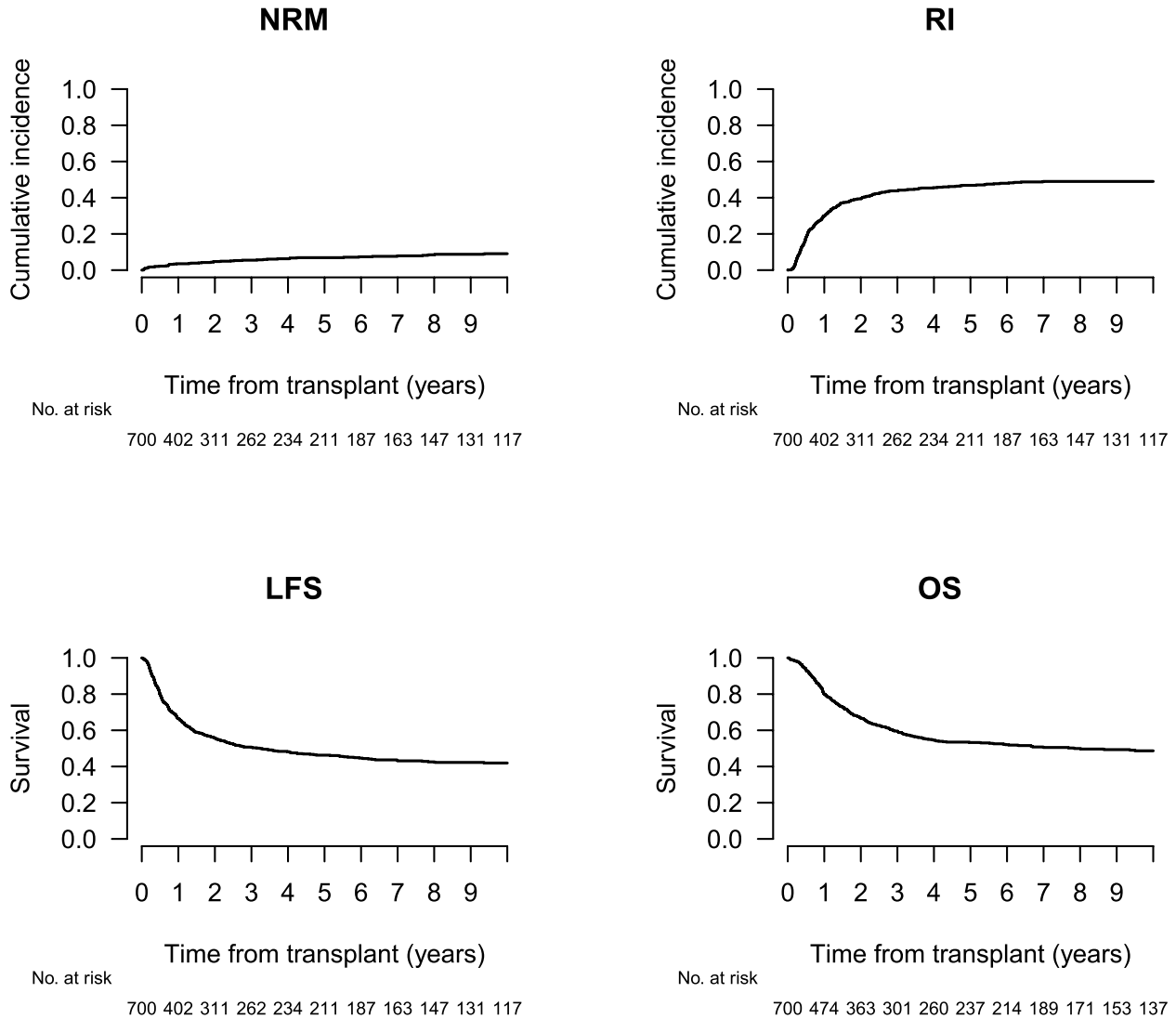

Fig. 1 Transplant outcomes in the whole population. NRM – non-relapse mortality; RI – relapse incidence; LFS – leukemia-free survival; OS – overall survival

