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Outcome of Allogeneic Hematopoietic Stem Cell Transplantation in Adult Patients with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia in the Era of Tyrosine Kinase Inhibitors: A Registry-Based Study of the Italian Blood and Marrow Transplantation Society (GITMO)

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A B S T R A C T

We performed a nationwide registry-based analysis to describe the clinical outcome of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph^+ ALL) who underwent an allogeneic hematopoietic stem cell transplantation (HSCT) after a tyrosine kinase inhibitor (TKI)-based treatment

A total of 441 patients were included in the study. The median age at HSCT was 44 years (range, 18 to 70 years). All 441 patients (100%) received TKI before HSCT (performed between 2005 and 2016). Of these 441 patients, 404 (92%) were in cytologic complete remission (CR), whereas the remaining 37 (8%) had active disease at the time of HSCT. Molecular minimal residual disease (MRD) was negative in 147 patients (36%) at the time of HSCT. The donor was unrelated in 46% of patients. The most prevalent source of stem cells was peripheral blood (70%). The conditioning regimen was myeloablative in 82% of cases (total body irradiation-based in 50%) and included antithymocyte globulin in 51% of patients. With a median follow-up after HSCT of 39.4 months (range, 1 to 145 months), the probability of overall survival (OS) at 1, 2, and 5 years was 69.6%, 61.1% and 50.3%, respectively, with a median OS of 62 months. Progression-free survival (PFS) at 1, 2, and 5 years was 60.2%, 52.1% and 43.7%, respectively. OS and PFS were significantly better in patients who were in CR and MRD-negative at the time of HSCT compared with patients who were in CR but MRD-positive (50% OS not reached versus 36 months; $P = .015$; 50% PFS not reached versus 26 months, $P = .003$). The subgroup of MRD-negative patients both at HSCT and at 3 months after HSCT had a better outcome (5-year OS, 70%). Conversely, the 37 patients who underwent a HSCT with active Ph^+ ALL had a median OS of 7 months and a median PFS of 5 months. The 5-year cumulative incidence of relapse was significantly lower in MRD-negative patients (19.5% versus 35.4%; $P = .001$). Nonrelapse mortality (NRM) after 1, 2, and 5 years was 19.1% (95% confidence interval [CI], 15.5% to 22.9%), 20.7% (95% CI, 17% to 24.7%), and 24.1% (95% CI, 20% to 28.5%), respectively. NRM was significantly lower with a modified European Society for Blood and Marrow Transplantation (mEBMT) risk score of 0 to 2 compared with ≥ 3 (15% versus 25%; $P = .016$). The median OS for Ph^+ ALL patients who underwent a TKI-based treatment followed by an allogeneic HSCT, in recent years at the GITMO centers, was 62 months. Evaluation of the mEBMT risk score can be useful to predict NRM. Our data confirm that HSCT is a potentially curative treatment for Ph^+ ALL with an excellent outcome for the subgroup of MRD-negative patients both at HSCT and at 3 months after HSCT (5-year OS, 70%).

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INTRODUCTION

Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph^+ ALL) accounts for 25% to 30% of adult ALL cases. It has historically been associated with a very unfavorable prognosis, with a 5-year overall survival (OS) rate of $<20\%$ according to the major epidemiologic studies available [1,2]. For many years, the treatment of Ph^+ ALL has been based on intensive chemotherapy regimens, followed by allogeneic hematopoietic stem cell transplantation (HSCT), which remains the sole established procedure with curative intent for this disease [2-4]. Over the last decade, tyrosine kinase inhibitors (TKIs), mainly imatinib and dasatinib and more recently ponatinib, have been incorporated into both chemotherapy-based and chemotherapy-free induction regimens [2,5-15]. The outcome improvement achieved by TKI-based treatments has challenged the concept that a transplantation-based consolidation of remission is always mandatory [16-18].

In light of these recent changes to treatment, several groups have conducted extensive data reviews to update the results of HSCT in patients with Ph^+ ALL in the TKI era, paying attention to both the pretransplantation and post-transplantation phases [2,12,14,19,20]. In particular, the European Society for Blood and Marrow Transplantation (EBMT) and the Japan Society for Hematopoietic Cell Transplantation (JSHCT) recently reviewed the outcomes of patients with Ph^+ ALL undergoing HSCT in their centers in recent decades (from 2000 to 2010 for the EBMT and from 1990 to 2000 for the JSHCT) [14,19]. Here we report the results obtained by the Italian Blood and Marrow Transplantation Society (GITMO) on the outcomes of adult Ph^+ ALL patients who underwent HSCT between 2005 and 2016 in the TKI-based treatment era.

METHODS

Study Design

This retrospective nationwide analysis was based on registry data collected by GITMO. Inclusion criteria were (1) diagnosis of Ph^+ ALL and age ≥ 18 years at HSCT; (2) patients undergoing first allogeneic HSCT from any type of donor (HLA-identical sibling donor, unrelated donor [UD], or alternative donor [haploidentical or cord blood]) between 2005 and 2016 in a GITMO center; (3) receipt of TKI-based treatment before HSCT; and (4) available pretransplantation minimal residual disease (MRD) status, as well as complete clinical data and outcome data. Data were extracted from the GITMO Registry (PROMISE Registry).

The endpoints of the study were OS, progression-free survival (PFS), cumulative incidence of relapse (CIR), nonrelapse mortality (NRM), cumulative incidence of extensive chronic graft-versus-host disease (EcGVHD), rate of MRD negativity, and rate of complete cytologic remission (CR) before and after transplantation.

Data were centrally reviewed following the initial collection, and specific queries for any conflicting and/or missing information were sent to the relevant parties.

All patients included in the registry provided informed consent. The study was conducted in compliance with current national and European legislation on clinical trials, in accordance with the Helsinki Declaration and the principles of good clinical practice. This study was approved by the GITMO Board and by the Institutional Review Boards of the coordinating center (Hematology, University of Udine) and all participating centers.

The institutions that provided data included in this study are listed in Supplementary Table 1.

Definitions

CR was defined as the absence of circulating blasts, $<5\%$ bone marrow blasts, and a platelet count of $\geq 100 \times 10^9$/L. Relapse was defined as the reappearance of $>5\%$ leukemic cells in bone marrow aspirates or extramedullary leukemia in patients with previously documented CR.

