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ARTICLE

Improved post-transplant outcomes since 2000 for Ph-positive acute lymphoblastic leukemia in first remission: A study from the EBMT Acute Leukemia Working Party

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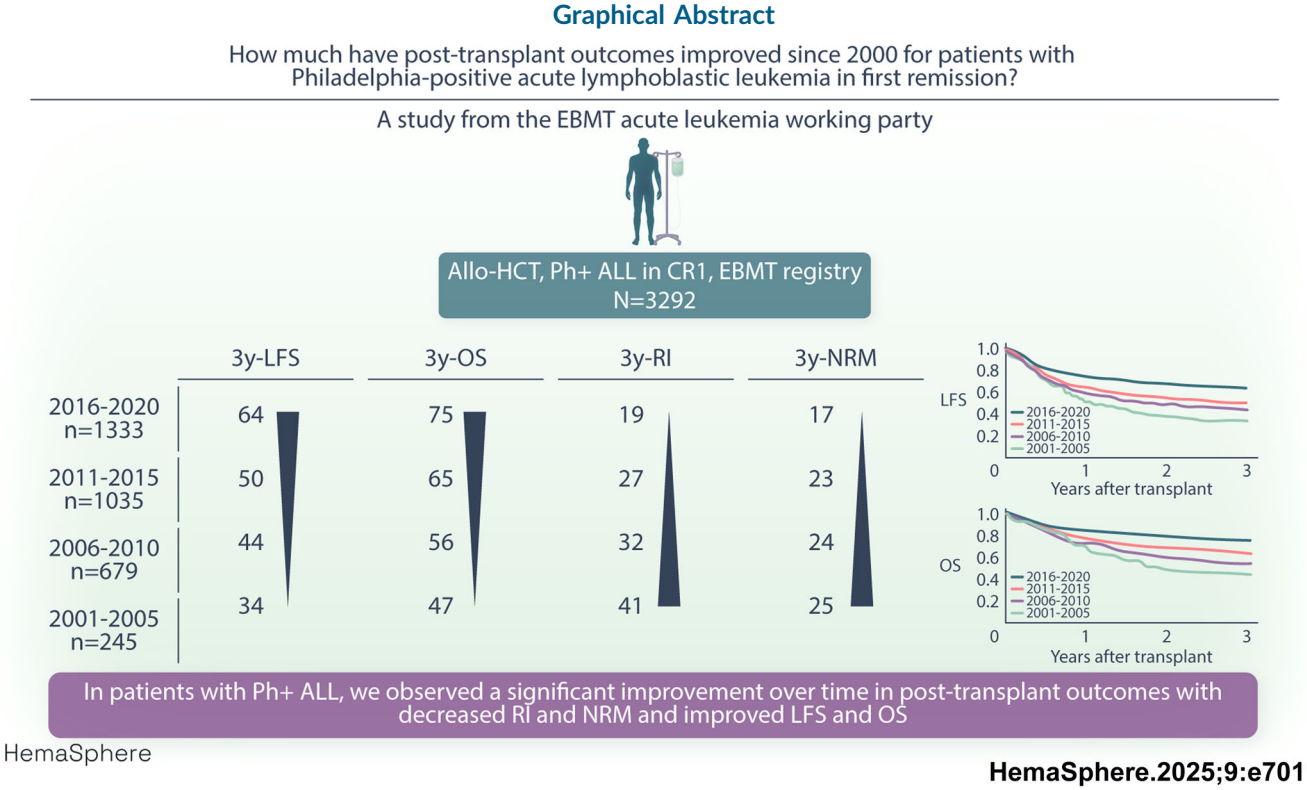
Graphical Abstract



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Improved post-transplant outcomes since 2000 for Ph-positive acute lymphoblastic leukemia in first remission: A study from the EBMT Acute Leukemia Working Party

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Abstract

Allogeneic hematopoietic cell transplantation (allo-HCT) remains a curative treatment for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) in their first complete remission (CR1). Recent results using the combination of blinatumomab and second- or third-generation tyrosine kinase inhibitors have challenged the necessity of allo-HCT in CR1. Here we assessed real-world changes over time in transplant characteristics and outcomes in adult patients with Ph+ ALL in CR1, using a large dataset from the European Society for Blood and Marrow Transplantation registry. A total of 3292 patients (45% female; median age 45 years) who underwent allo-HCT from 2001 to 2020 were included. Over four periods (2001–2005, 2006–2010, 2011–2015, and 2016–2020), the 3-year cumulative incidence of relapse decreased from 41% to 19%, and non-relapse mortality decreased from 25% to 17% ($p < 0.001$ for both). Correspondingly, 3-year leukemia-free survival (LFS) improved from 34% to 64%, and overall survival (OS) from 47% to 75% ($p < 0.001$ for both). Graft versus host disease-free and relapse-free survival also improved from 26% to 49% ($p < 0.001$). Factors negatively affecting LFS included older age, male gender, male donor and measurable residual disease (MRD) positivity pre-transplant, while total body conditioning (TBI) positively affected LFS. OS was positively influenced by younger age, female gender, matched sibling donor, TBI, and T cell depletion. Importantly, improvement in post-transplant outcomes over time was observed regardless of pre-transplant MRD status. In conclusion, we observed an impressive improvement over time in post-transplant outcomes of Ph+ ALL. These large-scale data can serve as a benchmark for future studies.

