20-Year Steady Increase in Survival of Adult Patients with Relapsed Philadelphia-Positive Acute Lymphoblastic Leukemia Post Allogeneic Hematopoietic Cell Transplantation

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ABSTRACT

Purpose: Relapse after allogeneic hematopoietic cell transplantation (allo-HCT) remains the first cause of transplant failure in patients with Philadelphia-positive (Ph^+) acute lymphoblastic leukemia (ALL). In other hematologic malignancies, therapeutic advances resulted in significant improvement over time in survival of patients relapsing after transplant.

Experimental Design: We compared outcomes at European Society for Blood and Marrow Transplantation (EBMT) participating centers of 899 adult patients with Ph^+ ALL who relapsed between 2000 and 2019 after allo-HCT performed in first complete remission. Median follow-up for alive patients was 56 months.

Results: Overall, 116 patients relapsed between 2000 and 2004, 225 between 2005 and 2009, 294 between 2010 and 2014, and 264 between 2015 and 2019. Patient and transplant characteristics were similar over the four time periods except for a progressive increase in unrelated donors, peripheral blood stem cells, reduced intensity conditioning, and *in vivo* T-cell depletion and a progressive decrease in total body irradiation. The 2-year overall survival (OS) after relapse increased from 27.8% for patients relapsing between 2000 and 2004 to 54.8% for 2015 and 2019 ($P = 0.001$). A second allo-HCT within 2 years after relapse was performed in 13.9% of patients resulting in a 2-year OS of 35.9%. In multivariate analysis, OS from relapse was positively affected by a longer time from transplant to relapse and the year of relapse.

Conclusions: We observed a major progressive improvement in OS from posttransplant relapse for patients with Ph^+ ALL over the years, likely multifactorial including transplant-related factors, posttransplant salvage, and improvement in supportive care. These large-scale real-world data can serve as a benchmark for future studies in this setting.

See related commentary by Gale, p. 813

Introduction

Allogeneic hematopoietic cell transplantation (allo-HCT) remains an important and potentially curative treatment modality for various hematologic malignancies including for patients with Philadelphia-positive (Ph^+) acute lymphoblastic leukemia (ALL), particularly those in first complete remission (CR1) who remain minimal/measurable residual disease (MRD) positive, as well as those beyond CR1 (1). Unfortunately, disease relapse after transplant remains the main cause of failure of allo-HCT. In Ph^+ ALL, posttransplant relapse occurs in up to 30% of transplanted patients (6–8), and in earlier studies, long-term overall survival (OS) was dismal (2).

In recent years, posttransplant pharmacologic interventions aimed at reducing the risk of relapse in Ph^+ ALL are now widely applied, using either a prophylactic approach with tyrosine kinase inhibitor (TKI)-based maintenance therapy or a preemptive approach based on regular MRD monitoring (3, 4). Furthermore, new strategies for the management of posttransplant relapse have become available, including the use of newer generation TKI (5–12), monoclonal antibodies, such blinatumomab and inotuzumab ozogamicin, as well as CAR-T-cell therapy (13–17). Finally, increased availability of alternative donors (either well-matched unrelated or haploidentical family donors) facilitate second allo-HCT as salvage therapy.

In other settings, improvement in the management of posttransplant relapse has resulted in progressive increase over time in the survival of young patients with acute myeloid leukemia relapsing after allo-HCT, or Hodgkin lymphoma patients relapsing after

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Clin Cancer Res 2022;28:1004–12

doi: 10.1158/1078-0432.CCR-21-2675

Translational Relevance

In this retrospective, registry-based, multicenter study including 899 adult patients with relapsed Philadelphia-positive acute lymphoblastic leukemia post allogeneic hematopoietic cell transplantation over a 20-year period, a steady progressive improvement in the overall survival was observed. The 2-year overall survival after relapse in the latest period (2015–2019) was 55%. This real-world outcome may serve as a benchmark to guide the development of new therapeutic strategies in future clinical trials in that setting.

auto-HCT (18, 19). The aim of this study was to evaluate, in the setting of Ph^+ ALL, changes over time between 2000 and 2019, in patients' characteristics, risk factors, and clinical outcomes following relapse after allo-HCT. We used a large sample from the European Society for Blood and Marrow Transplantation (EBMT) registry.

Materials and Methods

Study design and data collection

This is a retrospective, registry-based, multicenter analysis. Data were provided and approved by the Acute Leukemia Working Party of the 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.

Eligibility criteria for this analysis included age ≥18 years, first allo-HCT for B-cell Ph^+ ALL in CR1 and documented hematologic relapse after allo-HCT between 2000 and 2019. Patients only showing decreasing donor chimerism or cytogenetic/molecular relapse were excluded. Donor types included matched sibling donors (MSD) and unrelated donors (UD) regardless of HLA mismatch. Haploidentical donors (Haplo) were excluded because of small numbers. Cord blood transplants were excluded because of the missing opportunity for donor lymphocyte infusion (DLI) and second allo-HCT from the same donor for management of relapse. The stem cell source was bone marrow (BM) or G-CSF-mobilized peripheral blood (PB). Patients who received *in vitro* T-cell depletion (TCD) were excluded.