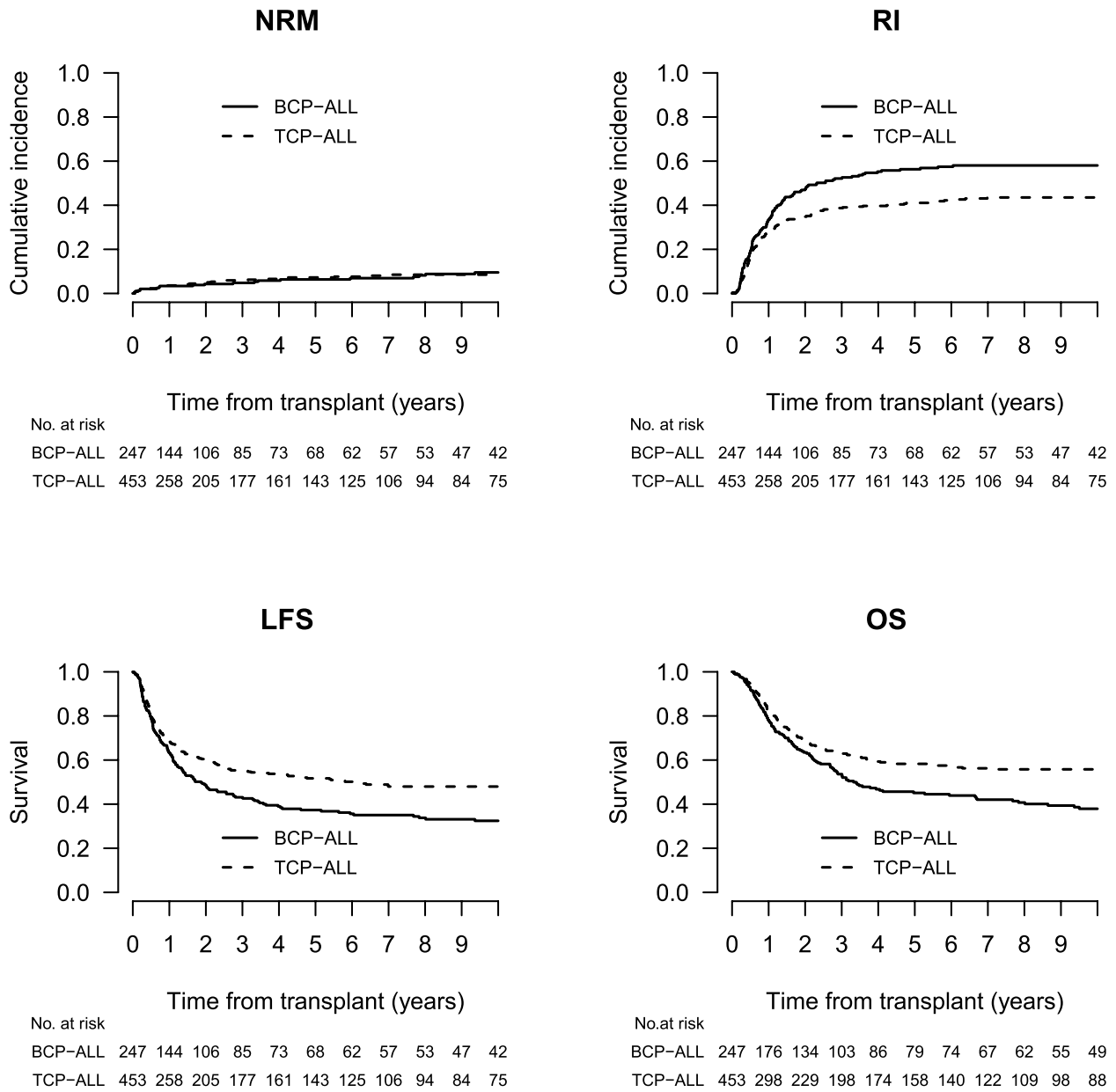

Fig. 2 Transplant outcomes in BCP- and TCP-ALL patients. NRM – non-relapse mortality; RI – relapse incidence; LFS – leukemia-free survival; OS – overall survival