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a genetically heterogenous disease. The Philadelphia (Ph) chromosome represents a distinct cytogenetic category in ALL characterized by increased incidence with age (50% of affected patients aged above 60 years) and historically associated with poor prognosis. Tyrosine kinase inhibitors (TKIs) have revolutionized its treatment. Nevertheless, allogeneic hematopoietic cell transplantation (allo-HCT) remains an important curative treatment modality for patients with Ph+ ALL, particularly for genetically high-risk patients in first complete remission (CR1), those who have persistent measurable residual disease (MRD), as well as those beyond CR1.[1] In recent years, the use of newer generation TKIs, bispecific antibodies, cellular therapies, improved transplant techniques, and post-transplant pharmacological interventions aimed at reducing the risk of relapse in Ph+ ALL has become widespread. These strategies include either a prophylactic approach with TKI-based maintenance therapy or a preemptive approach based on regular MRD monitoring.[2–6] Moreover, recent findings using a chemotherapy-free approach such as the combination of blinatumomab with second- or third-generation TKIs have questioned the necessity of allo-HCT in CR1 for Ph+ ALL.[7,8]

Little information is available about the global impact of the current standard of care for Ph+ ALL after allo-HCT and the predictive factors for outcomes. To address these challenges, we assessed real-world changes over time in transplant characteristics and post-transplant outcomes in adult patients with Ph+ ALL in CR1, using a large dataset from the European Society for Blood and Marrow Transplantation (EBMT) registry.

METHODS

Study design and data collection

This was a retrospective, registry-based, multicenter analysis. Data were provided and approved by the Acute Leukemia Working Party (ALWP) of the EBMT. The EBMT is a voluntary working group of more than 600 transplant centers, which 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 before data registration with the EBMT, following the guidelines of the Declaration of Helsinki, 1975.

Eligibility criteria for this analysis included adults older than 18 years and first allo-HCT for Ph+ ALL in CR1 between 2001 and 2020 with available pre-transplant MRD data. Donor types included matched sibling donor (MSD), unrelated donor (UD) regardless of whether 10/10 or 9/10, and haploidentical donor (Haplo). The stem cell source was bone marrow (BM) or granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood (PB). Patients who received in vitro T cell depletion (TCD) were excluded.

Definitions

Conditioning intensity was measured using the transplant conditioning regimen intensity myeloablative conditioning (MAC)/reduced intensity conditioning (RIC) classification[9] and transplant conditioning intensity score.[10] MAC was defined as a regimen containing either total body irradiation (TBI) with a dose greater than 6 Gy, a total dose of oral busulfan (Bu) greater than 8 mg/kg, or a total dose of intravenous Bu greater than 6.4 mg/kg. All other regimens were defined as RIC. The diagnosis and grading of acute and chronic graft versus host disease (GVHD) were performed by transplant centers using standard criteria.[11]

Statistical analysis

Endpoints included leukemia-free survival (LFS), overall survival (OS), non-relapse mortality (NRM), relapse incidence (RI), acute and chronic GVHD, and GVHD-free and relapse-free survival (GRFS). All outcomes were measured from the time of allo-HCT. LFS was defined as survival without leukemia relapse or progression; patients alive without leukemia relapse or progression were censored at the time of last contact. OS was defined as death from any cause. NRM was defined as death without previous leukemia relapse. GRFS was defined as survival without grades 3 and 4 acute GVHD, extensive chronic GVHD, relapse, or death. Follow-up was calculated using the reverse Kaplan–Meier method. All events were censored at 3 years post allo-HCT to allow for the difference in length of follow-up. The probabilities of OS, LFS, and GRFS were calculated using the Kaplan–Meier method. Cumulative incidence functions were used to estimate RI and NRM in a competing risk setting. Death and relapse were considered as competing events for acute and chronic GVHD. As planned in the study synopsis, univariate comparisons were stratified on pre-transplant MRD status. Univariate comparisons were performed using the log-rank test for LFS, OS, and GRFS, and Gray's test for cumulative incidences. A Cox proportional-hazards model was used for multivariate regression and included variables differing significantly between the time periods, and factors known to influence outcomes, including a frailty term to allow for center differences. We included donor type as MSD versus all other donors because of insufficient numbers of Haplo before 2010. The type-1 error rate was fixed at 0.05 for determination of factors associated with time-to-event outcomes. All analyses were performed using SPSS 27.0 (SPSS Inc., Chicago, IL, USA) and R 4.1.1 (R Development Core Team, Vienna, Austria, https://www.R-project.org/).

Data sharing statement

The data analyzed in this study were provided and approved by the ALWP of the EBMT. All relevant data are provided within the article and the Supporting Information. 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.

RESULTS

Patient and transplant characteristics

We identified 3292 adult patients (45% female; median age 45 years, range 18–76) with Ph+ ALL allografted between 2001 and 2020 in CR1 from an MSD (38%), UD (54%), or Haplo (8%). At transplant, 41% of patients were MRD-positive. The HCT-specific comorbidity index (HCT-CI) was zero in 63% of patients with available data. Conditioning was MAC in 77% of patients, and TBI in 64% of patients. In vivo TCD and PB stem cells (PBSC) were given to 52% and 83% of patients, respectively. Most patients (66%) and donors (55%) were cytomegalovirus (CMV) seropositive. Overall, 1229 patients (37%)

were reported to have received a TKI pre-transplant (no TKI or missing data for 2063 patients [63%]) (Table 1). The pre-transplant TKI was predominantly imatinib (62%) followed by nilotinib (12%) and dasatinib (11%) (Table 1). Conversely, 877 patients (27%) were reported to have received a TKI post-transplant (598 before relapse and 279 after relapse) (no TKI or missing data for 2415 patients [73%]) (Table 2). Post-transplant TKIs consisted of imatinib (35%) followed by dasatinib (27%) and ponatinib (11%) (Table 2). Median follow-up was 56 months (interquartile range [IQR] 53–59 months). Patient, donor, and transplant characteristics are summarized in Tables 1 and 2.

