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Improved outcomes over time in patients aged ≥60 years undergoing allogeneic hematopoietic cell transplantation for acute lymphoblastic leukemia in first complete remission: a large study by the EBMT acute leukemia working party

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Allogeneic hematopoietic cell transplantation remains an important curative treatment for patients with acute lymphoblastic leukemia (ALL). Over time, significant progress in transplant and post-transplant care has allowed the delivery of transplant to older patients. We assessed changes over time in characteristics and outcomes in patients ≥60 years with ALL using a dataset from the EBMT registry. We identified 832 adult patients, with T-cell ALL ($n = 143$), Philadelphia chromosome positive B-cell ALL ($n = 471$), or Philadelphia chromosome negative B-cell ALL, transplanted 2010–2022 in first remission irrespective of the donor type. Those included 280 patients transplanted in 2010–2015, and 552 patients transplanted in 2016–2022. Patients transplanted in recent years were slightly older, more likely to have T or Ph- B-ALL and to receive a myeloablative total body irradiation conditioning. The 2-year leukemia free survival (LFS) and overall survival (OS) increased over time from 42–55% and from 51–65%, respectively. In multivariate analysis, LFS, OS, chronic and extensive chronic graft-versus-host disease rates were better in recent years (hazard ratio[HR] 0.68, 0.71, 0.66 and 0.5, respectively). These real-world data can serve as a benchmark indicating that the opportunity for transplant for the fit elderly should be considered and offered when possible.

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INTRODUCTION

In contrast to pediatric patients who have excellent cure rates (exceeding 90%), adult patients diagnosed with acute lymphoblastic leukemia (ALL) have generally been characterized by poor outcomes with variable cure rates depending on treatment used, previously reported to be less than 40% [1–3]. The worse outcome noted for older patients with ALL is likely related to the increased prevalence of adverse-risk cytogenetics and molecular abnormalities as compared to the pediatric population, but also to the inability of delivering intensive therapies to less fit patients [4]. Despite the significant improvement recently noted with the introduction of novel therapies including tyrosine kinase inhibitors [5], bispecific antibodies [4, 6–8], antibody-drug conjugates [9] and chimeric antigen receptor (CAR)-T cell therapies [10, 11] among others, and their incorporation in the treatment of newly diagnosed as well as relapsed ALL patients older than 60 years, they remain a high risk category requiring an individualized and personalized approach to treatment. The identification of the optimal approach to management of these patients thus remains an unmet medical need. Specifically, the optimal use of allogeneic hematopoietic stem cell transplant (allo-HCT) in the treatment landscape for older patients with ALL has yet to be unraveled [12–14]. Over time, significant progress in allo-HCT has resulted in decreased non-relapse mortality (NRM) allowing the delivery of this potentially curative treatment modality to older patients. Moreover, recent data has reported a steady increase in survival of

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adult patients with relapsed Philadelphia chromosome positive (Ph+) ALL post allo-HCT with an increase in 2-year overall survival (OS) from around 28% (for those who relapsed between 2000 and 2004) to 55% (patients who relapsed during 2015–2019) [15]. However, little information is available about the global impact of the current standards of care for older ALL patients receiving allo-HCT in first remission (CR1) and the predictive factors for post-transplant outcomes [16]. To address these challenges, we assessed real-world data of post-transplant outcomes over more than a decade, reporting on changes over time in transplant characteristics and post-transplant outcomes in older patients (≥60 years) with ALL, comparing transplants performed in 2010–2015 with those performed in 2016–2022, using a large dataset from the European Society for Blood and Marrow Transplantation (EBMT) registry.

MATERIALS AND METHODS

Study design

This is a retrospective, registry-based, multicenter analysis of patients' data provided and approved by the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT). The EBMT is a voluntary working group of more than 600 transplant centers that are required to report all consecutive HCTs and follow-ups once a year. Audits are routinely performed to determine the accuracy of the data. Since January 2003, all transplant centers have been required to obtain written informed consent prior to data registration with the EBMT, following the guidelines of the Declaration of Helsinki, 1975.

We included in this analysis, patients aged ≥60 years with ALL, both Ph+ B-ALL and Philadelphia chromosome negative B-ALL (Ph- B-ALL) as well as T-cell ALL (T-ALL), who received their first allo-HCT in CR1, between 2010 and 2022, from either a matched sibling donor (MSD), matched or mismatched unrelated donor (UD), or haploidentical donor. The stem cell source was either granulocyte colony-stimulating factor mobilized peripheral blood, or bone marrow. We excluded patients with previous autologous HCT and those with ex-vivo T-cell depletion (TCD).

Variables collected included recipient and donor age at transplant, recipient and donor gender, type of ALL, year of transplant, Karnofsky performance status (KPS) score at transplant, in addition to transplant-related factors including conditioning regimen, graft-versus-host disease (GVHD) prophylaxis, the use of post-transplant cyclophosphamide (PTCy), in vivo TCD (utilizing anti-thymocyte globulin-ATG), donor type, recipient and donor cytomegalovirus status, and stem cell source.