who were mainly diagnosed with Ph- ALL, the authors showed better 5-year event-free survival (EFS) and OS in those treated with conventional-dose chemotherapy when compared to patients treated with AHSCT (41% vs. 32%, p= 0.02 and 46% vs. 37%, p= 0.03, respectively) [7]. In this study we showed markedly better outcomes after AHSCT, compared to the MRC UKALL XII/ECOG E2993 Trial with 5-year LFS and OS rates of 46.3% and 53.3%, respectively. The difference in AHSCT outcomes may result from both the selection of patients whose leukemia was deeply controlled and the improvement in the management of patients post AHSCT over the last decades. Although data on MRD were available in only a minority of patients, it may be hypothesized that in the 21st century, MRD status was considered for selection of patients more frequently than in the preceding period. Nevertheless, in this analysis we did not compare results of AHSCT to chemotherapy without transplantation as a late treatment intensification in the studied group. However, it would be warranted to determine the actual

Table 3 Univariate analysis for the whole population

	5 years			
	RI [95% CI]	**NRM [95% CI]**	**LFS [95% CI]**	**OS [95% CI]**
Year of AHSCT				
• 1999 - 2009	47% [42.4–51.6]	6.3% [4.3–8.8]	46.6% [42–51.1]	53.6% [48.8–58.1]
• 2010 - 2020	46.1% [37.2–54.5]	9.8% [5–16.4]	44.1% [34.9–52.9]	50.7% [40.7–59.9]
P value	0.67	0.3	0.97	0.91
ALL subtype:				
• BCP-ALL	56.1% [49.3–62.5]	6.4% [3.6–10.2]	37.5% [31–43.9]	45.1% [38.2–51.7]
• TCP-ALL	41.1% [36–46]	7.2% [4.9–10.2]	51.7% [46.4–56.7]	58.3% [52.9–63.3]
P value	0.001	0.81	0.002	0.001
Patient age (years)				
• 18–32	44.7% [38.9–50.3]	4.5% [2.5–7.3]	50.8% [44.9–56.4]	58.9% [52.9–64.5]
• 32+	48.8% [42.9–54.3]	9.4% [6.4–13]	41.9% [36.1–47.5]	47.6% [41.6–53.4]
P value	0.38	0.006	0.019	0.001
Patient sex				
• Male	46.7% [41.8–51.5]	6.4% [4.3–9.1]	46.8% [41.9–51.6]	54.5% [49.4–59.3]
• Female	47.1% [39.7–54.2]	8.3% [4.7–13.1]	44.6% [37.1–51.8]	49.8% [41.9–57.2]
P value	0.94	0.87	0.79	0.75
Conditioning:				
• CT-based	47.2% [41.7–52.5]	8.8% [6–12.2]	44% [38.5–49.3]	50.1% [44.4–55.6]
• TBI-based	46.2% [40–52.2]	4.5% [2.4–7.5]	49.3% [43.1–55.3]	57.4% [50.9–63.3]
P value	0.98	0.047	0.33	0.24
Time from diagnosis to AHSCT				
• <median (6.6 months)	48.8% [43.1–54.2]	6.7% [4.2–9.8]	44.6% [39–50]	51% [45.2–56.5]
• >=median	44.5% [38.5–50.3]	7.2% [4.5–10.8]	48.2% [42.1–54.1]	55.8% [49.4–61.7]
P value	0.3	0.97	0.3	0.29
Karnofsky score				
< 90	48.1% [35.1–60]	6.4% [2–14.7]	45.4% [32.6–57.4]	50.8% [37.3–62.8]
>= 90	42.4% [35.1–49.4]	9.8% [6–14.8]	47.8% [40.2–55]	55% [46.9–62.4]
P value	0.56	0.34	0.91	0.7

RI relapse incidence, *NRM* non-relapse mortality, *LFS* leukemia-free survival, *OS* overall survival, *AHSCT* autologous hematopoietic stem cell transplantation, *ALL* acute lymphoblastic leukemia, *BCP-ALL* B-cell precursor ALL, *TCP-ALL* T-cell precursor ALL, *CT* chemotherapy, *TBI* total body irradiation, *CI* confidence interval