We compared changes in patient and transplant characteristics over time in 245 patients transplanted in 2001–2005, 679 patients transplanted in 2006–2010, 1035 patients transplanted in 2011–2015, and 1333 patients transplanted in 2016–2020. Patients transplanted in recent years were older, less likely to be MRD-positive, and more likely to receive PBSC and TCD (Tables 1 and 2). Patients transplanted in recent years were more likely to receive a TKI pre- and post-transplant (Tables 1 and 2) with a progressive shift from imatinib toward nilotinib and dasatinib pre-transplant (Table 1) and toward dasatinib and ponatinib post-transplant (Table 2).

Changes over time in post-transplant outcomes

The 3-year RI gradually and significantly decreased from 41% to 32%, 27%, and 19% over the four time periods ($p < 0.001$) (Table 3 and Figure 1A), and NRM significantly decreased from 25% to 24%, 23%, and 17% ($p < 0.001$) (Table 2 and Figure 1B). The 3-year LFS and OS gradually and significantly improved over time from 34% to 64% ($p < 0.001$) (Table 2 and Figure 1C) and from 47% to 75% ($p < 0.001$) (Table 2, Figure 1d), respectively. Chronic GVHD and extensive chronic GVHD gradually and significantly decreased over time (Table 2 and Figure 1E). GRFS improved from 26% to 34%, 37%, and 49% ($p < 0.001$) (Table 2 and Figure 1F). In univariate analysis, LFS was negatively affected by older age, male donor, positive MRD at HCT, RIC, or non-TBI conditioning, whereas OS was negatively affected by older age and non-TBI conditioning (Table S1).

In the multivariate analysis, a progressive and significant improvement in all transplant outcomes over time was observed. Older age negatively affected most post-transplant outcomes. Male gender of both patients and donors and pre-transplant MRD positivity negatively affected LFS, while the use of TBI positively influenced it. Being a female recipient, MSD, TBI, and TCD positively affected OS (Table 4).

Changes over time according to MRD status at transplant

When analyzing the data according to MRD status at transplant, improvement in post-transplant outcomes over time was observed both in MRD-positive and in MRD-negative patients.

In MRD-negative patients (Table 5), 3-year CIR gradually and significantly decreased from 34% to 30%, 24%, and 17% ($p < 0.001$) over the four time periods. Three-year NRM decreased from 25% to 24%, 23%, and 17% ($p = 0.013$), and LFS improved from 41% to 46%, 52%, and 66% ($p < 0.001$) and OS improved from 52% to 58%, 64%, and 77% ($p < 0.001$). In these patients, chronic and extensive chronic GVHD gradually and significantly decreased over time. GRFS improved over time from 34% to 36%, 40%, and 53% ($p = 0.001$).

Similarly, in MRD-positive patients (Table 5), 3-year CIR gradually decreased from 48% to 34%, 32%, and 23% ($p = 0.001$) over the 4 time periods, 3-year NRM decreased from 25% to 24%, 21% and 17% ($p = 0.047$). LFS improved from 27% to 42%, 47%, and 60% ($p < 0.001$), and OS improved from 41% to 53%, 66%, and 73% ($p < 0.001$). In these patients, chronic and extensive chronic GVHD gradually and significantly decreased over time and GRFS improved from 18% to 31%, 35%, and 44% ($p < 0.001$).

Changes over time in post-transplant outcomes for patients who received pre-transplant TKI

For the 1229 patients reported to have received a TKI pre-transplant, the 3-year CIR remained stable at 31% to 34% from 2001 to 2015 but significantly decreased to 18% in the latest time period ($p = 0.001$) (Table S2), whereas NRM gradually and significantly decreased from 24% to 15% ($p = 0.05$). The 3-year LFS remained relatively stable at 43% to 47% from 2001 to 2015 but significantly and sharply improved to 67% in the latest period ($p = 0.001$). The 3-year OS gradually and significantly improved over time from 50% to 77% ($p = 0.001$). Chronic GVHD and extensive chronic GVHD gradually and significantly decreased over time. GRFS gradually and significantly improved over time from 21% to 43% ($p = 0.001$) (Table S2). For these patients, improvement over time in CIR, LFS, OS, and GRFS was noted regardless of pre-transplant MRD status, nevertheless with a more drastic improvement for MRD-positive patients (Table S2).

DISCUSSION

This registry study of a very large cohort of 3292 patients with Ph+ ALL allografted in CR1 analyzed trends in patients' characteristics and outcomes over the last two decades. Numbers of reported cases increased over the years, reflecting the general increase in numbers of allo-HCT and of reporting centers.

Over time, we observed a remarkable improvement of all post-transplant outcomes with decreased RI, NRM, and chronic GVHD and improved LFS, OS, and GRFS, all confirmed in the multivariate analysis. In the most recent period, 3-year LFS, OS, and GRFS were 64%, 75%, and 49%, respectively. We have shown a similar improvement in 2-year OS over time for patients with Ph+ ALL relapsing post allo-HCT from 28% to 55%.[12]

This improvement over time in post-transplant outcomes can be explained by the combined effect of decreased RI (from 41% to 19%) and NRM (from 25% to 17%). Advances in transplant techniques, including better donor matching and availability, conditioning regimens, and supportive care, likely explain the decreased NRM.[13] The decreased RI may be due to the introduction and widespread use of newer generation TKIs particularly as post-transplant maintenance.[14,15] The development of bispecific antibodies, such as blinatumomab, has also provided a powerful tool for targeting residual leukemia cells, leading to better control of the disease and higher rates of MRD negativity in recent years.[16] Over time, in our study, the reported use of prophylactic TKIs post-transplant increased from 5% in 2001–2005 to 27% in 2016–2020 with a more frequent use of the second- and third-generation TKIs in the most recent periods (Table 2). We also assume that a significant percentage of patients with missing data on TKI post-transplant received it with the same trend of increased use over time. This likely explains the reduction in CIR particularly in MRD-positive patients.