Variables collected included recipient age at transplant, recipient and donor gender, date of diagnosis, year of transplant, time from diagnosis to transplant, year of relapse and time from transplant to relapse, Karnofsky performance status (KPS) score at time of transplant, transplant-related factors including conditioning regimen, use of total body irradiation (TBI), graft-versus-host disease (GVHD) prophylaxis, donor type, stem cell source (BM or PB), patient and donor cytomegalovirus (CMV) status, and finally, the development of acute and chronic GVHD before relapse. Relapse-associated variables included the interval from allo-HCT to relapse, OS from relapse, and cause of death. For recipients of DLI, time from relapse to DLI was recorded. For recipients of a second allo-HCT, time from relapse to second transplant, conditioning intensity, donor type, and relapse after second allo-HCT were also recorded.

Definitions

Myeloablative conditioning (MAC) was defined as a regimen containing either TBI with a dose greater than 6 Gy, a total dose of oral busulfan greater than 8 mg/kg, or a total dose of intravenous Bu greater than 6.4 mg/kg. All other regimens were defined as reduced intensity conditioning (RIC). The diagnosis and grading of acute (20) and chronic GVHD were performed by transplant centers using standard criteria (20). Hematologic relapse was defined by recurrence of blasts in the PB or infiltration of the BM by ≥ 5% blasts. Second allo-HCT was defined as infusion of donor PB or BM stem cells, following MAC or RIC, with immunosuppression for GVHD prevention.

Statistical analysis

Patient, disease, and transplant-related characteristics for the four cohorts were compared using χ^2 statistics for categorical variables and the Kruskal–Wallis test for continuous variables.

The primary endpoint was the probability of OS after relapse. Secondary endpoints encompassed causes of death within two years post relapse, cumulative incidence of second allo-HCT after relapse and OS after second allo-HCT. Surviving patients were censored at last contact, and all events were censored at two years after the starting point (date of relapse or date of second transplant).

Probabilities of OS were calculated using the Kaplan–Meier estimates. Cumulative incidence functions (CIF) was used to estimate the incidence of salvage with second allo-HCT, death being a competing event. All probabilities are given in percentage at two years.

Univariate analyses were performed using Gray's test for CIF and the log-rank test for OS. For all univariate analyses, continuous variables were categorized, and the median was used as a cutoff point.

A Cox proportional hazards model was used for multivariate regression. All variables differing between the four time periods, associated with OS in univariate analysis with a nonrestrictive P value of 0.10 and variables known as potential prognostic factors, were included in the multivariate model. Continuous variables included in the Cox model were not categorized. All factors were tested for the proportional hazards assumption. Multivariate results are expressed as a hazard ratio (HR) with a 95% confidence interval (CI). All tests were two sided. 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 26.0 (SPSS Inc.) and R version 4.1.0 [R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.)

Data availability statement

Data will be available upon request by emailing the corresponding author at bazarbac@aub.edu.lb

Results

Patient and transplant characteristics

We identified 899 patients with a median age at transplant and at relapse of 44 and 45.4 years, respectively. Overall, 116 patients relapsed between 2000 and 2004, 225 between 2005 and 2009, 294 between 2010 and 2014, and 264 between 2015 and 2019. Patient characteristics (**Table 1**) revealed a progressive increase in patient age at transplant (from 40.6 to 46.1 years; $P = 0.007$). Regarding transplant characteristics (**Table 2**) over the four time periods, there was a progressive increase in the use of matched UD (from 34.5% between 2000 and 2004 to 56% between 2015 and 2019; $P = 0.0002$), PB stem cells (from 60.3% to 84.5%; $P < 0.0001$), RIC (from 16% to 34.5%; $P = 0.004$), and *in vivo* TCD (from 28% to 62%; $P < 0.0001$) as well as a progressive decrease in

Table 1. Patients' baseline characteristics.