Cytogenetic analysis was performed using the G-banding technique. BCR-ABL transcripts were detected by real-time quantitative polymerase chain reaction (qPCR) according to validated methods [21,22]. MRD negativity was defined as undetectable BCR-ABL mRNA transcripts by real-time qPCR. Investigators were asked to provide MRD data at the time of HSCT (within 30 days before the procedure) and after HSCT.

The HSCT-Specific Comorbidity Index (HCT-CI) and the modified EBMT (mEBMT) risk score (specific for ALL) were calculated according to recently published parameters [23,24].

Acute GVHD (aGVHD) was computed when graded >1 based on standard criteria and requiring therapy. cGVHD was classified as none, limited, or extensive according to the Seattle criteria [23,25]. aGVHD persisting or progressing after day +100 was scored as cGVHD.

The timing of HSCT, conditioning regimen, GVHD prophylaxis, and post-HSCT timing of BCR-ABL monitoring were defined by each institution according to their active protocols.

Statistical Analysis

To compare baseline characteristics or outcome measures among subgroups, we used the chi-square or Fisher exact test for categorical variables, the Student *t* test for normally distributed variables, and the Mann-Whitney or Kruskal-Wallis test for non-normally distributed variables. Median follow-up time was calculated among survivors.

OS was defined as the time from HSCT to death, regardless of the cause. PFS was considered to be survival following HSCT with no evidence of relapse or progression. Death from any cause was considered an event for OS, whereas relapse/progression and death from any cause were considered events for PFS. OS and PFS were computed using the Kaplan-Meier method. Univariate and multivariate analyses were performed using the Cox proportional hazard method.

The cumulative incidence method was used for computing CIR, NRM, and EcGVHD in a competing-risks setting. CIR was estimated by considering relapse as the event of interest and death without relapse as a competing event. NRM was defined as death without evidence of relapse or progression, with relapse as a competing event.

EcGVHD was estimated by considering the occurrence of EcGVHD as an event of interest and death without cGVHD as a competing risk, with leukemia relapse treated as a competing risk if it occurred without previous GVHD.

Predictive analyses for EcGVHD, CIR, and NRM were based on the proportional hazards model for subdistribution of competing risk. Univariate and multivariate analyses were then performed using Gray's test and the proportional subdistribution hazard regression model developed by Fine and Gray. In general, a stepwise backward procedure was used to construct a set of independent predictors for each endpoint. All predictors with a *P* value <.20 were initially considered and then sequentially removed if the *P* value in the multiple model was >.05. All tests were 2-sided. The type I error rate was fixed at .05. However, the whole procedure and the final model accounted for manual adjustments, that is, exclusion of variables with partial overlapping information (collinearity) or categorization of continuous or nondichotomous categorical variables according to clinical relevance. Factors considered were patient sex, disease characteristics at diagnosis [ie, presence of hyperleukocytosis, defined as $>30 \times 10^9$ WBC/L; additional cytogenetic abnormalities beyond t(9:22)], pretransplantation therapeutic strategy (ie, use of TKI plus steroids versus TKI plus chemotherapy), patient age at transplantation, donor sex, disease status at the time of transplantation (CR1 versus CR2 and subsequent CR versus advanced disease), donor type (matched sibling donor versus UD versus alternative donor, ie, haploidentical or cord blood), stem cell source (peripheral blood versus bone marrow versus cord blood), year of transplant, time from diagnosis to transplantation, recipient and donor cytomegalovirus serostatus, HCT-CI at transplantation, Karnofsky Performance Status (KPS) score at transplantation (≥90 versus <90), molecular remission status at transplantation, type of conditioning (reduced-intensity conditioning [RIC] versus myeloablative conditioning [MAC]), and the use of antithymocyte globulin (ATG) and total body irradiation (TBI) in the conditioning regimen. Patient age and year of transplant were analyzed as continuous variables. To evaluate the impact of the molecular response measured in the first 3 months after HSCT on survival endpoints, a landmark analysis was applied for OS and PFS using day 90 after HSCT as the landmark. All analyses were performed using Stata 12.0 (StataCorp, College Station, TX).

RESULTS

Patients and Ph$^+$ ALL Status at HSCT

A total of 441 patients were included in the study. The main clinical findings are reported in Table 1. The median age at transplantation was 44 years (range, 18 to 70 years). Additional karyotype abnormalities were reported in 30% of evaluable patients (124 of 416). All 441 patients (100%) received TKI therapy before transplantation; 80 (18%) had received TKI plus steroids, and 361 (82%) had received TKI plus chemotherapy. Compared with the patients treated with TKI plus steroids, those who received TKI plus chemotherapy had a significantly higher leukocyte count at the diagnosis of ALL (*P* = .001). The median number of TKI lines of therapy before HSCT were 1 (range, 1 to 3). In detail, as a first-line TKI therapy, 280 of 441 patients (63%) received imatinib, 148 (34%) received dasatinib, and only 13 (3%) received ponatinib or nilotinib. As second-line TKI therapy, 76% of patients (100 of 131) received dasatinib, 12% received ponatinib, 6% received imatinib, and 6% received other TKIs. The median interval between the diagnosis of Ph$^+$ ALL and HSCT was 7.7 months (range, 2.3 to 78.8 months) with no significant difference between the 2 pre-HSCT treatment groups (*P* = .83). Patients who underwent HSCT in CR1 had a shorter interval between diagnosis to HSCT (median, 6.5 months) compared with patients who underwent HSCT in >CR1 (median, 11.4 months) and patients with active disease at HSCT (median, 10 months; *P* for any difference among groups <.001).