Table 4 Multivariate analysis in the whole population

	RI		**NRM**		**LFS**		**OS**	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Year of AHSCT	1 (0.98–1.03)	0.94	1 (0.94–1.06)	0.99	1 (0.98–1.02)	0.85	1 (0.97–1.02)	0.72
TCP-ALL vs. BCP-ALL	0.7 (0.54–0.9)	0.006	1.26 (0.7–2.26)	0.45	0.76 (0.61–0.96)	0.023	0.75 (0.58–0.96)	0.024
Age (per 10 years)	1.05 (0.96–1.14)	0.3	1.49 (1.23–1.79)	< 0.0001	1.1 (1.02–1.19)	0.011	1.17 (1.08–1.28)	0.0001
Female vs. male patient	0.89 (0.69–1.16)	0.39	0.84 (0.46–1.53)	0.57	0.88 (0.69–1.11)	0.28	0.91 (0.71–1.18)	0.49
TBI- vs. CT-based conditioning	0.96 (0.72–1.27)	0.77	0.6 (0.31–1.13)	0.11	0.9 (0.7–1.17)	0.44	0.92 (0.7–1.21)	0.55
Time from diagnosis to AHSCT (per month)	0.95 (0.9–0.99)	0.018	0.95 (0.86–1.05)	0.35	0.95 (0.91–0.99)	0.01	0.94 (0.9–0.99)	0.013

RI relapse incidence, *NRM* non-relapse mortality, *LFS* leukemia-free survival, *OS* overall survival, *ALL* acute lymphoblastic leukemia, *BCP-ALL* B-cell precursor ALL, *TCP-ALL* T-cell precursor ALL, *TBI* total body irradiation, *CT* chemotherapy, *AHSCT* autologous hematopoietic stem cell transplantation, *HR* hazard ratio, *CI* confidence interval, *vs.* versus

Table 5 Univariate analysis in the BCP-ALL patients

	5 years			
	RI [95% CI]	**NRM [95% CI]**	**LFS [95% CI]**	**OS [95% CI]**
Year of AHSCT				
• 1999 - 2009	53.8% [46–60.9]	5.8% [3–10]	40.4% [33–47.6]	46.6% [38.9–53.9]
• 2010 - 2020	65.9% [47.6–79.1]	8.7% [2.4–20.2]	25.4% [12.4–40.6]	38.7% [22–55.1]
P value	0.15	0.55	0.08	0.33
Patient age (years)				
• 18–32	55.8% [44.5–65.7]	2.4% [0.4–7.6]	41.8% [31.2–52]	53.6% [42.3–63.6]
• 32+	56% [47.1–63.9]	9% [4.8–14.7]	35% [27–43.2]	39.6% [30.9–48.1]
P value	0.86	0.12	0.26	0.031
Patient sex				
• Male	56.5% [47.4–64.7]	6.9% [3.4–12.1]	36.6% [28.3–45]	45.1% [36.1–53.7]
• Female	55.1% [44.3–64.5]	6% [2.2–12.7]	38.9% [28.9–48.8]	44.8% [34–55.1]
P value	0.89	0.33	0.67	0.51
Conditioning:				
• CT-based	55% [46.2–63]	6.7% [3.3–11.8]	38.2% [30–46.4]	45% [36.4–53.3]
• TBI-based	57.9% [46.4–67.7]	5.8% [2.1–12.3]	36.3% [26.1–46.6]	45.4% [34–56.1]
P value	0.78	0.65	0.92	0.97
Time from diagnosis to AHSCT				
• <median (6.6 months)	58% [48.7–66.2]	5.7% [2.5–10.8]	36.3% [27.9–44.8]	39.2% [30.4–47.8]
• >=median	54.6% [43.8–64.1]	7.4% [3.2–13.9]	38.1% [28.1–47.9]	52.6% [41.6–62.5]
P value	0.4	0.92	0.39	0.08
Karnofsky score				
< 90	60.6% [41.3–75.2]	8.1% [2–19.9]	31.3% [16.5–47.3]	38.2% [21.9–54.3]
>= 90	53.3% [39.8–65.1]	12% [5.1–21.9]	34.7% [22.9–46.9]	42.5% [28.9–55.4]
P value	0.72	0.74	0.78	0.76