Limitations of our retrospective registry-based study are the high frequency of missing data regarding the pre-transplant therapies such as TKIs, immunotherapy, and CAR-T cells as well as prophylactic post-transplant maintenance therapy. Moreover, MRD positivity was recorded as reported by the centers regardless of the technique used and its sensitivity threshold, and post-transplant MRD status was

TABLE 1 Patient characteristics.

		Overall (*n* = 3292)	2001–2005 (*n* = 245)	2006–2010 (*n* = 679)	2011–2015 (*n* = 1035)	2016–2020 (*n* = 1333)	*p*
Patient age (years)	Median (min–max) [IQR]	45 (18–76)	41 (18–65)	43 (18–71)	45 (18–76)	47 (18–76)	<0.001
		[34–54]	[31–50]	[33–53]	[34–55]	[35–55]	
Patient sex	Male	1825 (56%)	159 (65%)	362 (53%)	545 (53%)	759 (57%)	0.002
	Female	1463 (45%)	86 (35%)	316 (47%)	489 (47%)	572 (43%)	
	Missing	4	0	1	1	2	
MRD pre-HCT	MRD-negative	1946 (59%)	125 (51%)	392 (58%)	628 (61%)	801 (60%)	0.033
	MRD-positive	1346 (41%)	120 (49%)	287 (42%)	407 (39%)	532 (40%)	
HCT-CI	HCT-CI = 0	1306 (63%)	5 (42%)	158 (67%)	359 (69%)	784 (59%)	
	HCT-CI = 1 or 2	427 (20%)	4 (33%)	48 (20%)	83 (16%)	292 (22%)	
	HCT-CI ≥ 3	357 (17%)	3 (25%)	30 (13%)	77 (15%)	247 (19%)	
	Missing	1202	233	443	516	10	
Karnofsky score	<90	762 (26%)	51 (68%)	141 (25%)	230 (23%)	340 (27%)	<0.001
	≥90	2128 (74%)	24 (32%)	429 (75%)	754 (77%)	921 (73%)	
	Missing	402	170	109	51	72	
Patient CMV status	Negative	1097 (34%)	74 (35%)	226 (35%)	350 (34%)	447 (34%)	0.97
	Positive	2100 (66%)	136 (65%)	424 (65%)	669 (66%)	871 (66%)	
	Missing	95	35	29	16	15	
TKI given pre-HCT	No TKI or missing	2063 (63%)	187 (76%)	318 (47%)	591 (57%)	967 (73%)	<0.001
	TKI given	1229 (37%)	58 (24%)	361 (53%)	444 (43%)	366 (28%)	
Type of TKI before HCT	Imatinib	762 (62%)	58 (100%)	306 (85%)	282 (64%)	116 (32%)	
	Dasatinib	130 (11%)	0 (0%)	14 (4%)	64 (14%)	52 (14%)	
	Nilotinib	143 (12%)	0 (0%)	0 (0%)	30 (7%)	113 (31%)	
	Ponatinib	18 (2%)	0 (0%)	0 (0%)	1 (0.2%)	17 (5%)	
	Two different TKIs	152 (13%)	0 (0%)	36 (11%)	58 (13%)	58 (13%)	
	Three different TKIs	9 (0.8%)	0 (0%)	2 (0.6%)	1 (0.2%)	6 (1.6%)	
	Other/not reported	15 (1%)	0 (0%)	3 (0.8%)	8 (2%)	4 (1%)	

Abbreviations: CMV, cytomegalovirus; HCT, hematopoietic cell transplantation; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; IQR, interquartile range; max, maximum; min, minimum; MRD, measurable residual disease; TKI, tyrosine kinase inhibitor.

TABLE 2 Donor and transplant characteristics. (continued on next page)

		Overall (*n* = 3292)	2001–2005 (*n* = 245)	2006–2010 (*n* = 679)	2011–2015 (*n* = 1035)	2016–2020 (*n* = 1333)	*p*
Follow-up (reverse KM) months	Median [IQR]	56 [53–59]	164 [148–195]	125 [117–133]	75 [72–80]	36 [35–37]	<0.001
Year transplant	Median (min–max) [IQR]	2014 (2001–2020) [2010–2017]	2004 (2001–2005) [2002–2005]	2008 (2006–2010) [2007–2009]	2013 (2011–2015) [2012–2014]	2018 (2016–2020) [2017–2019]	<0.001
Type of donor	MSD	1246 (38%)	129 (53%)	309 (46%)	392 (38%)	416 (31%)	
	UD	1776 (54%)	114 (47%)	347 (51%)	587 (57%)	728 (55%)	
	Haplo	270 (8%)	2 (1%)	23 (3%)	56 (5%)	189 (14%)	
Donor sex	Male	2063 (64%)	165 (68%)	441 (66%)	614 (60%)	843 (64%)	0.044
	Female	1186 (37%)	78 (32%)	232 (35%)	405 (40%)	471 (36%)	
	Missing	43	2	6	16	19	
Female to male combination	No	2696 (83%)	197 (81%)	567 (84%)	840 (82%)	1092 (83%)	0.65
	Yes	567 (17%)	46 (19%)	108 (16%)	185 (18%)	228 (17%)	
	Missing	29	2	4	10	13	
Cell source	BM	561 (17%)	78 (32%)	136 (20%)	166 (16%)	181 (14%)	<0.001
	PB	2731 (83%)	167 (68%)	543 (80%)	869 (84%)	1152 (86%)	
Donor CMV	Not CMV neg to neg	2377 (76%)	156 (77%)	496 (78%)	752 (76%)	973 (75%)	0.72
	CMV neg to neg	751 (24%)	46 (23%)	144 (23%)	243 (24%)	318 (25%)	
	Missing	164	43	39	40	42	
Conditioning	MAC	2517 (77%)	209 (85%)	531 (78%)	753 (73%)	1024 (77%)	<0.001
	RIC	775 (24%)	36 (15%)	148 (22%)	282 (27%)	309 (23%)	
Type of conditioning	Chemo alone	1196 (36%)	47 (19%)	236 (35%)	424 (41%)	489 (37%)	<0.001
	TBI-based	2094 (64%)	198 (81%)	442 (65%)	610 (59%)	844 (63%)	
	Missing	2	0	1	1	0	
TBI dose	RIC < 6 Gy	204 (10%)	15 (8%)	38 (9%)	65 (11%)	86 (10%)	<0.001
	8 Gy	352 (17%)	9 (5%)	36 (8%)	71 (12%)	236 (28%)	
	10 Gy	78 (4%)	9 (5%)	14 (3%)	23 (4%)	32 (4%)	
	12 Gy	1237 (60%)	124 (69%)	310 (72%)	393 (65%)	410 (49%)	
	13–14 Gy	183 (9%)	24 (13%)	35 (8%)	53 (9%)	71 (9%)	
	Missing	42	17	9	5	9	
If no TBI	BuCy	242 (20%)	21 (48%)	65 (28%)	97 (23%)	59 (12%)	NA
	BuFlu	388 (33%)	4 (9%)	64 (28%)	160 (38%)	160 (33%)	