Table 1
Patients and Ph$^+$ ALL Characteristics

Characteristic	Value
Number of patients	441
Age at diagnosis, yr, median (range)	43 (16-68)
Sex, male/female, n	230/211
Ph$^+$ ALL mature phenotype, n/N (%)	39/397 (9.8)
Additional cytogenetic abnormalities, n/N (%)	124/416 (30)
BCR-ABL transcript type, n/N (%)	
p190	293/431 (68)
p210	108/431 (25)
p190/p210	30/431 (7)
WBC at diagnosis, $\times 10^9$/L, median (range)	59.1 (.2-451)
WBC >30, $\times 10^9$/L, n/N (%)	160/374 (43)
WBC >100, $\times 10^9$/L, n/N (%)	62/374 (17)
Number of TKI lines, median (range)	1 (1-3)
Number of TKI lines, mean	1.5
Time from diagnosis to HSCT, median (range)	7.67 (2.3-78.8)
Ph$^+$ ALL status at HSCT, n/N (%)	
CR	404/441 (92)
CR1	337/404 (83)
CR >1	67/404 (17)
Relapsed/refractory	37/441 (8)
MRD status at HSCT, n/N (%)	
CR, MRD$^+$	257/404 (64)
CR, MRD$^-$	147/404 (36)

Of these 441 patients, 404 (92%) were in CR at the time of HSCT, whereas 37 (8%) had active disease. In detail, of the 404 patients in CR at the time of HSCT, 337 (83%) were in CR1, whereas 67 (17%) were in CR2 or subsequent CR. A significantly higher percentage of patients who underwent HSCT in >CR1 had been treated with TKI plus chemotherapy (CHT) before HSCT (20% versus 4%; *P* < .001).

One hundred forty-seven of 404 patients (36%) in CR were MRD-negative at the time of HSCT. Overall, a significantly higher proportion of patients treated with TKI plus steroids were MRD-negative at the time of transplantation compared with patients treated with TKI plus CHT (40 of 76 [53%] versus 107 of 328 [33%]; *P* = .001). However, there was no difference when we compared only the cases who underwent transplantation in CR1.

Transplantation Characteristics and Outcomes

Patients received a variety of HSCT preparative regimens based on existing available protocols at the time of treatment. Only 27% (118 of 441) of HSCTs were performed between 2005

Table 2
HSCT Characteristics

Characteristic	Value
Number of patients	441
Age at transplantation, yr, median (range)	44 (18-70)
Donor type, n/N (%)	
Sibling HLA-identical	159/441 (36)
Matched unrelated	201/441 (46)
Haploidentical	68/441 (15)
Cord blood	13/441 (3)
Stem cell source, n/N (%)	
Bone marrow	117/441 (27)
Peripheral blood	311/441 (70)
Cord blood	13/441 (3)
Conditioning regimen, n/N (%)	
MAC	362/441 (82)
RIC	79/441 (18)
TBI-based	221/441 (50)
GVHD prophylaxis, n/N (%)	
ATG	226/441 (51)
CNI + MTX/MMF	352/441 (80)
Use of PT-CY	23/441 (5)
Other	66/441 (15)
HCT-CI, n/N (%)	
0-2	382/402 (95)
≥3	20/402 (5)
GVHD, n/N (%)	
aGVHD requiring therapy (grade >1)	181/441 (41)
cGVHD requiring therapy (limited or extensive)	127/441 (29)

CNI indicates calcineurin inhibitor; MTX, methotrexate; MMF, mycophenolate mofetil;
PT-CY, post-transplantation cyclophosphamide.

and 2010, whereas 73% (323 of 441) were performed between 2011 and 2016. The main characteristics of the HSCTs are reported in Table 2. The donor was unrelated in 46% of cases and the prevalent source of stem cells was peripheral blood-PB (70%). The conditioning regimen was MAC in 82% of cases and TBI-based in 50% of cases. ATG was used in 51% of cases. The HCT-CI score (available in 402 cases) ranged from 0 to 2 in 95% of patients. The median duration of follow-up after transplantation was 39.4 months (range, 1 to 145 months), and 26.3% (116 of 441) of patients experienced a cytologic relapse; of these 72% died, at a median of 4.5 months after relapse.

The OS probability at 1, 2, 3, and 5 years post-transplantation was 69.6% (95% confidence interval [CI], 65% to 73.8%), 61.1% (95% CI, 56.2% to 65.7%), 52.4% (95% CI, 46.8% to 57.1%), and 50.3% (95% CI, 44.9% to 55.4%), respectively. The PFS probability at 1, 2, 3, and 5 years was 60.2% (95% CI, 55.7% to 64.7%), 52.1% (95% CI, 47.4% to 56.8%), 45.1% (95% CI, 40.2% to 50%), and 43.7% (95% CI, 38.7% to 48.7%), respectively.

Among patients in CR, OS and PFS after HSCT were significantly better in patients who were MRD-negative at the time of HSCT compared with MRD-positive patients ($P = .015$ for OS and $P = .003$ for PFS) (Figure 1A-D). The CIR was 27.9% (95% CI, 23.6% to 32.3%) at 2 years and 31.8% (95% CI, 27.1% to 36.5%) at 5 years (Figure 2A). As expected, CIR was significantly lower in patients who were MRD-negative at the time of transplantation compared with those who were MRD-positive (Gray's test: subdistribution hazard ratio [SHR], .47; 95% CI, .31 to .73; $P = .001$) (Figure 2B). NRM occurred in 96 of the 441 patients (22%); causes of NRM were GVHD in 49 patients (51%), infections in 33 (35%), thrombotic thrombocytopenic purpura in 6 (6%), veno- occlusive disease in 1 (1%), and other causes in 7 (7%). For the entire study population, the cumulative incidence of NRM at 1, 2, 3, and 5 years was 19.1% (95% CI, 15.5% to 22.9%), 20.7% (95% CI, 17% to 24.7%), 24.1% (95% CI, 20% to 28.5%), and 24.1% (95% CI, 20% to 28.5%), respectively (Figure 2C). According to the mEBMT risk score, NRM was 6% (2 of 35) in patients with score of 0 to 1, 18% (23 of 127) in patients with a score of 2, 23% (31 of 133) in patients with a score of 3, and 27% (40 of 146) in those with a score >3. NRM was significantly higher in patients with an mEBMT risk score ≥3 compared with those with a score of 0 to 2 (25% versus 15%; $P = .016$).

aGVHD requiring therapy was reported in 41% of patients, and cGVHD requiring therapy was documented in 29% of patients. The cumulative incidence of extensive cGVHD at 2 and 5 years post-HSCT was 18.5% (95% CI, 14.9% to 22.4%) and 19.8% (95% CI, 16% to 23.9%), respectively (Figure 2D). The CIR was lower in patients with aGVHD requiring therapy (14.6% versus 23.5%; $P < .001$) in univariate analysis, but this result was not confirmed in the multivariate analysis.