RI relapse incidence, *NRM* non-relapse mortality, *LFS* leukemia-free survival, *OS* overall survival, *AHSCT* autologous hematopoietic stem cell transplantation, *ALL* acute lymphoblastic leukemia, *BCP-ALL* B-cell precursor ALL, *TCP-ALL* T-cell precursor ALL, *CT* chemotherapy, *TBI* total body irradiation, *CI* confidence interval

role of AHSCT in the present high-intensity chemotherapy era. Encouraging outcomes after AHSCT have also recently been reported in a Chinese single center study including 89% patients with Ph- ALL [18]. LFS and OS rates at 5 years were 59%. Moreover, the authors highlighted the significant role of MRD in the choice of treatment option for ALL patients suggesting patients with MRD-negativity to be the best candidates for AHSCT [18]. In another retrospective analysis of 155 Ph- ALL patients from Japanese database, the authors showed a 10-year OS rate of 41% after AHSCT with a long-term survival plateau, which was similar to OS in patients after HLA mismatched allo-HSCT but lower compared to matched allo-HSCT recipients [19]. AHSCT was associated with lower NRM and higher RI at 4 years when compared to allo-HSCT (9% vs. 16%, $p= 0.04$, 46% vs. 23%, $p< 0.01$, respectively) [19]. Those data are similar to our results in regard to 10-year OS (48.7%) and 5-year transplant outcomes (NRM 6.9%, RI 46.8%).

MRD is considered one of the most important prognostic determinants of post-transplant outcomes in ALL patients [20, 21]. The minimum MRD threshold of 0.01% has been established to distinguish positive from negative MRD before transplantation. However, more precise methods including next-generation sequencing have been used more and more in many centers enabling detection of one leukemic cell per 1 million nucleated cells [22–24]. Moreover, post-transplant MRD was also shown to be a prognostic factor for relapse after transplantation regardless of MRD status before allo-HSCT, indicating the role of regular MRD monitoring after transplantation [24]. Based on a large retrospective study from the EBMT registry, ALL patients with negative MRD before allo-HSCT had lower RI and better LFS and OS [20]. The role of MRD before AHSCT in ALL patients has not been investigated as much as before allo-HSCT. However, in a study from the European LeukemiaNet restricted to Ph- ALL, the authors showed significantly better LFS at 5 years for patients with pre-AHSCT MRD-negative status when compared to MRD-positive status (57% vs. 17%, $p= 0.0002$) [9]. The difference achieved statistical significance in TCP-ALL subgroup (62% vs.

Table 6 Univariate analysis in the TCP-ALL patients

	5 years			
	RI [95% CI]	**NRM [95% CI]**	**LFS [95% CI]**	**OS [95% CI]**
Year of AHSCT				
• 1999 - 2009	42.8% [37–48.5]	6.6% [4.1–9.9]	50.5% [44.5–56.2]	58.1% [52–63.7]
• 2010 - 2020	36.1% [26–46.4]	10.2% [4.4–18.7]	53.7% [41.9–64.1]	56.7% [44.2–67.4]
P value	0.16	0.37	0.29	0.57
Patient age (years)				
• 18–32	39.8% [33.1–46.3]	5.3% [2.8–9]	54.9% [47.9–61.4]	61.4%[54.2–67.9]
• 32+	42.6% [34.8–50.1]	9.7% [5.7–14.9]	47.7% [39.8–55.3]	54.4% [46.1–61.9]
P value	0.71	0.017	0.11	0.053
Patient sex				
• Male	42.1% [36.2–47.8]	6.2% [3.8–9.4]	51.7% [45.7–57.4]	59% [52.8–64.6]
• Female	39% [28.8–49]	10.6% [5.1–18.4]	50.4% [39.3–60.4]	55.1% [43.5–65.2]
P value	0.35	0.43	0.52	0.76
Conditioning:				
• CT-based	41.7% [34.7–48.5]	10.3% [6.5–15.2]	48% [40.7–54.9]	53.8% [46.2–60.8]
• TBI-based	40.4% [33.1–47.6]	3.8% [1.7–7.4]	55.7% [48–62.7]	63.1% [55.2–69.9]
P value	0.91	0.029	0.33	0.27
Time from diagnosis to AHSCT				
• <median (6.6 months)	42.9% [35.8–49.8]	7.3% [4.2–11.6]	49.8% [42.5–56.7]	58.9%[51.4–65.7]
• >=median	38.8% [31.7–45.8]	7.1% [3.9–11.6]	54.1% [46.5–61.1]	57.7% [49.7–64.8]
P value	0.52	0.98	0.55	0.88
Karnofsky score				
< 90	33.4% [17.1–50.6]	4.8%[0.3–20.4]	61.8% [41.2–77.1]	66.4% [44.8–81.2]
>= 90	37.3% [28.7–45.8]	8.6% [4.5–14.5]	54.1% [44.7–62.5]	61% [51.1–69.5]
P value	0.68	0.26	0.32	0.47