TABLE 2 (Continued)

		Overall (*n* = 3292)	2001–2005 (*n* = 245)	2006–2010 (*n* = 679)	2011–2015 (*n* = 1035)	2016–2020 (*n* = 1333)	*p*
	FluMel	202 (17%)	6 (14%)	42 (18%)	69 (16%)	85 (17%)	
	TBF	189 (16%)	0 (0%)	3 (1%)	40 (9%)	146 (30%)	
	Other	169 (14%)	13 (30%)	59 (25%)	58 (14%)	39 (8%)	
	Missing	8	3	3	0	0	
In vivo TCD	No	1563 (48%)	145 (64%)	370 (56%)	463 (45%)	585 (44%)	<0.001
	ATG	1419 (44%)	54 (24%)	233 (35%)	485 (47%)	647 (49%)	
	Campath	259 (8%)	26 (12%)	61 (9%)	78 (8%)	94 (7%)	
	Missing	51	20	15	9	7	
TKI given post HCT	No TKI or missing	2415 (73%)	216 (88%)	568 (83%)	809 (78%)	822 (62%)	<0.001
	TKI given	877 (27%)	29 (12%)	111 (17%)	226 (22%)	511 (38%)	
Timing of TKI post-HCT	Prophylaxis	598 (18%)	12 (5%)	52 (8%)	131 (13%)	403 (30%)	<0.001
	Therapeutic	279 (9%)	17 (7%)	59 (9%)	95 (9%)	108 (8%)	
Type of TKI post-HCT	Imatinib	310 (35%)	22 (76%)	41 (37%)	56 (25%)	191 (37%)	
	Dasatinib	235 (27%)	1 (3%)	35 (32%)	79 (35%)	120 (24%)	
	Nilotinib	21 (2%)	0 (0%)	2 (2%)	7 (3%)	12 (2%)	
	Ponatinib	95 (11%)	0 (0%)	1 (0.9%)	18 (8%)	76 (15%)	
	Two different TKIs	173 (20%)	4 (14%)	29 (26%)	49 (22%)	91 (19%)	
	Three different TKIs	39 (4.8%)	1 (3%)	3 (3%)	17 (7%)	18 (3%)	
	Other/not reported	4 (0.5%)	1 (3%)	0 (0%)	0 (0%)	3 (0.6%)	
PTCy	No PTCy	2878 (89%)	223 (99.6%)	660 (99.8%)	948 (93%)	1047 (79%)	NA
	PTCy	347 (11%)	1 (0.4%)	1 (0.2%)	70 (7%)	275 (21%)	
	Missing	67	21	18	17	11	

Abbreviations: ATG, antithymocyte globulin; BM, bone marrow; BuCy, busulfan and cyclophosphamide; BuFlu, busulfan and fludarabine; Chemo, chemotherapy; CMV, cytomegalovirus; FluMel, fludarabine and melphalan; Haplo, haploidentical donor; IQR, interquartile range; KM, Kaplan–Meier; MAC, myeloablative conditioning; max, maximum; min, minimum; MSD, matched sibling donor; neg to neg, negative donor to negative recipient; PB, peripheral blood; PTCy, post-transplant cyclophosphamide; RIC, reduced-intensity conditioning; TBF, thiotepa, busulfan, and fludarabine; TBI, total body irradiation; TCD, T cell depletion; TKI, tyrosine kinase inhibitor; UD, unrelated donor.

TABLE 3 Univariate analysis of changes over time in post-transplant outcomes.

3 years							
	Relapse	NRM	LFS	OS	Chronic GVHD	Ext. chronic GVHD	GRFS
2001–2005	41% [35–47]	25% [20–31]	34% [28–40]	47% [40–53]	50% [44–57]	27% [22–33]	26% [21–32]
2006–2010	32% [28–35]	24% [21–28]	44% [40–48]	56% [52–60]	45% [41–49]	22% [19–26]	34% [30–38]
2011–2015	27% [25–30]	23% [20–25]	50% [47–53]	65% [62–68]	47% [43–50]	22% [20–25]	37% [34–40]
2016–2020	19% [17–22]	17% [15–19]	64% [61–67]	75% [73–78]	39% [36–42]	18% [16–21]	49% [46–52]
p value	<0.001	<0.001	<0.001	<0.001	<0.001	0.004	<0.001

Abbreviations: ext., extensive; GRFS, GVHD-free and relapse-free survival; GVHD, graft versus host disease; LFS, leukemia-free survival; NRM, non-relapse mortality; OS, overall survival.