The 37 patients who underwent transplantation with active Ph^+ ALL had very unfavorable outcomes, with a median post-HSCT OS of only 7 months and PFS of 5 months (Figure 1C and D).

Univariate analysis identified numerous factors as associated with a favorable OS, including younger age, shorter interval between diagnosis and CR1, early disease phase (CR1) at the time of transplant, CR with MRD negativity at the time of transplantation, KPS >90%, and use of a matched sibling or unrelated donor (Table 3). The inclusion of TBI in the conditioning regimen was an additional favorable factor for PFS (Table 3).

However, on multivariate analysis, the following favorable predictive factors for OS and PFS remained: the use of a matched sibling or unrelated donor ($P = .001$), being in CR1 at the time of HSCT ($P < .001$), a CR with MRD negativity at the time of transplantation, younger age ($P = .013$ for OS), transplantation in the most recent period (P = .008), and the use of TKI plus CHT before HSCT ($P = .035$) (Table 4).

Early disease phase, MRD negativity ($P = .008$), younger age, and more recent period of transplantation were also found to significantly predict the incidence of relapse. The donor type had no significant effect, whereas the use of TBI in the conditioning regimen confirmed its protective effect on relapse ($P = .001$).

In multivariate analysis, the incidence of EcGVHD was significantly associated with the use of HLA-mismatched donors (alternative versus UD and sibling; HR, .41; $P = .019$) and female donors (HR, 1.77; $P = .01$). Of note, the use of ATG was associated with a reduced risk of EcGVHD (HR, .56; $P = .011$) without an increased risk of relapse.

Impact of Disease Status at 3 Months Post-HSCT on Outcome

A total of 421 patients were reevaluated for MRD within the third month after HSCT, and 302 (72%) were MRD-negative. In particular, 177 of the 294 patients (60%) who were MRD-positive or had active disease converted to a MRD-negative status within 3 months after HSCT (Supplementary Table 2).

A landmark analysis for OS and PFS showed that post-transplantation MRD negativity (at the third month) had a significantly favorable effect on OS and PFS post-HSCT (Supplementary Figure 1). However, roughly one-third (100 of 302) of the patients who were MRD-negative at 3 months post-HSCT experienced subsequent molecular relapse, at a median of 8 months after transplantation (range, 5 to 108 months). Unfortunately, in these cases of molecular relapse, a

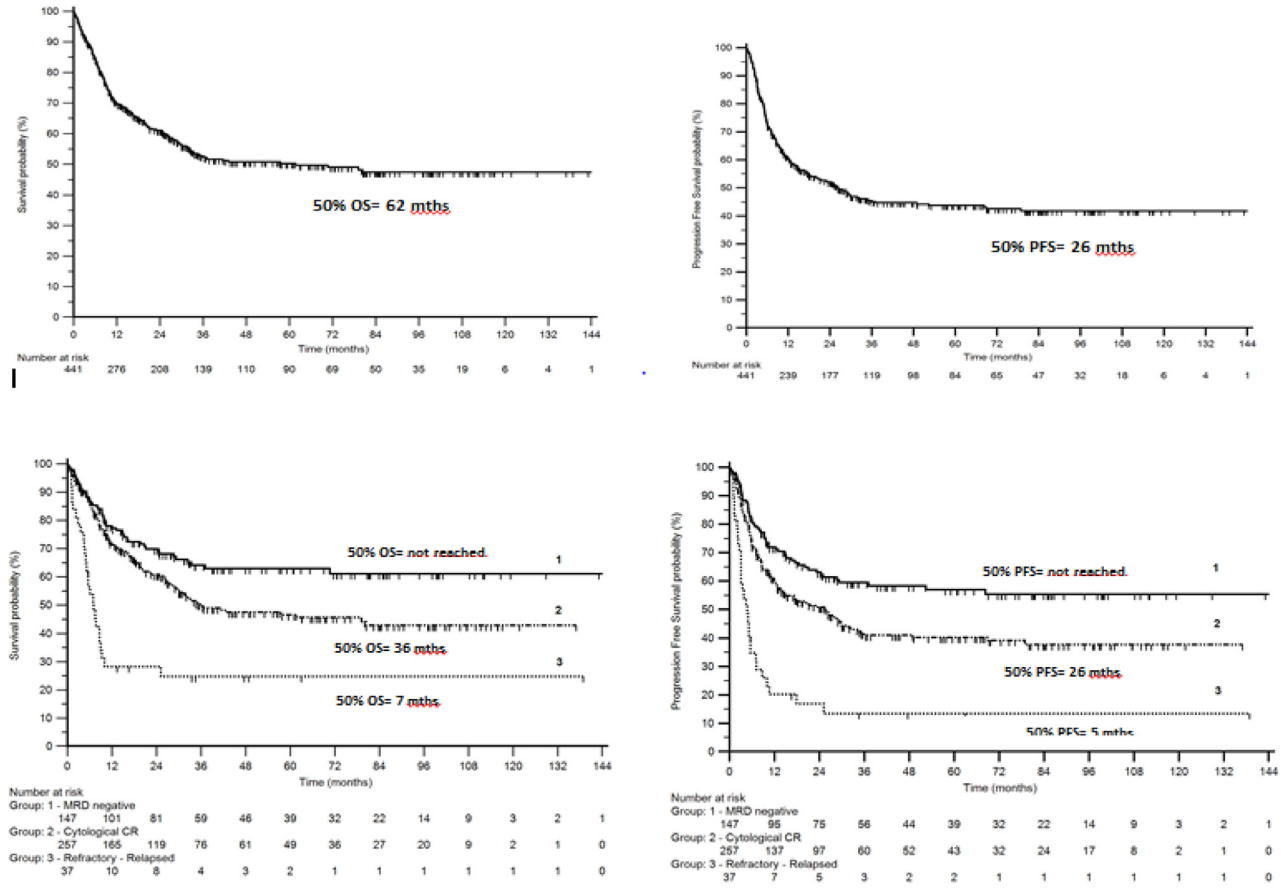

Figure 1. (A) Post-HSCT OS of the entire study population (median OS, 62 months). (B) Post-HSCT PFS of the entire study population (median PFS, 26 months). (C) OS according to status at HSCT (1, MRD-negative; 2, cytologic CR but MRD-positive; 3, refractory or relapsed MRD-negative versus MRD-positive ($P = .0015$). (D) PFS from according to status at HSCT (1, MRD-negative; 2, cytologic CR but MRD-positive; 3, refractory or relapsed MRD-negative versus MRD-positive; $P = .003$).