	Entire population *N* (%)	2000–2004 *N* (%)	2005–2009 *N* (%)	2010–2014 *N* (%)	2015–2019 *N* (%)	*P*
Patient age HCT1 in years median (range)	44 (18–72.7)	40.6 (18–62.7)	42.9 (18.1–70.5)	45.1 (18.4–70.9)	46.1 (18.1–72.7)	**0.007**
Patient age (per classes) years						
18–39	326 (36.3%)	50 (43.1%)	88 (39.1%)	104 (35.4%)	84 (31.8%)	**0.021**
40–59	458 (50.9%)	62 (53.4%)	111 (49.3%)	147 (50%)	138 (52.3%)	
60+	115 (12.8%)	4 (3.4%)	26 (11.6%)	43 (14.6%)	42 (15.9%)	
Total number of patients	899 (100)	116 (100)	225 (100)	294 (100)	264 (100)	
Patient gender						
Male	527 (59)	69 (59.5)	140 (62)	167 (57)	151 (57)	0.6
Female	372 (41)	47 (40.5)	85 (38)	127 (43)	113 (43)	
Time from diagnosis to HCT1 (months) median (range)	5.4 (1.5–23.7)	5.1 (2.4–16.4)	5.3 (2–15.1)	5.7 (1.5–23.2)	5.4 (2.6–23.7)	0.08
Time from HCT1 to relapse (months) median (range)	7.1 (0.2–153.8)	7.3 (0.9–57.8)	6.7 (0.5–113.5)	6.8 (0.2–153.8)	8 (1.1–128.4)	0.25
Year of HCT1 median	2010 (1999–2019)	2001 (1999–2004)	2006 (1999–2009)	2011 (1999–2014)	2016 (2004–2019)	**<0.0001**
Patient CMV serology (missing)	44	10	19	10	5	
CMV negative	302 (35)	38 (36)	61 (30)	108 (38)	95 (37)	0.25
CMV positive	553 (65)	68 (64)	145 (70)	176 (62)	164 (63)	
Patient Karnofsky before HCT1 (missing)	71	25	16	18	5	
<80	29 (3.5)	2 (2.2)	7 (3.3)	11 (4)	95 (37)	0.88
≥80	799 (96.5)	89 (97.8)	202 (96.7)	265 (96)	164 (63)	

Note: Values in bold are statistically significant.
Abbreviation: HCT1, first hematopoietic stem cell transplantation.

the use of TBI (from 73% to 53%; $P = 0.0002$), respectively. Acute GVHD grade II–IV and chronic GVHD had occurred before relapse in 21% and 21% of patients, respectively.

Overall survival and cause of death

Median follow-up for surviving patients was 56 months. For the entire cohort, the two-year OS after relapse was 41.5% (95% CI, 38–44.9). Importantly, in univariate analysis, the two-year OS after relapse increased from 27.8% for patients relapsing between 2000 and 2004 to 31.7% for 2005 and 2009, 44.5% for 2010 and 2014 and 54.8% for 2015 and 2019 ($P = 0.001$; **Fig. 1**). Original disease was the cause of death in 68.5% of patients, followed by infections (14.3%) and GVHD (8.9%; **Table 3**). A notable change in the cause of death was observed over time with original disease decreasing from 72.2% for patients relapsing between 2000 and 2004 to 50% for 2015 and 2019, whereas infections increased from 8.2% to 30.6% for the same periods (**Table 3**).

Univariate analysis

On univariate analysis (**Table 4**), OS after relapse was positively affected by the year of relapse, a longer time from transplant to relapse, and patient CMV negativity. Similarly, the cumulative incidence of a subsequent transplant was significantly affected by patient age, the year of relapse, the intensity of conditioning, use of TBI in first transplant, and the time from first transplant to relapse (**Table 4**).

Multivariate analysis

On multivariate analysis (**Table 5**), factors that positively influenced OS were a longer time from transplant to relapse ($P = 0.0006$) and the year of relapse (HR 0.71; $P < 0.033$ for patients relapsing from 2005 to 2009; HR 0.51; $P < 0.0001$ for patients relapsing from 2010 to 2014, and HR = 0.37; $P < 0.0001$ for patients relapsing from 2015 to 2019) and negatively affected by patient age at relapse ($P = 0.034$). Other patient, donor, and transplant characteristics had no significant effect on OS.

Donor lymphocyte infusion

For 537 patients with available data, DLI was given after relapse to 260 (48%) patients after a median of 79.5 days from relapse (IQR 36.8–162.2; **Table 6**). Trends over time showed a nonsignificant decrease in the use of DLI from 59% for patients relapsing between 2000 and 2004 to 44% for 2015 and 2019, together with a nonsignificant increase in the time from relapse to DLI from 58 to 102 days for the same periods (**Table 6**).

Second transplant

A second allo-HCT was performed in 115 patients (**Table 6**). The cumulative incidence of second allo-HCT within two years after relapse was 22%, 13%, 10%, and 16% for the four time periods ($P = 0.009$; **Tables 4** and 5). The cumulative incidence of second allo-HCT was significantly higher following late relapse (19.7% for patients relapsing after more than 7.1 months versus 8.1% for those with an early relapse; $P = 0.001$; **Tables 4** and 5). RIC was utilized in 66 (59%) patients. For 90 patients with available data, the same donor as for first allo-HCT was used in 23 (26%) patients (**Table 6**).