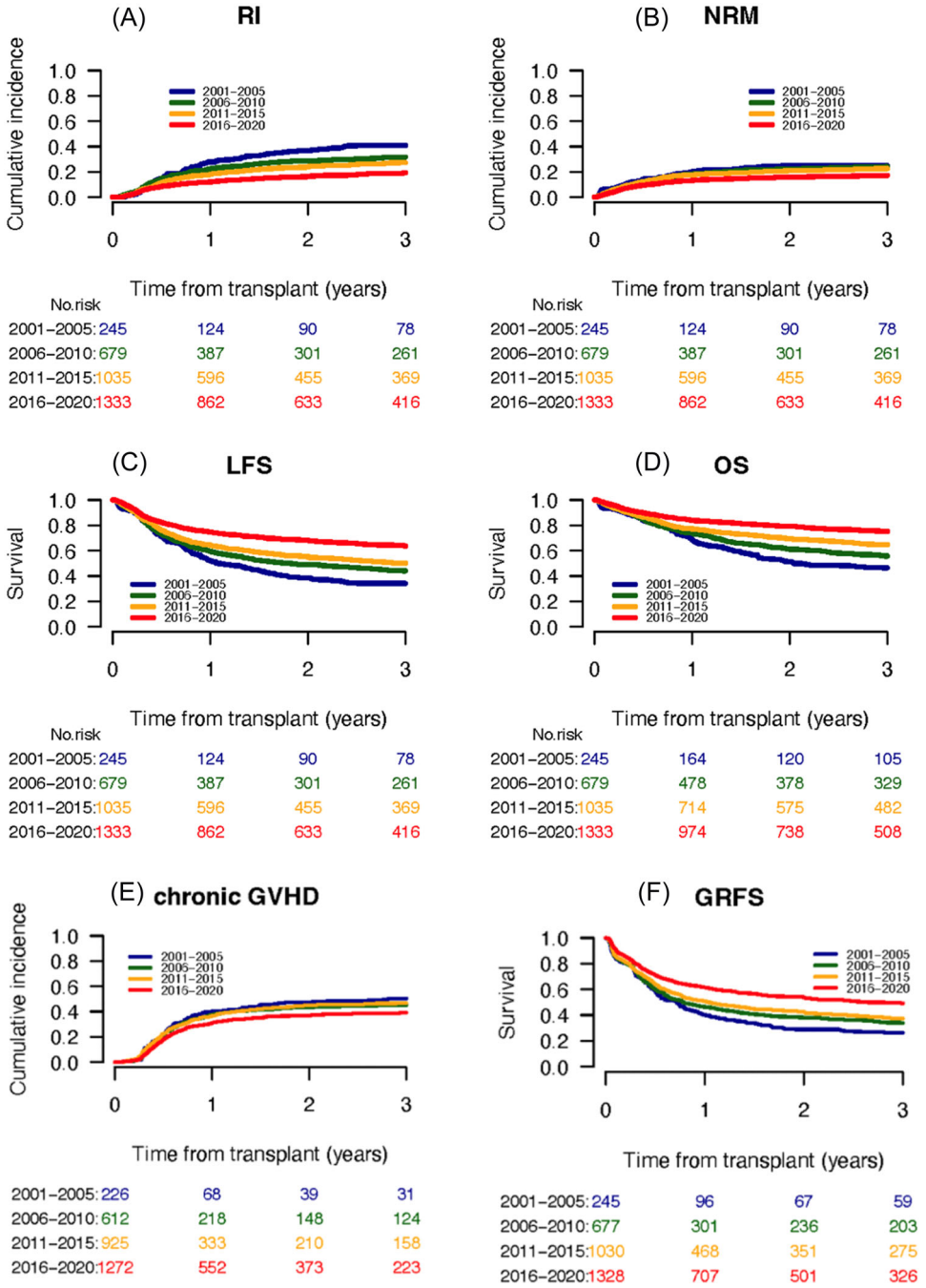

FIGURE 1 (A) Relapse incidence (RI), (B) non-relapse mortality (NRM), (C) leukemia-free survival (LFS), (D) overall survival (OS), (E) chronic GVHD incidence, and (F) GVHD-free and relapse-free survival (GRFS) of patients with Ph+ ALL allotransplanted in CR1 over four time periods (2001–2005/2006–2010/2011–2015/2016–2020).

TABLE 4 Multivariate analysis of post-transplant outcomes over time.