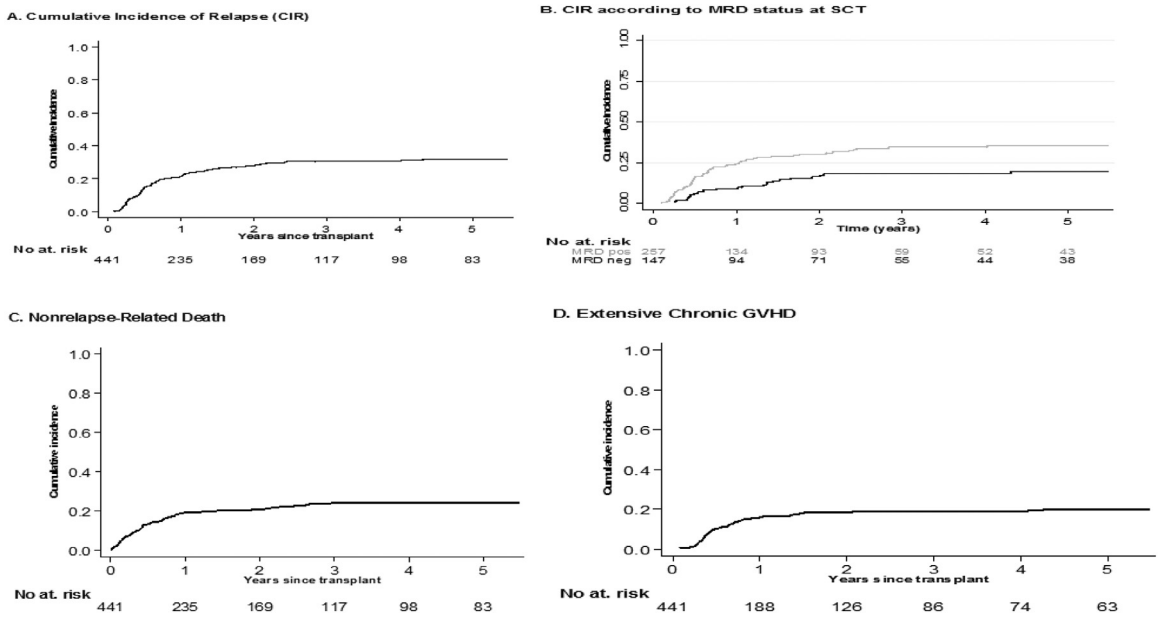

Figure 2. (A) CIR at 2 years, 27.9% (95% CI, 23.6% to 32.3%), and 5 years, 31.8% (95% CI, 27.1% to 36.5%). (B) CIR according to MRD status at SCT. Gray test, SHR, .47 (95% CI, .31 to .73); $P = .001$. CIR at 1, 2, and 5 years for MRD-negative patients: 9.1% (95% CI, 5.1% to 14.5%), 16.3% (95% CI, 1.6% to 23.1%), and 19.5% (95% CI, 13% to 27%), respectively; CIR at 1, 2, and 5 years for MRD-positive patients: 24.3% (95% CI, 19.2% to 29.8%), 30.3% (95% CI, 24.6% to 36.2%), and 35.4% (95% CI, 29.1% to 41.7%), respectively. (C) NRM at 1, 2, 3, and 5 years: 19.1% (95% CI, 15.5% to 22.9%), 20.7% (95% CI, 17% to 24.7%), 24.1% (95% CI, 20% to 28.5%), and 24.1% (95% CI, 20% to 28.5%), respectively. (D) Cumulative incidence of extensive cGVHD at 1, 2, 3, and 5 years: 16% (95% CI, 12.7% to 19.6%), 18.5% (95% CI, 14.9% to 22.4%), 18.8% (95% CI, 15.2% to 22.7%), and 19.8% (95% CI, 16% to 23.9%), respectively.