Definitions and objectives

Myeloablative conditioning was defined as a regimen containing either total body irradiation (TBI) with a dose greater than 8 Gy, a total dose of oral busulfan greater than 8 mg/kg, or a total dose of intravenous busulfan greater than 6.4 mg/kg [17].

The primary objective of this study was to evaluate the post-transplant outcomes of older patients with ALL and their variations with time across two time periods (2016–2022 compared to 2010–2015), aiming to identify important prognostic factors for this group of patients. Non-relapse mortality (NRM) was used to define death with no evidence of disease relapse. The probability of leukemia free survival (LFS) and OS was defined as survival with no evidence of disease relapse or progression, and time to death from any cause, respectively. The diagnosis and grading of acute GVHD (aGVHD) [13] and chronic GVHD (cGVHD) [14] were performed by transplant centers using standard criteria.

Statistical analysis

Patient-, disease-, and transplant-related characteristics were compared between groups using the chi-squared test, Fisher's exact test, or the Wilcoxon rank-sum test for categorical data and the Mann-Whitney U test for continuous data. All outcomes were measured from the time of transplant. NRM was calculated using cumulative incidence curves in a competing risk setting. Death and relapse were considered competing events. When assessing the cumulative incidence of acute and cGVHD, relapse and death were considered as competing events. LFS and OS were evaluated using the Kaplan-Meier method. Univariate analyses were performed using the log-rank test for LFS and OS.

A Cox regression multivariate analysis was used for all endpoints. In order to test for a center effect, we introduced a random effect or frailty for each center into the model. All tests were two-sided with the type I error set at 0.05. All analyses were performed using SPSS 27.0 (SPSS Inc, Chicago, IL, USA) and R 4.1.1 (R Development Core Team, Vienne, Austria, URL: https://www.R-project.org/). Follow-up was calculated using the reverse Kaplan Meier method, and proportional hazards assumptions were checked using the Grambsh-Therneau residual-based test.

RESULTS

We identified a total of 832 patients (median age 64 years; 49% female), including 471 (57%) patients with Ph+ B-ALL, 218 (26%) with Ph- B-ALL and 143 (17%) with T-ALL (Table 1). The median year of transplant for the total cohort was 2017 (interquartile range [IQR] 2014–2020). Sixty-six percent ($n = 552$) of the patients received their transplant during the period 2016 to 2022, compared to 34% ($n = 280$) who had a transplant between 2010 and 2015; a significant increase in the number of transplants during recent years was noted (Supplementary Fig. 1 shows the number and type of transplant by year). We compared the patient and transplant characteristics across these two time periods in addition to evaluating the changes noted over time in post-transplant outcomes for this high-risk group of patients.

Patient and transplant characteristics across the two time periods

Ph+ B-ALL was the most common subtype of ALL in both time periods but was more frequent in those who received transplantation between 2010 and 2015 compared to the more recent period ($n = 184$; 66% and $n = 287$; 52%, respectively). Patients who received a transplant during 2016–2022 were more likely to have Ph- B-ALL (29% vs. 20%) or T-ALL (19% *vs.* 14%) respectively; $p < 0.001$. Patients in the later period were slightly older median age 64; IQR [62–66] as compared to those in 2010–2015 (median age 63; IQR [61–65]); $p < 0.001$. There was no statistically significant difference in other variables across the two time periods, including gender, KPS or cytomegalovirus status. Table 1 shows a summary of patient characteristics at transplant.

We observed a gradual increase in the number of transplants across the first time period (from 33 in 2010 to 66 in 2015, except for 2011 which had the lowest number ($n = 30$) of transplants). During the second time period the number increased gradually from 70 in 2016 to a peak of 98 in 2021 then decreased slightly to 80 during 2022. Reduced intensity conditioning was used in more than half of the patients in the total cohort, with a decrease from 63% during 2010–2015 to 54% during 2016–2022 ($p < 0.001$). The use of TBI-based conditioning increased from 24% during 2010–2015 to 35% during 2016–2022, and thiotepa-busulfan-fludarabine-based conditioning increased from 6–12% respectively. We also observed a decrease in the use of in vivo TCD over time (from 89–70%) with an increase in the use of PTCy (from 13–31%; $p < 0.001$). To note that, PTCy was used in most patients receiving transplant from a haploidentical donor (81/91; 89%). Methotrexate-cyclosporin- based GVHD prophylaxis was the most used regimen during 2010–2015 (33%) and the second most frequently used regimen during 2016–2022 (28%) after mycophenolate mofetil-cyclosporin (32%). Interestingly, the donor age was younger for transplants performed between 2016–2022 (35 compared to 41 respectively; $p < 0.001$). Table 2 shows the transplant characteristics for the total cohort and according to the two time periods.

Transplant outcomes and prognostic factors across the two time periods

The median follow-up for all patients was 3 years with a significant difference between the two time periods (7 years for transplants performed during 2010–2015 compared to 2 years during 2016–2022) (Table 2); thus follow-up was censored at 2 years. During this follow up, a total of 324 (39%) patients died (157 [56%]

Table 1. Patient characteristics according to the two time periods.