Overall, second allo-HCT resulted in a two-year OS from the date of second transplant of 35.9% (95% CI, 26.5–45.4%). Trends over time showed a progressive decrease in two-year relapse incidence from second transplant from 74% for 2000–2004, to 54% for 2005–2009, 46% for 2010–2014, and 33% for 2015–2018, respectively ($P = 0.03$; **Table 6**).

Discussion

This retrospective analysis of a homogeneous cohort of 899 patients with hematologic relapse after allo-HCT for Ph^+ ALL in CR1, analyzed trends in patient characteristics and outcomes over the last two decades. Overall, the two-year OS from relapse was 41.5%, with the original disease being the primary cause of death. Over time, we observed a steady increase in two-year survival from 27.8% to

Table 2. First transplant characteristics.

	Entire population *N* (%)	2000–2004 *N* (%)	2005–2009 *N* (%)	2010–2014 *N* (%)	2015–2019 *N* (%)	*P*
Donor type		24	25	29	45	*P*[a]
MSD	475 (53)	76 (65.5)	134 (60)	148 (50)	117 (44)	**0.0002**
UD	424 (47)	40 (34.5)	91 (40)	146 (50)	147 (56)	
Donor gender (missing)	6	1	0	1	4	
Male	597 (67)	69 (60)	160 (71)	191 (65)	177 (68)	0.19
Female	296 (33)	46 (40)	65 (29)	102 (35)	83 (32)	
Female→male transplant (missing)	1	1	0	0	0	
No female→male	738 (82)	92 (80)	185 (82)	237 (81)	224 (85)	0.54
Female→male	160 (18)	23 (20)	40 (18)	57 (19)	40 (15)	
Donor CMV serology (missing)	49	11	19	11	8	
CMV negative	391 (46)	46 (44)	89 (43)	128 (45)	128 (50)	0.46
CMV positive	459 (54)	59 (56)	117 (57)	155 (55)	128 (50)	
MRD at transplant (missing)	192	39	56	61	36	
Negative	369 (52.2%)	28 (36.4%)	88 (52.1%)	132 (56.7%)	121 (53.1%)	**0.022**
Positive	338 (47.8%)	49 (63.6%)	81 (47.9%)	101 (43.3%)	107 (46.9%)	
Stem cell source						
BM	183 (20)	46 (40)	47 (21)	49 (18)	41 (15.5)	<**0.0001**
PB	716 (80)	70 (60)	178 (79)	245 (83)	223 (84.5)	
Conditioning intensity						
MAC	641 (71)	97 (84)	163 (72)	208 (71)	173 (65.5)	**0.004**
RIC	258 (29)	19 (16)	62 (28)	86 (29)	91 (34.5)	
TBI						
TBI	534 (59)	85 (73)	148 (66)	161 (55)	140 (53)	**0.0002**
CT	365 (41)	31 (27)	77 (34)	133 (45)	124 (47)	
In vivo TCD (missing)	23	5	14	3	1	
No *in vivo* TCD	434 (49.5)	80 (72)	130 (62)	125 (43)	99 (38)	<**0.0001**
In vivo TCD	442 (50.5)	31 (28)	81 (38)	166 (57)	164 (62)	
aGVHD II–IV before relapse	182 (20.8)	27 (23.5)	53 (24)	57 (20.2)	45 (17.6)	ND
cGVHD before relapse	177 (21.3)	21 (20.2)	53 (25.9)	59 (21.9)	44 (17.5)	0.19
Median follow-up in months (IQR)	55.93 [46.3–62.2]	164.56 [113.84–177.77]	116.98 [102.95–121.97]	66.36 [61.54–70.98]	25.8 [22.89–27.34]	<**0.0001**

Note: Values in bold are statistically significant.

Abbreviations: aGVHD II-IV, acute graft-versus-host disease grade II or more; BM, bone marrow; CT, chemotherapy; cGVHD chronic graft-versus-host disease; MAC, myeloablative conditioning; MSD, matched sibling donor; ND, not done; PB, peripheral blood stem cells; RIC, reduced intensity conditioning; TBI, total body irradiation; TCD, T-cell depletion; UD, unrelated donor.

[a]Chi-square statistics for categorical variables and the Kruskal–Wallis test for continuous variables.

54.8% ($P = 0.001$) despite a significant increase in patient age at relapse from 44 to 56 years ($P < 0.001$).

Historically, patients with Ph^+ ALL relapsing post allo-HCT had a dismal prognosis with a two-year OS not exceeding 15% (21, 22). Younger age at relapse, longer duration of first response, achievement of second remission on salvage treatment and the performance of allo-HCT were the main factors positively influencing the long-term OS of relapsing Ph^+ ALL patients (21).