Table 3
Univariate Analysis of Predictors for OS, PFS, RI, NRM, and EcGVHD

Variable	Comparison	OS		PFS		NRM		RI		EcGVHD	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	SHR (95% CI)	*P* Value	SHR (95% CI)	*P* Value	SHR (95% CI)	*P* Value
Age	Per 10 yr more	1.13 (1.01-1.28)	.037	1.09 (.97-1.21)	.143	1.36 (1.13-1.62)	.001	.88 (.76-1.01)	.074	1.1 (.92-1.31)	.291
Male recipient	Yes vs no	1.16 (.88-1.54)	.297	1.22 (.94-1.58)	.131	1.41 (.95 − 2.1)	.089	1.03 (.73-1.45)	.877	.98 (.63-1.51)	.922
WBC at diagnosis, $\times 10^9$/L	> 30 vs < 30	1.24 (.91-1.69)	.18	1.11 (.83-1.49)	.473	1.02 (.66-1.58)	.93	1.14 (.77-1.67)	.51	1 (.63-1.59)	.996
Additional karyotypic abnormalities	Yes vs no	1.05 (.77-1.43)	.77	1.05 (.78-1.4)	.754	.94 (.6-1.47)	.771	1.09 (.74-1.61)	.657	1.06 (.67-1.7)	.795
Transplantation year	Each year later	.96 (.92-1.01)	.119	.97 (.93-1.01)	.178	.98 (.92-1.04)	.525	.96 (.91-1.02)	.177	.95 (.89-1.01)	.129
Pretransplantation therapy	TKI + CHT vs TKI + steroid	.8 (.58-1.11)	.177	.78 (.58-1.05)	.106	.86 (.54-1.35)	.51	.81 (.55-1.19)	.283	1.46 (.82-2.61)	.202
Interval diagnosis to CR1	> median vs < median	1.51 (1.14-2)	.005	1.54 (1.18-2)	.001	1.36 (.92-2.03)	.127	1.42 (1-2)	.047	.75 (.49-1.17)	.207
Disease status at HSCT	$CR2^+$ vs CR1	2 (1.4-2.86)	≤.001	2.03 (1.45-2.84)	≤.001	1 (.56-1.8)	.988	2.42 (1.58-3.71)	≤.001	.59 (.28-1.23)	.159
	Adv vs CR1	3.46 (2.28-5.27)	≤.001	3.67 (2.49-5.42)	≤.001	1.54 (.79-3)	.202	3.31 (1.94-5.63)	≤.001	.8 (.35-1.84)	.601
MRD status at HSCT	Negative vs positive	.59 (.43-.82)	.002	.56 (.42-.76)	≤.001	.96 (.63-1.46)	.849	.43 (.28-.65)	≤.001	1.7 (1.1-2.62)	.018
HCT-CI	HCT-CI ≥3 vs <3	.83 (.53-1.3)	.417	.69 (.45-1.05)	.082	.8 (.43-1.5)	.492	.69 (.39-1.2)	.19	.68 (.33-1.41)	.305
KPS at HSCT	KPS ≥90%	.62 (.45-.85)	.003	.76 (.56-1.04)	.091	.78 (.49-1.24)	.295	.86 (.56-1.32)	.49	1.08 (.61-1.91)	.79
Donor type	Sibling vs MUD	.88 (.64-1.22)	.444	.91 (.67-1.22)	.517	.59 (.36-.97)	.039	1.25 (.86-1.82)	.25	1.39 (.88-2.2)	.157
	Alternative vs MUD	1.8 (1.26-2.57)	.001	1.67 (1.2-2.33)	.003	1.78 (1.11-2.84)	.017	1.15 (.71-1.87)	.562	.54 (.25-1.17)	.117
Female donor	Yes vs no	.87 (.65-1.17)	.363	.86 (.66-1.12)	.259	.89 (.59-1.34)	.575	.91 (.64-1.3)	.609	1.7 (1.1-2.63)	.016
Cytomegalovirus serostatus	D-/R- vs D+/R+	.76 (.45-1.29)	.313	.88 (.56-1.39)	.584	.74 (.33-1.68)	.478	.98 (.57-1.69)	.948	1.1 (.56-2.17)	.787
	D-/R+ vs D+/R+	1.23 (.89-1.71)	.204	1.08 (.79-1.47)	.637	1.64 (1.06-2.53)	.027	.7 (.45-1.09)	.112	.68 (.38-1.21)	.188
	D+/R- vs D+/R+	.87 (.49-1.54)	.629	.93 (.55-1.57)	.787	1.08 (.49-2.36)	.85	.86 (.42-1.74)	.666	1.3 (.62-2.72)	.485
Conditioning regimen	MAC vs RIC	.83 (.59-1.17)	.289	.84 (.61-1.17)	.305	.86 (.53-1.4)	.546	.86 (.56-1.33)	.497	.97 (.55-1.69)	.91
Source of HSC	BM vs PB	1.04 (.75-1.43)	.832	1.03 (.76-1.38)	.867	1.24 (.8-1.94)	.333	.83 (.55-1.25)	.369	.74 (.44-1.26)	.267
	CB vs PB	1.83 (.9-3.73)	.098	1.66 (.85-3.24)	.141	2.11 (.81-5.5)	.127	.96 (.34-2.71)	.943	.34 (.05-2.33)	.27
Use of ATG	Yes vs no	.82 (.62-1.09)	.177	.88 (.68-1.15)	.357	.78 (.53-1.17)	.229	1.03 (.73-1.45)	.878	.54 (.34-.85)	.007
TBI-containing regimen	Yes vs no	.86 (.65-1.14)	.305	.72 (.55-.94)	.014	1.16 (.78-1.72)	.471	.56 (.39-.79)	.001	1.45 (.93-2.26)	.099

systematic evaluation of BCR-ABL mutations was not available, and thus these data were not evaluable in this study.

TKI Use Post-HSCT

A detailed analysis of TKI use post-HSCT is not included in the endpoints of this study; however, a TKI inhibitor was used in 40% of patients (178 of 441) in the post-transplantation phase. In 74% of these patients, TKIs were used as preemptive (53%; n = 94) or prophylactic (21%; n = 38) therapy before cytologic relapse. The reasons for TKI use post-HSCT (eg, prophylaxis, preemptive, cytologic recurrence) were highly variable across the various centers. As expected, the time to TKI initiation was shorter in the prophylaxis (median, 102 days from transplantation; range, 17 to 259 days) and preemptive (median, 128 days; range, 26 to 3233 days) groups compared with the relapse group (median, 192 days; range, 35 to 964 days).

Among the 38 patients who started on TKI post-HSCT prophylactically, 13 (34%) experienced molecular relapse after a median of 5.1 months (range, .9 to 47.6 months); of these, 5 had a concurrent relapse and 3 had a later cytologic relapse, and 5 never relapsed cytologically. Ninety-four patients started on TKI after HSCT because of molecular relapse (preemptive strategy); of these, 38 (40%) had a cytologic relapse after a median of 4.8 months (range, .4 to 76.6 months) from the start of TKI therapy. In this group of patients treated preemptively (complete data available for 88 patients), the probability of cytologic relapse-free survival (from the start of TKI) was 64.7% (95% CI, 53.2% to 74%) at 1 year, 57% (95% CI, 45.1% to 67.3%) at 2 years, and 55.1% (95% CI, 43% to 65.6%) at 5 years.

The TKI used after HSCT was dasatinib in 45.5% of the patients (81 of 178), imatinib in 35.3% (n = 63), ponatinib in 16.3% (n = 29), and nilotinib in 2.2% (n = 4). When analyzed according to treatment strategy, dasatinib was still the most widely used TKI in the prophylactic group (45%; n = 17) and the relapse group (59%), whereas imatinib was the most widely used in the pre-emptive group (46%; n = 43). As expected, ponatinib was used mostly in the relapse group (n = 14; 48% of 29 patients using ponatinib after HSCT).