Variable	Total ($n = 832$)	HCT 2010–2015 ($n = 280$)	HCT 2016–2022 ($n = 552$)	*P* value
ALL type (%)				<0.001
-Ph+B-ALL	471 (57)	184 (66)	287 (52)	
-Ph- B-ALL	218 (26)	57 (20)	161 (29)	
-T-ALL	143 (17)	39 (14)	104 (19)	
Patient age at HCT (yrs)				<0.001
Median	64	63	64	
Min-max	(60–76)	(60–76)	(60–76)	
[IQR]	[62–66]	[61–65]	[62–66]	
Gender (%)				
Male	428 (51)	133 (48)	295 (53)	0.11
Female	404 (49)	147 (52)	257 (47)	
KPS (%)				0.51
<90	241 (30)	78 (29)	163 (31)	
≥90	555 (70)	193 (71)	362 (69)	
Missing	36	9	27	
Recipient CMV (%)				0.61
Negative	247 (30)	86 (31)	161 (29)	
Positive	579 (70)	191 (69)	388 (71)	
Missing	6	3	3	
Measurable residual disease (MRD) negativity	345 (63)	119 (62)	226 (63)	0.73

ALL acute lymphoblastic leukemia, *CMV* cytomegalovirus, *HCT* hematopoietic cell transplant, *IQR* interquartile range, *KPS* Karnofsky performance status, *Min* minimum, *Max* maximum, *Ph+* Philadelphia chromosome positive, *Ph-* Philadelphia chromosome negative, *yrs* years.

during 2010–2015 and 167 [30%] during 2016–2022; $p = 0.067$). Disease progression was the cause of death in 81 (52%) and 62 patients (37%), respectively, while the main cause of death was related to transplant in 62 (40%) and 83 patients (50%), respectively (Supplementary Table 1). To note, there was no statistically significant difference in the 30-day mortality ($p = 0.083$).

There was a significant decrease in relapse incidence with time (from 35–23%, respectively); with a significant improvement in 2-year LFS and OS when comparing transplants performed in 2010–2015 with those in 2016–2022 (42–55% and 51% to 65%, respectively). We also observed a non-significant decrease in NRM from 24–22% (Fig. 1). There was a slight increase in 180-day aGVHD grade ≥II from 23–27%, with however, a decrease in cGVHD from 40–36%, and extensive cGVHD from 22–17%, respectively (Supplementary Table 1 and Fig. 2). These outcomes were also evaluated and compared across the three types of ALL with similar results (Table 3). The 2-year LFS and OS for Ph+ B-ALL increased from 45% during 2010–2015 to 60% during 2016–2022, and from 53–71%, respectively. For Ph- B-ALL, the 2-year LFS and OS increased from 37–49% and from 45–56%, respectively. For T-ALL, the 2-year LFS and OS increased from 35–54% and from 51–60%, respectively (Table 3).

On multivariate analysis, a more recent year of transplant was associated with a lower risk of relapse with HR of 0.52 (95% CI 0.36–0.75; $p = 0.001$), and improved LFS with HR 0.68 (95% CI 0.51–0.91; $p = 0.009$), as well as OS with HR 0.71 (95% CI 0.52–0.98; $p = 0.037$). A later year of transplant was also associated with lower risk of cGVHD with HR 0.66 (95% CI 0.45–0.98; $p = 0.038$). Among other variables, older age was associated with a lower NRM (HR 0.91, 95% CI 0.84–0.98; $p = 0.012$), improved OS (HR 0.93, 95% CI 0.88–0.98; $p = 0.009$) but an increased risk of cGVHD (HR 1.06, 95% CI 1–1.12; $p = 0.039$). There was a suggestion of improved LFS with older age (HR 0.96, 95% CI 0.92–1; $p = 0.056$) and with use of PTCy (HR 0.7, 95% CI 0.49–1.02; $p = 0.063$). None of the evaluated variables had an impact on the risk of aGVHD ≥II (Table 4).

DISCUSSION

This study shows the increase in the number of allo-HCTs for older patients with ALL during the more recent period, reflecting the improvement in transplant-related care that is enabling more patients previously deemed unfit for transplant to receive this potentially curative therapy. Additionally, we report a significant improvement in post-transplant outcomes over time with an increase in 2-year LFS and OS. This is explained by the significant decrease in risk of relapse. There was no impact for the intensity of the conditioning on outcomes. We also report an increase in aGVHD in the setting of fewer patients receiving TCD, with however a decrease in cGVHD likely related to the increase in the use of PTCy during recent years [18]. These results suggest that allo-HCT is a feasible treatment option for many elderly patients with ALL, providing the possibility of long-term disease control for a high proportion of patients. These data are similar to those recently reported for older patients with acute myeloid leukemia with a median follow up of 40 months, where the 3-year incidence of relapse decreased from 37 to 30% ($p = 0.001$) from 2000 to 2021, with improvement in OS from 37 to 49% ($p = 0.001$) [19]. This reflects the improvement in patient selection, utilization of reduced intensity conditioning, and better prophylactic and supportive care; as well as the advancements in pre-transplant treatments and the adoption of post-transplant maintenance across many centers during more recent years irrespective of the disease type and/or status at transplant.