	Relapse	NRM		LFS		OS		GRFS		Chronic GVHD		Ext chronic GVHD		
	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	HR (95% CI)	*p* value
2001–2005 (reference)	1		1		1		1		1		1		1	
2006–2010	0.7 (0.5–0.9)	0.004	0.9 (0.7–1.2)	0.52	0.8 (0.6–0.9)	0.012	0.8 (0.6–1)	0.019	0.8 (0.7–1)	0.37	0.7 (0.6–0.9)	0.01	0.6 (0.5–0.9)	0.004
2011–2015	0.6 (0.5–0.7)	<0.001	0.8 (0.6–1)	0.079	0.7 (0.5–0.8)	<0.001	0.6 (0.4–0.7)	<0.001	0.7 (0.6–0.9)	0.36	0.8 (0.6–0.1)	0.039	0.6 (0.5–0.9)	0.003
2016–2020	0.4 (0.3–0.5)	<0.001	0.5 (0.4–0.7)	<0.001	0.4 (0.4–0.5)	<0.001	0.4 (0.3–0.4)	<0.001	0.5 (0.5–0.7)	0.35	0.6 (0.5–0.7)	<0.001	0.5 (0.4–0.7)	<0.001
Age (per 10 years)	0.9 (0.9–1)	0.046	1.3 (1–1.4)	<0.001	1.1 (1–1.1)	<0.001	1.2 (1.1–1.3)	<0.001	1.1 (1–1.1)	0.55	1.1 (1–1.1)	0.01	1.1 (1–1.2)	0.002
Other donor versus MSD	0.6 (0.5–0.7)	<0.001	1.6 (1.3–2)	<0.001	1 (0.8–1.1)	0.45	1.2 (1–1.4)	0.025	1.1 (1–1.2)	<0.001	1 (0.9–1.2)	0.72	1 (0.8–1.2)	0.96
Female patient	0.9 (0.8–1)	0.067	0.9 (0.8–1)	0.22	0.9 (0.8–1)	0.022	0.8 (0.7–1)	0.006	0.9 (0.8–1)	0.15	0.9 (0.8–1)	0.037	0.9 (0.7–1)	0.072
Female donor	0.8 (0.7–0.9)	0.001	1 (0.9–1.3)	0.54	0.9 (0.8–1)	0.039	1 (0.8–1.1)	0.51	1 (0.9–1.1)	0.22	1.2 (1.1–1.3)	0.006	1.1 (1–1.4)	0.13
MRD pos	1.3 (1.2–1.6)	<0.001	1 (0.9–1.2)	0.99	1.2 (1.1–1.3)	0.004	1.1 (1–1.3)	0.1	1.2 (1.1–1.3)	0.25	1 (0.9–1.2)	0.7	1.1 (0.9–1.3)	0.51
TKI versus (no or not reported)	1.1 (0.9–1.3)	0.27	0.9 (0.8–1.1)	0.27	1 (0.9–1.1)	0.71	1 (0.8–1.1)	0.5	1.2 (1–1.3)	0.38	1.3 (1.1–1.5)	<0.001	1.5 (1.2–1.8)	<0.001
PBSC versus BM	1 (0.8–1.2)	0.69	1.1 (0.8–1.3)	0.7	1 (0.9–1.2)	0.98	1 (0.9–1.3)	0.68	1.1 (1–1.3)	0.6	1.5 (1.2–1.7)	<0.001	1.7 (1.3–2.2)	<0.001
RIC versus MAC	1.4 (1.1–1.6)	0.003	0.7 (0.6–0.9)	0.002	1 (0.9–1.2)	0.9	0.9 (0.7–1)	0.13	1 (0.8–1.1)	0.055	1 (0.9–1.2)	0.95	0.9 (0.7–1.1)	0.22
TBI versus CT	0.7 (0.6–0.8)	<0.001	0.8 (0.7–1)	0.032	0.7 (0.7–0.8)	<0.001	0.8 (0.7–0.9)	0.001	0.9 (0.8–1)	0.26	1.2 (1.1–1.4)	0.007	1.3 (1–1.6)	0.024
In vivo TCD	1.2 (1–1.5)	0.021	0.7 (0.6–0.9)	0.002	1 (0.9–1.1)	0.51	0.8 (0.7–1)	0.008	0.8 (0.7–0.9)	<0.001	0.7 (0.6–0.8)	<0.001	0.6 (0.5–0.8)	<0.001

Abbreviations: BM, bone marrow; CI, confidence interval; CMV, cytomegalovirus; CT, chemotherapy; ext, extensive; GRFS, GVHD-free and relapse-free survival; GVHD, graft versus host disease; HR, hazard ratio; LFS, leukemia-free survival; MAC, myeloablative conditioning; MRD, measurable residual disease; MSD, matched sibling donor; NRM, non-relapse mortality; OS, overall survival; PBSC, peripheral blood stem cells; pos, positive; RIC, reduced intensity conditioning; TBI, total body irradiation; TCD, T-cell depletion.

TABLE 5 Univariate analysis according to pre-transplant MRD status.

3 years								
		Relapse	NRM	LFS	OS	chronic GVHD	Ext. chronic GVHD	GRFS
MRD-negative	2001–2005	34% [26–43]	25% [18–33]	41% [32–49]	52% [43–60]	47% [37–55]	26% [18–34]	34% [26–43]
	2006–2010	30% [25–35]	24% [20–29]	46% [41–51]	57.5% [52–62]	47% [41–52]	25% [21–30]	36% [31–41]
	2011–2015	24% [21–28]	23% [20–27]	52% [48-56.5]	64% [60–68]	47% [43–51]	23% [19–27]	40% [35–43]
	2016–2020	17% [14–20]	17% [14.5–20]	66% [62–70]	77% [73.5–80]	39% [35–42]	16% [13–19]	53% [49–57]
	p value	<0.001	0.013	<0.001	<0.001	0.006	0.001	0.001
MRD-positive	2001–2005	48% [39–57]	25% [17–33]	27% [19–35]	41% [32–49]	55% [45–64]	29% [20.5–38]	18% [11–25]
	2006–2010	34% [28.5–40]	24% [19.5–29.5]	42% [36–47]	53% [47-59.]	43% [37–49]	18% [14–23]	31% [26–37]
	2011–2015	32% [27–37]	21% [17–26]	47% [42–52]	66% [61–70]	46% [41–51]	21% [17–26]	35% [30–40]
	2016–2020	23% [19–27]	17% [14–21]	60% [55–65]	73% [68–77]	40% [35–44]	22% [18–25.5]	44% [39–48]
	p value	0.001	0.047	<0.001	<0.001	0.036	0.12	<0.001

Abbreviations: Ext., extensive; GRFS, GVHD-free and relapse free survival; GVHD, graft-versus-host disease; LFS, leukemia-free survival; MRD, measurable residual disease; NRM, non-relapse mortality; OS, overall survival.

missing for many patients. This unfortunately precluded the precise definition of the role of different innovations in the observed improvement in clinical outcomes. Nevertheless, this study reports the landscape of activity and outcomes over time using a large dataset of transplantations of more than 600 EBMT centers.