In addition, 49 of the 441 patients (11%) received donor lymphocyte infusion (DLI) after HSCT, including 27 of 49 (55%) after a cytologic relapse and 22 (45%) after a molecular relapse. The median number of DLIs was 3 (range, 1 to 10), and DLI was combined with TKI in the majority of cases (41 of 49; 84%). After a median follow-up of 13 months (range, 1 to 110) from the first DLI, 23 of 49 patients (47%) were alive and 26 (53%) had died (70% due to leukemia). As expected, the median OS was longer for patients who received preemptive DLI (61 months versus 13 months).

DISCUSSION

For many years, the curative options for Ph^+ ALL have been extremely limited, with chemotherapy followed by HSCT, when appropriate, the primary standard of care for this most unfavorable subgroup of patients. This approach was associated with a 5-year OS rate of 30% to 35% and an expected 5-year OS rate of 10% to 15% for patients who could not undergo HSCT [11,17,26]. In recent years, the therapeutic landscape for patients with Ph^+ ALL has improved significantly with the introduction of new drugs, including second- and third-generation TKI, followed by anti-CD19 and anti-CD22 monoclonal antibodies (blinatumomab and inotuzumab), and, more recently, chimeric antigen receptor T cell (CAR-T cell) therapy [27-34]. With TKI treatment, with or without systemic chemotherapy, virtually all patients can attain CR status, and some proportion become MRD-negative. Thus, the key question is how to best consolidate patients in CR. Little data and few studies are available on the outcomes of therapeutic programs including both TKIs and HSCT, and HSCT is still considered a standard of care for consolidating remission in Ph^+ ALL, even though recent results suggest that long-lasting remission can be achieved and maintained even without an allogeneic transplantation [10,27,35-37].

The retrospective nationwide analysis hereby reported was undertaken to evaluate the clinical outcomes of adults with Ph + ALL who underwent HSCT in the TKI-based therapy era. In keeping with previous registry studies, our results confirm the potential curative effect of HSCT in patients with Ph^+ ALL (Table 5) [14,19]. The long-term follow-up of this large series of patients who received a TKI before HSCT indicates that survival rates close to 50% can be achieved, a significant improvement compared with the pre-TKI era [11,14,17,19,26]. A strength of this study is the inclusion of a large number of patients undergoing HSCT in a relatively short and recent period (73% of HSCTs performed between 2011 and 2016), as well as the long duration of follow-up. In addition, all included patients received a TKI-based therapy and underwent qPCR evaluation of MRD before HSCT. As expected, for patients in CR, the main parameter that negatively affected outcome was undergoing HSCT with measurable levels of MRD. Patients with negative MRD before HSCT had significantly better 5-year OS and PFS compared with those with measurable MRD. According to previous studies and registry data, these improved clinical outcomes were due mainly to the reduced CIR in MRD-negative patients [14,19,38-40].

This observation emphasizes the importance of achieving a deep molecular remission before undergoing HSCT, and with this aim, innovative treatment strategies, such as second- and third-generation TKIs (ponatinib and others) and anti-CD19 or anti-CD22 monoclonal antibodies, should be tested in the first-line setting to increase the rate of complete molecular response in patients with Ph^+ ALL. This is indeed the strategy of the current GIMEMA LAL 2116 protocol for adults of all ages with Ph^+ ALL who are treated with dasatinib plus steroids in first induction followed by consolidation with blinatumomab. The primary endpoint of this ongoing GIMEMA LAL 2116 study is the rate of complete molecular response. Unsurprisingly, the importance of achieving complete molecular remission also applies for patients who are excluded from HSCT as part of the front-line treatment, and the long-term PFS that has been reported in some patients who achieve a MRD-negative status without HSCT highlights the need for future prospective clinical trials comparing HSCT with the available innovative treatments based on TKIs and immunotherapy [35,36,41]. The interesting results arising from some recent, but not randomized, clinical trials confirm the clinical relevance of achieving a complete molecular remission and also pose a challenge to the indication to perform allogeneic HSCT in all MRD-negative patients as essential postremission therapy [27,35].

Interestingly, despite the evident advantage of being molecularly negative before transplantation, our data confirm that HSCT is able to convert a significant proportion of patient (60%) from MRD-positive at the time of conditioning to MRD-negative. Moreover, the subgroup of patients who were MRD-negative both at HSCT and at 3 months post-HSCT had better outcomes, with a 5-year OS rate of 70%. Conversely, the presence at conditioning of documented cytologic active disease (relapsed or refractory) was associated with very dismal outcomes, with median OS and PFS of only 7 and 5 months, respectively. These observations clearly demonstrate that

Table 4
Multivariate Analysis of Significant Predictors for OS, PFS, RI, NRM, and EcGVHD

Variable	Comparison	HR (95% CI)	*P*Value
OS			
Donor	Alternative vs other (sibling + UD)	1.77 (1.26-2.49)	.001
Disease status at HSCT	$CR2^+$ vs CR1	1.99 (1.39-2.87)	<.001
	Adv vs CR1	2.75 (1.76-4.31)	<.001
Age	Per 10 yr more	1.17 (1.03-1.32)	.013
MRD status at HSCT	Negative vs positive	.65 (.46-.91)	.011
Pre-HSCT strategy	TKI + CHT vs TKI + steroids	.7 (.5-.97)	.035
Transplantation year	Each year later	.94 (.9-.98)	.008
PFS			
Donor	Alternative vs other (sibling + UD)	1.61 (1.16-2.22)	.004
Disease status at HSCT	$CR2^+$ vs CR1	2.05 (1.46-2.89)	<.001
	Adv vs CR1	2.71 (1.78-4.11)	<.001
MRD status at HSCT	Negative vs positive	.6 (.44-.81)	.001
Pre-HSCT strategy	TKI + CHT vs TKI + steroids	.63 (.46-.86)	.003
Transplantation year	Each year later	.95 (.91-1)	.036
NRM			
Donor	Sibling vs UD	.58 (.35-.94)	.027
	Alternative vs UD	1.74 (1.09-2.8)	.021
Age	Per 10 yr more	1.4 (1.16-1.68)	<.001
Male recipient	Yes vs no	1.52 (1.01-2.28)	.047
RI			
Disease status at HSCT	$CR2^+$ vs CR1	2.55 (1.66-3.91)	<.001
	Adv vs CR1	2.38 (1.39-4.06)	.002
Age	Per 10 yr more	.8 (.69-.93)	.003
MRD status at HSCT	Negative vs positive	.54 (.35-.85)	.007
TBI-containing regimen	Yes vs no	.52 (.36-.75)	.001
Transplantation year	Each year later	.94 (.89-1)	.047
EcGVHD			
Donor	Alternative vs other (sibling + UD)	.41 (.2-.87)	.019
Use of ATG	Yes vs no	.56 (.35-.88)	.011
Female donor	Yes vs no	1.77 (1.15-2.74)	.01