RI relapse incidence, *NRM* non-relapse mortality, *LFS* leukemia-free survival, *OS* overall survival, *AHSCT* autologous hematopoietic stem cell transplantation, *ALL* acute lymphoblastic leukemia, *BCP-ALL* B-cell precursor ALL, *TCP-ALL* T-cell precursor ALL, *CT* chemotherapy, *TBI* total body irradiation, *CI* confidence interval

8%, p= 0.0001), while a tendency was shown in BCP-ALL subjects (54% vs. 26%, p= 0.17) [9]. In our study, a median time from diagnosis to AHSCT was 6.6 months and was markedly longer than in the MRC UKALL XII/ECOG E2993 Trial [7]. This means that AHSCT was considered rather as a late intensification following regular induction and conventional-dose consolidation. Furthermore, longer time from diagnosis to AHSCT was associated with lower risk of RI and better LFS and OS. This may suggest that intensive preceding chemotherapy is important to achieve optimal disease response and contributes to improved outcome of AHSCT. On the other hand, the observed better outcomes in patients with a longer interval from diagnosis to AHSCT could be attributed to the fact that AHSCT was performed in patients who did not relapse for an extended period and thus the necessity of further treatment intensification in such patients may be uncertain. Myeloablative conditioning is the most important component of the AHSCT procedure. In our study we observed higher NRM in patients after chemotherapy-based conditioning than in the group of TBI-based therapy. The difference was observed both in the whole population (8.8% vs. 4.5%, p= 0.047) and in the TCP-ALL patients (10.3% vs. 3.8%, p= 0.029), but not in the BCP-ALL group. Moreover, we did not show significant differences between patients transplanted after chemotherapy- or TBI-based conditioning in relation to other transplant outcomes, which is contrary to results of several prospective and retrospective studies showing superiority of TBI over chemotherapy among recipients of allo-HSCT [20, 25–27]. Also, in a Japanese study on AHSCT for Ph- ALL the use of TBI was associated with reduced RI and improved OS rates [19]. The lack of positive effect of TBI on main transplant outcomes observed in our study could be a consequence of bias in patient selection according to which TBI may have been used for patients being at a higher risk of relapse.

A number of new therapeutic options dedicated to Ph- BCP-ALL patients over the last decade, such as blinatumomab, inotuzumab ozogamicin, or chimeric antigen receptor T cells (CAR-T cells) have been introduced during the last decade. Blinatumomab, a bispecific