The observed improvement in OS in our study can be explained in several ways, all of which most likely play a certain role in achieving higher responses to post-relapse treatments: first, RIC was used more often in recent years whereas TBI was used less frequently. Hence, patients were less heavily pretreated and may have been able to tolerate more intensive treatments for relapse. Further, patients relapsing more recently had received more T-cell–depleted grafts. Therefore, in these patients, the graft-versus-leukemia (GVL) effect may have been less exploited after the first allo-HCT, rendering the disease more potentially sensitive to GVL-based treatments for posttransplant relapse, such as the use of DLI.

Unlike acute myeloid leukemia, where relapses are likely due to immune function dysregulation, including loss of expression of an HLA haplotype, or an increased expression of inhibitory checkpoint ligands (23–25), the majority of posttransplant relapses in Ph^+ ALL are the result of the emergence of ABL kinase domain (KD) mutations (26, 27). Almost 70% of imatinib-treated patients are positive for an ABL KD mutation at time of relapse, with T315I mutation being the most frequent (26). The recent wider use of second-generation TKIs, mainly dasatinib and nilotinib in the first-line setting, has resulted in a higher percentage of T315I-mutant relapses in up to 65% of cases (26). Those patients harboring the T315I mutation can benefit from ponatinib, a known third-generation TKI that became available in 2014 for the treatment of Ph^+ ALL (28).

Thus, the probability of achieving a complete remission after salvage treatment is increasing with the availability of second- and third-generation TKIs, selected based on the underlying ABL KD mutation. A recent EBMT registry study confirmed the efficacy of second-/third-generation TKIs in 140 patients with Ph^+ ALL, suffering from persistent MRD positivity ($n = 6$), molecular relapse ($n = 23$), or hematologic relapse ($n = 111$) following allo-HCT (12). Treatment included dasatinib in 104, nilotinib in 18, or ponatinib in 18 patients. Response rates were 71%, with a two- and five-year OS of 49% and 33%, respectively (12). OS was comparable among patients treated for MRD positivity or for hematologic relapse.

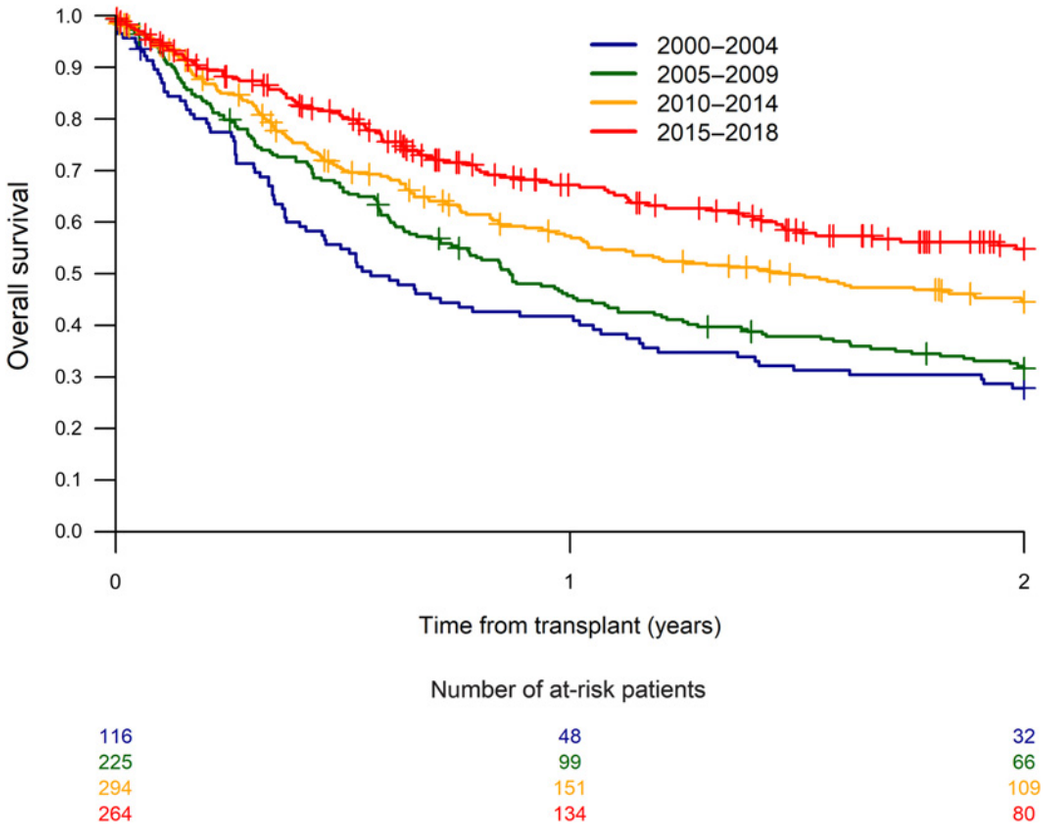

Figure 1.
Overall survival from relapse over time according to treatment period.