Regular monitoring of MRD allows for the early detection of relapse, enabling timely interventions and referral for allo-HCT. Preemptive treatments based on MRD status, whether pre- or post-transplant, have certainly improved long-term outcomes.[17] Importantly, the improvement of post-transplant outcomes in our study was also observed in patients with pre-transplant MRD negativity. In the group of patients with positive MRD, the 3-year LFS impressively increased from 27% to 60% and the 3-year OS increased from 41% to 73%. Conversely, for patients with pre-transplant MRD negativity, the 3-year LFS increased from 41% to 66% and the 3-year OS increased from 52% to 77%. Hence, in the most recent period, post-transplant outcomes for patients who were MRD-positive pre-transplant are only slightly inferior to those who were MRD-negative, likely indicating that the combined effects of allo-HCT and possibly post-transplant TKI maintenance attenuate/eliminate the poor prognostic value associated with pre-transplant MRD positivity. As previously mentioned, over time, we observed a significant increase in use of a prophylactic TKI post-transplant with more frequent use in second and third generation TKIs in the most recent periods (Table 2).

The integration of various TKIs, particularly newer generation agents, along with novel treatment combinations in initial induction regimens, has raised doubts about the necessity of allo-HCT for all patients. This is especially true for those who attain deep molecular responses early during induction. Consequently, many now consider allo-HCT primarily for those who fail to achieve or maintain MRD negativity.[18]

Patients treated with hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) and ponatinib had excellent long-term outcomes with a reported 6-year OS of 75%[19]; only 23% of patients in the study underwent allo-HCT in CR1 mainly because of detectable MRD, 60% of them received post-transplant TKI maintenance. The 6-year OS was 70% for all transplanted patients (only one patient succumbed to the disease, whereas the others died from transplant-related complications).[19]

In the context of newly diagnosed Ph+ ALL, promising results are reported with chemotherapy-free regimens including blinatumomab and dasatinib/ponatinib, potentially obviating the need for allo-HCT, especially in patients achieving undetectable MRD.[7,8,20] The D-ALBA trial that enrolled 63 patients treated with dasatinib and steroids as induction followed by at least two cycles of blinatumumab, resulted in an impressive 4-year OS of 89.4% for those who achieved a molecular response. Twenty-four (38%) patients were allo-grafted, 54% of them were non-molecular responders. At a median follow-up of 49 months, 83.3% of transplanted patients were alive without evidence of disease.[7] The *IKZF1* (plus) signature was associated with worse outcomes.[20]

In another study by the MD Anderson leukemia team, among patients who received at least one complete cycle of ponatinib–blinatumomab, with a median of five cycles administered, the majority (97%) maintained an ongoing hematological response. Notably, only one patient underwent allo-HCT during the first response, driven by persistently detectable MRD. For the 37 patients who did not undergo allo-HCT, the median duration of response was 15 months, with an estimated 1-year OS of 95%.[8] These findings suggest that the blinatumomab–TKI regimens yield favorable outcomes, potentially eliminating the necessity for allo-HCT in certain cases.

Despite the promising outcomes observed with chemotherapy-free regimens, combinations pose challenges due to their high cost and limited availability, particularly in resource-limited settings.[21] Moreover, the durability of responses with these therapies is still being evaluated, and long-term outcomes are not yet fully established. On the other hand, recent data from the GMALL trial 08/2013, which included 138 patients with Ph+ ALL treated with imatinib and dose-reduced induction followed by allo-HCT, showed a 3-year OS of 81%.[22]

Additionally, our data suggest that a chemotherapy regimen combined with TKIs followed by allo-HCT in CR1 has demonstrated excellent survival rates, nearing 75% at 3 years. This approach becomes a viable option, especially in scenarios where newer agents such as blinatumomab and ponatinib are not available. Allo-HCT also remains a crucial option for patients who do not achieve MRD negativity with novel agents or experience relapse post-treatment.

In summary, this study represents the largest analysis to date assessing trends over time and predictive factors for outcomes of Ph+ ALL patients after allo-HCT in CR1. In this population, we observed an impressive improvement over time in post-transplant outcomes with decreased CIR and NRM and improved LFS, OS, and GRFS, both in MRD-positive and MRD-negative patients. While newer generation TKIs and chemotherapy-free regimens offer promising alternatives,

allo-HCT continues to play a vital role in the comprehensive management of Ph+ ALL, providing a curative option for eligible patients, particularly in situations where access to novel therapies is limited or when deep and sustained molecular responses are not achieved.[23] These large-scale, real-world data can serve as a benchmark for future studies in this setting, including those testing the combination of a TKI and blinatumomab as an alternative to transplant.

AUTHOR CONTRIBUTIONS

Ali Bazarbachi proposed the study, interpreted the data, and wrote the manuscript. Myriam Labopin and Mohamad Mohty participated in the study design, interpreted the data, and edited the manuscript. Myriam Labopin was responsible for statistical analysis. All other authors reported updated patient data and read and commented on the manuscript. All authors proofread the manuscript and agreed on the data presented.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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