Table 2. Donor and transplant characteristics.

Variable	Total ($n = 832$)	HCT 2010–2015 ($n = 280$)	HCT 2016–2022 ($n = 552$)	*P* value
Follow-up (yrs)				
Median	3	7	2	
Range	[2.7–3.3]	[6–7.9]	[1.9–2.3]	
Median year of Transplant (IQR)	2017 (2014–2020)	2013 (2012–2014)	2019 (2017–2021)	<0.001
Type of donor (%)				NA
MSD	216 (26)	97 (35)	119 (22)	
UD	509 (61)	169 (60)	340 (62)	
Haplo	91 (11)	11 (4)	80 (14)	
Other	15 (2)	3 (1)	12 (2)	
Missing	1	0	1	
Donor age (yrs)				<0.001
Median	36	41	35	
IQR	26–53	29–57	26–50	
Min-Max	19–75	19–74	19–75	
Donor gender (%)				0.38
Male	530 (64)	172 (62)	358 (66)	
Female	293 (36)	104 (38)	189 (34)	
Missing	9	4	5	
Female donor to male recipient (%)				0.20
No	701 (85)	241 (87)	460 (84)	
Yes	126 (15)	36 (13)	90 (16)	
Missing	5	3	2	
Cell source (%)				0.11
PB	775 (93.2)	255 (91)	520 (94)	
BM	55 (6.6)	25 (9)	30 (5)	
BM+PB	2 (0.2)	0 (0)	2 (1)	
Donor CMV (%)				0.60
Neg	406 (50)	138 (51)	268 (49)	
Pos	412 (50)	133 (49)	279 (51)	
Missing	14	9	5	
CMV Abs donor to Patient (%)				0.74
Neg to Neg	188 (23)	63 (23)	125 (23)	
Neg to Pos	217 (27)	75 (28)	142 (26)	
Pos to Neg	58 (7)	22 (8)	36 (7)	
Pos to Pos	353 (43)	111 (41)	242 (44)	
Conditioning intensity (%)				<0.001
RIC	473 (57)	175 (63)	298 (55)	
MAC-TBI	223 (27)	51 (18)	172 (31)	
MAC-Chemo	131 (16)	53 (19)	78 (14)	
Missing	5	1	4	
Conditioning regimen (%)				NA
TBI-based	258 (31)	66 (24)	192 (35)	
TBF-based	83 (10)	17 (6)	66 (12)	
Other[a]	491 (59)	197 (70)	294 (53)	
GVHD prophylaxis regimen (used in>20% of patients)				NA
MTX+CSA based	248 (30)	93 (33)	155 (28)	
MMF+CSA based	256 (31)	78 (28)	178 (32)	
CSA based	144 (17)	60 (21)	84 (15)	
Other[b]	184 (22)	49 (18)	135 (25)	

Table 2. continued

Variable	Total ($n = 832$)	HCT 2010–2015 ($n = 280$)	HCT 2016–2022 ($n = 552$)	*P* value
In vivo TCD (%)				<0.001
No	137 (24)	18 (11)	119 (30)	
Yes	428 (76)	149 (89)	279 (70)	
Missing	267	113	154	
PTCy (%)				<0.001
No	419 (74)	146 (87)	273 (69)	
Yes	146 (26)	21 (13)	125 (31)	
Missing	267	113	154	

Abs antibodies, *ALL* acute lymphoblastic leukemia, *BM* bone marrow, *Chemo* chemotherapy, *CMV* cytomegalovirus, *CSA* cyclosporin A, *GVHD* graft-versus-host-disease, *Haplo* haploidentical donor, *HCT* hematopoietic cell transplant, *IQR* interquartile range, *KPS* Karnofsky performance status, *MAC* myeloablative conditioning, *Max* maximum, *Min* minimum, *MMF* mycophenolate mofetil, *MSD* matched sibling donor, *MTX* methotrexate, *Neg* negative, *PB* peripheral blood, *Ph+* Philadelphia chromosome positive, *Ph-* Philadelphia chromosome negative, *Pos* positive, *PTCy* post-transplant cyclophosphamide, *RIC* reduced intensity conditioning, *TBF* Thiotepa, busulfan and fludarabine, *TBI* total body irradiation, *TCD* T-cell depletion, *UD* unrelated donor, *yrs* years.

[a]Other regimens include Treosulfan-fludarabine based, busulfan-fludarabine based, busulfan-cyclophosphamide based, fludarabine-melphalan based among others.

[b]Other GVHD prophylaxis regimens include single agent or combinations of Methotrexate, mycophenolate mofetil, cyclosporin, tacrolimus, and/or sirolimus.