These results compared favorably to an earlier study by the EBMT, where Spyridonidis and colleagues reported a two-year OS of 13% among 465 patients with relapsed ALL of all subtypes after allo-HCT between 1995 and 2000, including 157 with Ph^+ ALL, 61% receiving imatinib ± chemotherapy (29), suggesting that the consequent use of a second-/third-generation TKI might have substantially contributed to the superior results, given that therapies applied in addition to TKI (chemotherapy, DLI, second allo-HCT) had not changed over time. Unfortunately, we did not have enough details on treatment modalities of relapse to prove this. However, a

Table 3. Causes of death.

Causes of death	Overall (n = 566) *N* (%)	2000–2004 *N* (%)	2005–2009 *N* (%)	2010–2014 *N* (%)	2015–2019 *N* (%)
Original disease	378 (68.5%)	70 (72.2%)	125 (74%)	129 (72.5%)	54 (50%)
Infection	79 (14.3%)	8 (8.2%)	15 (8.9%)	23 (12.9%)	33 (30.6%)
GVHD	49 (8.9%)	8 (8.2%)	13 (7.7%)	19 (10.7%)	9 (8.3%)
CNS toxicity	10 (1.8%)	4 (4.1%)	4 (2.4%)	1 (0.6%)	1 (0.9%)
Other transplant related	9 (1.6%)	1 (1%)	4 (2.4%)	1 (0.6%)	3 (2.8%)
IP	7 (1.3%)	1 (1%)	2 (1.2%)	1 (0.6%)	3 (2.8%)
MOF	7 (1.3%)	4 (4.1%)	1 (0.6%)	1 (0.6%)	1 (0.9%)
Hemorrhage	4 (0.7%)	0 (0%)	2 (1.2%)	1 (0.6%)	1 (0.9%)
Other second malignancy	3 (0.5%)	0 (0%)	2 (1.2%)	1 (0.6%)	0 (0%)
VOD	2 (0.4%)	0 (0%)	1 (0.6%)	0 (0%)	1 (0.9%)
Cardiac toxicity	2 (0.4%)	0 (0%)	0 (0%)	0 (0%)	2 (1.9%)
Failure/rejection	1 (0.2%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Lymphoproliferative disorder	1 (0.2%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)
Missing	14	0	3	6	5
Total number of deaths	**566**	**97**	**172**	**184**	**113**

Abbreviations: CNS, central nervous system; GVHD, graft-versus-host disease; IP, interstitial pneumonia; MOF, multiorgan failure; VOD, veno-occlusive disease.

Table 4. Univariate analysis.

		OS	Subsequent HCT
Year of relapse	2000–2004	27.8% (20–36.2)	22% (14.7–29.7)
	2005–2009	31.7% (25.6–37.9)	13% (8.8–17.6)
	2010–2014	44.5% (38.5–50.4)	10% (6.7–13.9)
	2015–2019	54.8% (47.8–61.3)	16% (11.2–20.9)
	P value	**0.001**	**0.027**
Type of donor	MSD	38.1% (33.5–42.8)	15.3% (12.1–18.8)
	UD	45.1% (40–50)	12.3% (9.2–15.8)
	P value	0.08	0.23
Patient age at time of relapse (year)	<median (45.4year)	42.9% (38–47.8)	18.9% (15.3–22.8)
	>median	40% (35.2–44.7)	8.9% (6.4–11.9)
	P value	0.13	**0.001**
Three classes (year)	18–39	42.9% (37–48.6)	21.1% (16.7–26)
	40–59	42.3% (37.5–47)	11.6% (8.8–14.9)
	60+	34.3% (25.5–43.3)	2.7% (0.7–7.2)
	P value	0.12	**0.001**
Patient sex	Male	39.1% (34.7–43.5)	14.1% (11.1–17.3)
	Female	44.8% (39.3–50.1)	13.5% (10.1–17.4)
	P value	0.13	0.76
Donor sex	Donor male	40.7% (36.5–44.9)	15.2% (12.3–18.3)
	Donor female	42.6% (36.7–48.4)	11.6% (8.1–15.7)
	P value	0.88	0.11
Female-to-male combination	No female to male	42.3% (38.5–46)	14.6% (12–17.4)
	Female to male	38% (30.2–45.8)	10.6% (6.3–16.1)
	P value	0.44	0.17
Patient CMV	Negative	44.6% (38.7–50.4)	12.8% (9.2–17)
	Positive	38.9% (34.6–43.2)	13.8% (10.9–16.9)
	P value	**0.02**	0.82
Donor CMV	Negative	42.8% (37.5–47.9)	13.6% (10.3–17.4)
	Positive	40.4% (35.7–45.1)	13.2% (10.2–16.6)
	P value	0.15	0.94
Cell source	BM	43.5% (35.9–50.8)	15.1% (10.2–20.9)
	PB	40.9% (37.1–44.7)	13.5% (11–16.3)
	P value	0.66	0.46
Conditioning	MAC	42.5% (38.4–46.5)	15.7% (12.9–18.8)
	RIC	38.9% (32.6–45.1)	9.2% (6–13.3)
	P value	0.12	**0.004**
TBI	Chemotherapy	39.8% (34.4–45.2)	10.5% (7.5–14.2)
	TBI	42.5% (38.1–46.8)	16.1% (13–19.5)
	P value	0.11	**0.025**
MRD at HCT1	MRD neg	40.7% (35.2–46.1)	13.4% (10–17.4)
	MRD pos	45.4% (39.7–50.8)	16% (12.2–20.3)
	P value	0.6	0.49
Karnofsky score	<80	48.3% (29.5–64.8)	3.4% (0.2–15.6)
	≥80	41.1% (37.5–44.7)	14.8% (12.3–17.5)
	P value	0.79	0.06
In vivo T-cell depletion	No *in vivo* TCD	38.4% (33.6–43.3)	15% (11.7–18.7)
	In vivo TCD	43.9% (39–48.8)	12.1% (9.1–15.5)
	P value	0.18	0.17
Time HCT1 relapse	<median (7.1 mo)	34.5% (29.9–39.1)	8.1% (5.7–11)
	>median	48.6% (43.6–53.5)	19.7% (16–23.7)
	P value	**0.001**	**0.001**
Acute GVHD before relapse	No aGVHD II before relapse	41.5% (37.6–45.4)	14.2% (11.6–17.1)
	aGVHD II before relapse	42.2% (34.8–49.4)	12.6% (8.2–18)
	P value	0.98	0.3
Chronic GVHD before relapse	No cGVHD before relapse	42.6% (38.5–46.5)	13.2% (10.6–16)
	cGVHD before relapse	41% (33.3–48.5)	14.5% (9.6–20.3)
	P value	0.13	0.91