monoclonal antibody construct engaging CD3-positive cytotoxic T-cells against CD19-positive B-cells, was shown to be more effective than chemotherapy in advanced ALL [28] and was able to eradicate MRD in 78% of ALL patients being in ≥CR1 [29]. Similarly, inotuzumab ozogamicin, an anti-CD22 antibody conjugated to calicheamicin, was shown to be superior to standard intensive chemotherapy in relapsed/refractory ALL in relation to the rate of CR and eradication of MRD [30]. Moreover, blinatumomab and inotuzumab have been intensively investigated as a frontline therapy in Ph- ALL patients showing encouraging results with high rates of CR with negative MRD, especially in older patients [26, 31–33]. The role of AHSCT in this new therapeutic landscape appears uncertain. In contrast, patients with TCP-ALL still represent an unmet need as no modern immunotherapeutic agents have been approved in this disease subtype. Patients defined as high-risk are preferentially candidates for allo-HSCT. Those with standard-risk disease and negative MRD status could potentially benefit from treatment intensification i.e., high dose therapy supported by AHSCT. Indeed, results of our study demonstrate better outcome after AHSCT for TCP-ALL than BCP-ALL with acceptable long-term LFS of 52% and OS of 58% for the former. This finding may partly results from selection bias connected with retrospective analyses. In our study, patients with BCP-ALL were older and had lower Karnofsky performance score than patients diagnosed with TCP-ALL. Moreover, BCP-ALL patients accounted for only 35% of the whole study population, which could also affect these results. Regardless, TCP-ALL seems to be more dependent on treatment intensity than BCP-ALL. Indirect evidence for this is provided by the meta-analysis of five randomised trials evaluating the prophylactic use of granulocyte-colony stimulating factor (G-CSF) during remission induction given with intention to maintain treatment intensity. In TCP-ALL, but not in BCP-ALL the use of G-CSF was associated with significantly improved 5-year OS and LFS [34]. However, it should be stressed that the current treatment of adult ALL patients is based on the pediatric-inspired regimens which show very similar outcomes in TCP- and BCP-ALL with 3-year disease free survival of 65% in patients with TCP-ALL [35]. Therefore, results of this study should be taken with caution and prospective trials comparing AHSCT and intensive chemotherapy in the group of standard risk ALL are needed. The results of our study are also in line with previous report by the Russian Federation ALL study group showing excellent outcomes for TCP-ALL patients treated with regular induction-consolidation chemotherapy followed by AHSCT [36]. However, taking into account the new drugs being now commonly available especially for BCP-ALL patients, the difference in transplant outcomes stratified with ALL phenotype should be taken with caution.

This study has some limitations resulting from its retrospective nature. Missing data on pre-transplant MRD status, precise genetic characteristics including karyotype as well as details on preceding chemotherapy appear the most important obstacle to identify patients who are most likely to benefit from AHSCT. The distribution of missing data in BCP- and TCP-ALL was uneven, which makes full interpretation difficult. Moreover, probable selection bias connected with different national recommendations and centres policy might affect the results of this analysis. The lack of data on maintenance therapy, which is used in many centres after AHSCT is another limitation of this study.

Conclusions

Autologous hematopoietic stem cell transplantation is relatively safe option of late treatment intensification in adults with Ph- ALL. The target population should rather be restricted to patients defined as standard risk, particularly, those with negative MRD status. AHSCT may be a valuable option especially in patients with TCP-ALL, however it should be proved in prospective clinical trials.

Abbreviations

AHSCT	Autologous hematopoietic stem cell transplantation
ALL	Acute lymphoblastic leukemia
ALWP	Acute Leukemia Working Party
EBMT	European Society for Blood and Marrow Transplantation
Ph- ALL	Philadelphia negative acute lymphoblastic leukemia
LFS	Leukemia-free survival
MRD	Minimal residual disease
CR	Complete remission
OS	Overall survival
RI	Relapse incidence
NRM	Non-relapse mortality
Ph+ ALL	Philadelphia positive acute lymphoblastic leukemia
BCP	B-cell precursor
TCP	T-cell precursor
CR1	First complete remission
TBI	Total body irradiation
HR	Hazard ratio
CI	Confidence interval
EFS	Event-free survival
CAR-T cells	Chimeric antigen receptor T cells

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Authors' contributions

RS and SG interpreted the data and wrote the manuscript. SG designed the study. ML performed the statistical analyses. MM, AN and FC interpreted the data and edited the manuscript. JM, EP, JV, JP, AK, SC, LR, AR, DC, FF, DN, MO, MA, MTR, NCG, FL reviewed the manuscript and provided clinical data. All authors approved the final version of the manuscript.

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

Declarations

Ethics approval and consent to participate
The study was approved by the ALWP of the EBMT institutional review board and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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