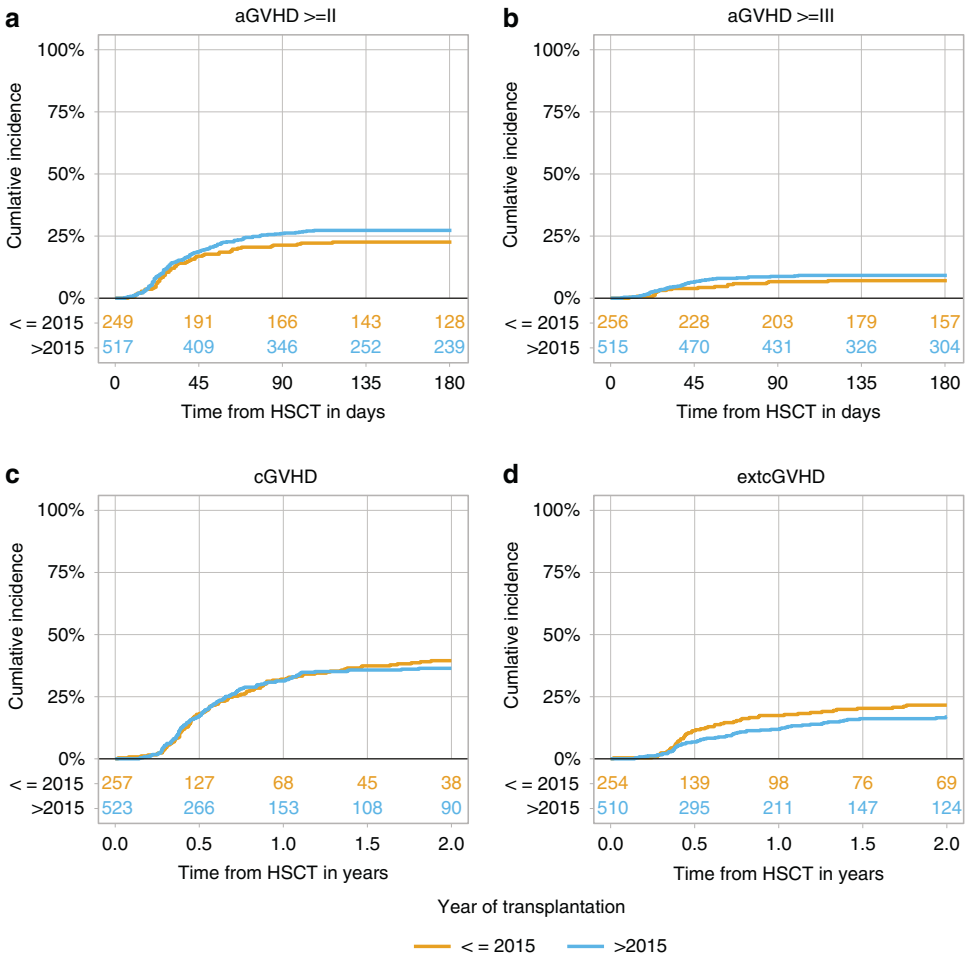

Fig. 1 Univariate survival curves for post-transplant outcomes. a Overall Survival (OS); **b** Leukemia free survival (LFS); **c** Relapse incidence (RI); **d** Non-relapse mortality (NRM). These curves show a significant improvement in 2-year LFS and OS when comparing transplants performed in 2010–2015 with those in 2016–2022 (42–55% and 51–65%, respectively). In addition, there was a significant decrease in relapse incidence with time (from 35–23%, respectively), and a slight decrease in NRM from 24 to 22%.