Note: Values in bold are statistically significant.

Abbreviations: aGVHD II, acute graft-versus-host disease grade 2; BM, bone marrow; cGVHD, chronic graft-versus-host disease; HCT, hematopoietic cell transplantation (cumulative incidence and Gray test); MAC, myeloablative conditioning; MRD, minimal residual disease; MSD, matched sibling donor; OS, overall survival (Kaplan–Meier and log-rank test); PB, peripheral blood stem cells; RIC, reduced intensity conditioning; TBI, total body irradiation; TCD, T-cell depletion; UD, unrelated donor.

Table 5. Multivariate analysis.

	OS	
	HR (95% CI)	***P***
2000–2004 (reference)	1	
2005–2009	0.71 (0.52–0.97)	**0.033**
2010–2014	0.51 (0.37–0.7)	**<0.0001**
2015–2019	0.37 (0.27–0.53)	**<0.0001**
Age at relapse (per 10 years)	1.1 (1.01–1.21)	**0.034**
MSD (reference)	1	
UD	0.98 (0.57–1.68)	0.93
KPS <80 (reference)	1	
KPS ≥80	1.05 (0.83–1.33)	0.7
Not female D to male R (reference)	1	
Female D to male R	1.01 (0.78–1.3)	0.97
BM (reference)	1	
PB	1.05 (0.81–1.36)	0.7
MAC (reference)	1	
RIC	0.98 (0.75–1.27)	0.85
CT (reference)	1	
TBI	0.87 (0.69–1.11)	0.27
Patient CMV negative (reference)	1	
Patient CMV positive	1.06 (0.85–1.33)	0.59
Donor CMV negative (reference)	1	
Donor CMV positive	1.03 (0.83–1.29)	0.78
Time HCT1 relapse (months)	0.99 (0.98–0.99)	**0.0006**
No *in vivo* T depletion (reference)	1	
In vivo T depletion	0.9 (0.71–1.14)	0.37

Note: Values in bold are statistically significant.
Abbreviations: BM, bone marrow; CT, chemotherapy; HCT1, first hematopoietic cell transplantation; KPS, Karnofsky performance status; MAC, myeloablative conditioning; MSD, matched sibling donor; OS, overall survival; PB, peripheral blood; RIC, reduced intensity conditioning; TBI, total body irradiation; UD, unrelated donor.

diminishing frequency of leukemia-related death over the years suggests a better disease control, although at the possible expense of a relative increase in other causes of mortality.

Besides the year of relapse, multivariate analysis confirmed the predictive value of the time from transplant to relapse. The duration of first response is usually associated with a higher response to salvage treatment (21, 30). More therapeutic options may be made available to patients with late relapse, including a second allo-HCT. However, we could not support this hypothesis due to missing information on applied treatments. In addition, we could not assess whether those with a longer time from transplant to relapse received any type of prophylactic TKI maintenance that may have also influenced the choice of salvage treatment.