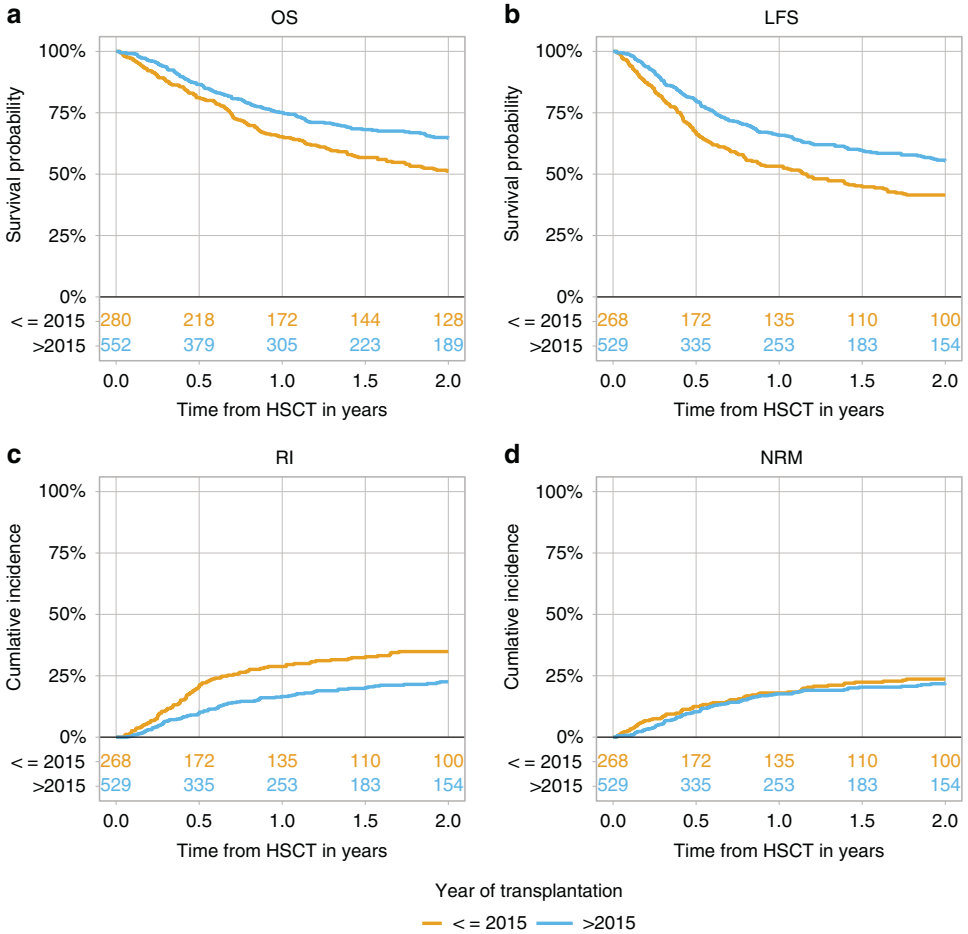

Fig. 2 Cumulative incidence curves for GVHD. a Acute graft-versus-host-disease (aGVHD) ≥II; **b** aGVHD≥III; **c** Chronic graft-versus-host-disease (cGVHD); **d** Extensive (ext) cGVHD. These curves show a slight increase in 180-day aGVHD grade ≥II from 23 to 27%, with however, a decrease in cGVHD from 40 to 36%, and extensive cGVHD from 22 to 17%.

A significantly higher proportion of patients had Ph- B-ALL or T-ALL during 2016–2022 compared to 2010–2015, respectively, which can affect post-transplant outcomes given the established role of tyrosine kinase inhibitors as post-transplant maintenance therapy in Ph+ B-ALL [20–23]. However, the type of ALL had no impact on post-transplant outcomes on multivariate analysis. There was a minimal although statistically significant difference in median age of patients at transplant across the two periods (64 years during 2016–2022 and 63 years during 2010–2015; $p < 0.001$). The significantly younger age of donors during more recent years could have also contributed to these improvements. On multivariate analysis, a more recent transplant maintained its impact on risk of relapse, LFS, OS and cGVHD. Performance status had no impact on outcomes, while older age was associated with lower NRM, with no correlation to other variables such as performance status. It is worth mentioning that we had fewer patients over 70 years which can affect the interpretation of this HR, and generally, patients older than 65 years proceeding to transplant is restricted to those with fewer comorbidities and better fitness. Interestingly, female donor to male recipient combination had no impact on any outcome, which contrasts to previously reported data [24, 25]. This needs to be further evaluated in future studies to identify whether these results were affected by patient and donor selection or whether this is characteristic for older patients receiving a transplant. Further data is needed to identify the optimal conditioning regimen for older patients with ALL, as previous data has been controversial with respect to the impact of reduced intensity regimens which may be preferred for many patients due to the reduced toxicity, albeit with a possible increased risk of relapse for some patients [26–28].

The use of TBI increased over time; an observation likely related to data suggesting better outcomes compared to non-TBI-based conditioning especially for patients with Ph- B-ALL and T-ALL [29–31]. However, the persistent controversy regarding use of TBI, and data suggesting the utilization of non-TBI based regimens, at least for some patients [32], suggests a need for better identification of patients for whom TBI can be skipped in order to reduce toxicities, especially in older patients.

The limitations of this study are those related to a registry-based design which may have conferred some bias. The fact that this cohort of patients was selected to receive an allo-HCT indicates better fitness and thus might be an important factor affecting outcomes. Unfortunately, the Hematopoietic Stem Cell Transplant Comorbidity Index (HCT-CI) is not available for this cohort of patients. Additionally, the heterogeneity of ALL subtype and donor age across the two time periods might have also contributed to the results. In particular, the availability of novel agents have affected the treatment landscape and decisions related to transplant in patients with Ph+ B-ALL, where chemotherapy-free protocols have been utilized showing promising efficacy. Nonetheless, this needs further exploration especially in areas with delayed access to such therapies; in addition to the need to explore the utility of these agents in the peri-transplant period.

The lack of data regarding cytogenetic and molecular risk stratification, measurable residual disease (MRD) status at

Table 3. Post-transplant outcomes by ALL subtype.

ALL subtype	Outcomes % (range)	Total (*n* = 832)	HCT 2010–2015 (*n* = 280)	HCT 2016–2022 (*n* = 552)
Ph+B-ALL	OS (2-yr)	63 (58.2–67.9) N = 471	53 (45.5–60.4) N = 184	71 (64.8–77) N = 287
	LFS (2-yr)	53 (48.1–58.4) N = 448	45 (36.8–52) N = 174	60 (52.8–66.6) N = 274
	RI (2-yr)	22 (18.1–26.6) N = 448	28 (21.7–35.4) N = 174	17 (12.5–23) N = 274
	NRM (2-yr)	24 (20.1–28.9) N = 448	27 (20.5–34) N = 174	23 (17–28.5) N = 274
	aGVHD ≥II (180 days)	25 (20.6–28.9) N = 426	21 (14.9–27.6) N = 159	27 (21.7–32.4) N = 267
	cGVHD (2-yr)	37 (32.4–42.4) N = 438	41 (33.5–48.8) N = 168	33 (26.8–39.7) N = 270
	Ext cGVHD	18 (14–22) N = 432	23 (16.9–30) N = 167	13 (8.7–18.5) N = 265
Ph- B-ALL	OS (2-yr)	52 (44.3–59.3) N = 218	45 (31.6–57.7) N = 57	56 (46–64) N = 161
	LFS (2-yr)	45 (37.6–52.5) N = 211	37 (24.5–49.8) N = 55	49 (39.2–57.4) N = 156
	RI (2-yr)	31 (24.6–38.2) N = 211	46 (32.3–58.9) N = 55	25 (18–33.3) N = 156
	NRM (2-yr)	24 (17.4–30.1) N = 211	17 (8.1–28) N = 55	26 (18.5–34.2) N = 156
	aGVHD ≥II (180 days)	26 (20–31.9) N = 206	27 (16.2–39.5) N = 55	25 (18.6–32.4) N = 151
	cGVHD (2-yr)	37 (30.3–44.6) N = 206	43 (29.2–56.7) N = 52	35 (26.3–42.9) N = 154
	Ext cGVHD	22 (15.7–28.3) N = 200	22 (11.8–34.9) N = 51	21 (14.2–29.3) N = 149
T-ALL	OS (2-yr)	58 (47.8–66) N = 143	51 (34.5–65.4) N = 39	60 (48.2–70.5) N = 104
	LFS (2-yr)	47 (37.8–56.3) N = 138	35 (20.7–50.2) N = 39	54 (41.6–64.3) N = 99
	RI (2-yr)	36 (27.5–45.3) N = 138	47 (30.1–61.6) N = 39	32 (21.2–42.3) N = 99
	NRM (2-yr)	16 (10.2–23.6) N = 138	18 (7.8–31.8) N = 39	15 (8–23.7) N = 99
	aGVHD ≥II (180 days)	29 (21.7–37.1) N = 134	23 (10.6–37.9) N = 35	32 (22.6–40.9) N = 99
	cGVHD (2-yr)	41 (31.7–49.7) N = 136	27 (13.7–42.3) N = 37	47 (35.6–57.8) N = 99
	Ext cGVHD	18 (11.4–25.6) N = 132	14 (4.9–27.4) N = 36	20 (11.6–29.7) N = 96

aGVHD acute graft-versus-host disease, *ALL* acute lymphoblastic leukemia, *cGVHD* chronic graft-versus-host disease, *CMV* cytomegalovirus, *HCT* hematopoietic cell transplant, *Ext* extensive, *IQR* interquartile range, *KPS* Karnofsky performance status, *LFS* leukemia-free survival, *NRM* non-relapse mortality, *OS* overall survival, *Ph+* Philadelphia chromosome positive, *Ph-* Philadelphia chromosome negative, *RI* relapse incidence, *yr* year.

transplant for many patient, as well as type of pre-transplant treatment and use of post-transplant maintenance should also be considered. With the advancements in induction therapies and availability of novel agents in recent years, patients during the second time-period might have received transplant in a deeper remission compared to previous years, which might contribute to the changes in post-transplant outcomes. From the available data in this analysis, there was no significant difference in MRD negativity at time of transplant when comparing transplants done till 2015 to those done after 2015. Additionally, the impact of post-transplant maintenance for patients with Ph+ B-ALL needs to be evaluated, and this data is not available in our registry. These results, however, provide an essential basis for future studies aiming to identify patients who would benefit the most from alloHCT in CR1, in addition to determining the optimal timing and conditioning for these high-risk patients.

CONCLUSION

Our study showed a significant improvement over time in post-transplant outcomes for older patients with ALL, with decreased risk of relapse, cGVHD and extensive cGVHD in addition to improved LFS and OS. These large-scale, real-world data suggest that transplant should be offered to fit elderly patients providing the possibility of cure and long-term survival, in addition to serving as a benchmark for future prospective studies in this setting aiming to identify optimal patient selection, timing of transplant and conditioning, among others.

Table 4. Multivariable analysis of post-transplant outcomes.