Some limitations of our retrospective study must be considered. These include the lack of information on MRD status prior to overt hematologic relapse, of relevance if patients were receiving pre-emptive treatment with TKI prior to their hematologic relapse posttransplant. As discussed above, the lack of detailed information on the treatment of posttransplant relapse (besides second allo-HCT) and DLI in a considerable percentage of patients is another limitation, including the use of blinatumomab, inotuzumab ozogamicin and CAR-T cell therapies. Similarly, we lacked reliable data on maintenance therapy, once a second remission had been achieved. This unfortunately precluded the definition of the role of different innovations in the observed improvement in outcome among younger patients, which, however, was not the main focus of this study investigating overall trends in relapsed patients over time.

In summary, this study represents the largest analysis to date assessing trends over time and predictive factors for outcome of relapsed Ph^+ ALL after allo-HCT. We observed a major progressive

Table 6. DLI and second transplant characteristics.

	Entire population	**2000–2004**	**2005–2009**	**2010–2014**	**2015–2019**	***P***
DLI (missing)	362	47	84	107	124	
No DLI post relapse	277 (52)	28 (41)	70 (50)	100 (53.5)	79 (56)	0.16
DLI post relapse	260 (48)	41 (59)	71 (50)	87 (46.5)	61 (44)	
Time relapse-DLI1 (missing)	639	75	154	207	203	
Median (min–max) [IQR]	79.5 (1–2,021) [36.8–162.2]	58 (1–761) [14–122]	70 (1–1,532) [37.5–194]	83 (1–2,021) [39–160.5]	102 (2–1,355) [48–146]	0.15
Subsequent allo						
No subsequent allo	784 (87)	91 (78)	197 (88)	267 (91)	229 (87)	**0.009**
Subsequent allo	115 (13)	25 (22)	28 (12)	27 (9)	35 (13)	
Relapse after HCT2 (missing)	10	2	2	1	5	
No second relapse	52 (49.5)	6 (26)	12 (46)	14 (54)	20 (67)	**0.031**
Second relapse	53 (50.5)	17 (74)	14 (54)	12 (46)	10 (33)	
Two-year CIR after HCT2	46% [39.4–55.4]	60% [37–76.9]	39.3% [21–57.1]	42.4% [21.7–61.8]	45.1% [24.1–64]	0.43
Same donor (missing)	25	13	10	2	0	
No	67 (74)	4 (33)	15 (83)	22 (88)	26 (74)	
Yes	23 (26)	8 (67)	3 (17)	3 (12)	9 (26)	
Conditioning HCT2 (missing)	3	1	0	1	1	
MAC	46 (41)	12 (50)	7 (25)	13 (50)	14 (41)	0.2
RIC	66 (59)	12 (50)	21 (75)	13 (50)	20 (59)	

Note: Values in bold are statistically significant.

improvement in OS from posttransplant relapse for patients with Ph$^+$ ALL, likely reflecting the efficacy of posttransplant salvage strategies. These large-scale real-world data can serve as a benchmark for future studies in this setting.

Authors' Disclosures

No disclosures were reported.

Authors' Contributions

A. Bazarbachi: Conceptualization, data curation, formal analysis, supervision, investigation, methodology, writing–original draft, writing–review and editing. **M. Labopin:** Conceptualization, data curation, formal analysis, validation, investigation, methodology, writing–review and editing. **M. Aljurf:** Investigation, writing–review and editing. **R. Niittyvuopio:** Investigation, writing–review and editing. **M. Balsat:** Investigation, writing–review and editing. **D. Blaise:** Investigation, writing–review and editing. **I. Yakoub-Agha:** Investigation, writing–review and editing. **A. Grassi:** Investigation, writing–review and editing. **H.C. Reinhardt:** Investigation, writing–review and editing. **S. Lenhoff:** Investigation, writing–review and editing. **P. Jindra:** Investigation, writing–review and editing. **J. Passweg:** Investigation, writing–review and editing. **I.A. Dalle:** Investigation, writing–review and editing. **M. Stadler:** Investigation, writing–review and editing. **B. Lioure:** Investigation, writing–review and editing. **P. Ceballos:** Investigation, writing–review and editing. **E. Brissot:** Investigation, writing–review and editing. **S. Giebel:** Investigation, writing–review and editing. **A. Nagler:** Investigation, writing–review and editing. **C. Schmid:** Conceptualization, investigation, writing–review and editing. **M. Mohty:** Conceptualization, resources, data curation, formal analysis, investigation, writing–review and editing.

Acknowledgments

There is no funding source for this project.

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Received July 22, 2021; revised September 22, 2021; accepted November 4, 2021; published first January 12, 2022.

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