	RI		NRM		LFS		OS		aGVHD ≥II		cGVHD	
Variable	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Yr of HCT (2016–2022 *Vs.* 2010–2015)	0.52 (0.36–0.75)	0.001	1.02 (0.65–1.62)	0.921	0.68 (0.51–0.91)	0.009	0.71 (0.52–0.98)	0.037	1.17 (0.76–1.8)	0.482	0.66 (0.45–0.98)	0.038
Type of ALL												
Ph+ B-ALL *Vs.* T-ALL	0.63 (0.38–1.04)	0.071	1.84 (0.83–4.05)	0.132	0.92 (0.6–1.4)	0.698	0.79 (0.5–1.25)	0.312	0.85 (0.51–1.41)	0.521	0.91 (0.54–1.52)	0.706
Ph- B-ALL *Vs.* T-ALL	1.05 (0.62–1.78)	0.862	1.76 (0.75–4.14)	0.194	1.22 (0.78–1.9)	0.388	1.24 (0.76–2.02)	0.38	0.85 (0.48–1.49)	0.562	0.98 (0.55–1.73)	0.937
KPS (<90 *Vs.* ≥90)	1.08 (0.72–1.61)	0.724	1.44 (0.92–2.26)	0.11	1.21 (0.9–1.64)	0.205	1.28 (0.91–1.78)	0.154	1.16 (0.77–1.73)	0.48	0.99 (0.66–1.48)	0.947
Patient age at HCT	0.99 (0.93–1.05)	0.675	0.91 (0.84–0.98)	0.012	0.96 (0.92–1.)	0.056	0.93 (0.88–0.98)	0.009	0.96 (0.91–1.02)	0.196	1.06 (1–1.12)	0.039
MAC Vs. RIC	0.79 (0.55–1.14)	0.213	0.88 (0.57–1.34)	0.542	0.82(0.62–1.09)	0.175	0.88 (0.65–1.2)	0.43	1.11 (0.74–1.65)	0.623	0.92 (0.62–1.36)	0.686
GVHD prophylaxis												
PTCy Vs. ATG	0.69 (0.41–1.15)	0.155	0.71 (0.41–1.23)	0.221	0.7 (0.49–1.02)	0.063	0.69 (0.45–1.06)	0.093	1.14 (0.73–1.8)	0.558	0.84 (0.53–1.33)	0.458
Female donor to male recipient	1.08 (0.64–1.84)	0.773	0.88 (0.44–1.75)	0.707	1 (0.65–1.52)	0.983	0.87 (0.55–1.4)	0.577	1.26 (0.73–2.19)	0.406	1.49 (0.91–2.46)	0.115
CMV donor to recipient (Any combination *Vs.* Neg to Neg)	0.88 (0.58–1.33)	0.544	1.56 (0.86–2.82)	0.145	1.07 (0.77–1.5)	0.681	1.12 (0.76–1.64)	0.563	0.72 (0.48–1.09)	0.121	1.4 (0.88–2.21)	0.155

aGVHD acute graft-versus-host disease, *ALL* acute lymphoblastic leukemia, *ATG* antithymocyte globulin, *cGVHD* chronic graft- versus-host disease, *CI* confidence interval, *CMV* cytomegalovirus, *HCT* hematopoietic cell transplant, *HR* hazard ratio, *KPS* Karnofsky performance status, *LFS* leukemia-free survival, *MAC* myeloablative conditioning, *Neg* negative, *NRM* non-relapse mortality, *OS* overall survival, *Ph+* Philadelphia chromosome positive, *Ph-* Philadelphia chromosome negative, *PTCy* post-transplant cyclophosphamide, *RI* relapse incidence, *RIC* reduced intensity conditioning, *Vs.* versus, *yr* year.

DATA AVAILABILITY

The data analyzed in this study were provided and approved by the Acute Leukemia Working Party (ALWP) of the EBMT. All relevant data are provided within the Article and the Supplementary File. The relevant working party of the EBMT will review requests from qualified external researchers for data from the EBMT studies in a responsible manner that includes protecting patient privacy, assurance of data security and integrity, and furthering scientific and medical innovation. Additional details on data sharing criteria and process for requesting access should be sent to ebmt.do-paris@ebmt.org. Individual patient data will not be shared.

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AUTHOR CONTRIBUTIONS

AB, NM, MM and FC designed the study, interpreted data, wrote the original draft of the manuscript, reviewed and edited the manuscript. AF collected and interpreted data, provided the statistical analysis, reviewed the results and discussion accordingly, and reviewed the final draft of the manuscript. DB, AEB, CC, EW, CH, TS, JP, IY, PD, NK, RF, LG, IW, EB, AN, and SG interpreted data, reviewed and edited the manuscript. The final version was approved by all authors.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS DECLARATION

All methods used were performed in accordance with the relevant guidelines and regulations. The study was approved by the Institutional Review Boar of the ALWP of the EBMT and complied with country-specific regulatory requirements. The study was performed according to the declaration of Helsinki. Patients provide informed consent authorizing the use of their personal information for research purposes.

ADDITIONAL INFORMATION

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