patients with Ph^+ ALL with refractory disease should be offered new experimental treatments to induce at least a hematologic response before being considered eligible for HSCT [27-33].

Despite clear progress, NRM, even when reduced, remains a major concern (22% in this cohort) affecting the decision to perform allogeneic HSCT in these patients, but in this regard, the evaluation of the mEBMT risk score can be useful for predicting NRM [23,24]. Of course, receipt of a transplant from a mismatched donor remains associated with a significantly higher risk of NRM, most likely as a consequence of increased GVHD [14,19]. In this study, a large proportion of patients (49%) did not undergo in vivo T cell depletion, and we observed a relatively high incidence of EcGVHD (5-year cumulative incidence of 19%), and this should be carefully considered when planning future clinical trials with specific GVHD prophylaxis [42]. In this regard, we emphasize that in the present study, the use of ATG was associated with a reduced risk of EcGVHD without an increased risk of relapse (Tables 3 and 4).

Moreover, the deep molecular remission achievable in a proportion of patients before HSCT strongly suggests that the use of RIC regimens should be considered in patients with Ph^+ ALL, particularly those who are MRD-negative and >50 years old. In this setting, preliminary uncontrolled studies suggest that RIC regimens may represent a good alternative to MAC regimens [37,43].

Another controversial issue is the use of TKIs in the post-transplantation setting to prevent the risk of relapse. In the present study, this analysis was not included in the endpoints, but we noted that post-HSCT TKI treatment was provided to 40% of the patients, in most cases with a preemptive strategy. As expected, outside the context of a prospective clinical study, there was a significant lack of uniformity regarding the criteria on when and how to start and stop TKI treatment after transplantation, precluding our ability to draw any useful conclusions.

Of note, the EBMT Acute Leukemia Working Party recently published a position paper providing detailed recommendations on the post-transplantation use of TKIs [44]. These recommendations clearly emphasize that MRD assessments should be a standard component of post-HSCT disease monitoring, allowing timely initiation of TKI therapy to reduce the risk of overt leukemia relapse [41,44-46].

Some additional limitations of the present study need to be considered, including the heterogeneity of pretransplantation TKI-based programs (with or without chemotherapy), type of conditioning regimens, GVHD prophylaxis, and post-transplantation TKI therapy strategy. All of these limitations preclude us from drawing definitive conclusions regarding the optimal standard of care in this context. In addition, our registry database did not contain specific information about BCR/ABL mutations, such as T315I and others, or on TKI-related complications and doses.

In conclusion, our data confirm that allogeneic HSCT is a potentially curative treatment for Ph^+ ALL, associated with

Table 5
Comparison of the GITMO Study and EBMT/JSHCT Studies

Parameter	GITMO Study	EBMT Study (Brissot et al 2015 [14])	JSHCT Study (Nishiwaki et al 2016 [19])
Number of patients	441	473	432
Study type (time period)	Retrospective (2005-2016)	Retrospective (2000-2010)	Retrospective (1990-2000)
Pretransplantation TKI, n (%)	441 (100)	390 (82.5)	432 (100)
Age at HSCT, yr, median (range)	45 (19-70)	42 (18-70)	43 (16-68)
Status at HSCT, %	CR, 92 (CR1, 83) REF/REL, 8	CR1 (100)	CR1 (100)
MRD-negative at HSCT, %	36	65	64
MAC regimen, %	82	79	86
HSCT from HLA-identical sibling donor, %	36	49	32
OS, %	5 yr: 50.3; 63 MRD^-; 47 MRD^+	5 yr: 46	4 yr: 67 MRD^-; 55 MRD^+
PFS, %	5 yr: 44; 57 MRD^-; 40 MRD^+	5 yr: 38	4 yr: 60 MRD^-; 46 MRD^+
RI, %	5 yr: 19.5 MRD^-; 35.4 MRD^+	5 yr: 36	4 yr: 19 MRD^-; 29 MRD^+
NRM, %	5 yr: 24	5 yr: 26	4 yr: 21 MRD^-; 25 MRD^+
Post-transplantation TKI, n/N (%)	178/441 (40)	157/319 (49)	103/425 (24)
aGVHD, %	41	40 (100 days)	7-9
cGVHD, %	29	53 (5 yrs)	32-33
Impact of MRD negativity	Favorable on OS, PFS, RI	No impact on OS, PFS, RI	Favorable on OS, PFS, RI

Compared with the EBMT and JSHCT registry studies, which included only patients in first CR1 at the time of HSCT, the GITMO study included both patients in CR (337 in CR1 and 67 in >CR1), as well as patients with active disease (37 Ph^+ ALL refractory or relapsed) at the time of HSCT. Accordingly, we found a lower percentage of Ph^+ ALL patients who were MRD-negative at the time of transplantation compared with the other 2 studies (36% versus 65% and 64%). In addition, in the GITMO study, as in the JSHCT study, only the molecular MRD was considered, whereas the EBMT study included several methodologies for the MRD evaluation, such as PCR and flow cytometry. In agreement with the JSHCT registry study, we observed that in patients in CR at the time of HSCT, those attaining pretransplantation MRD-negativity did significantly better than those who were MRD-positive, in terms of OS and PFS.

excellent outcomes in patients who achieve molecular remission before transplantation. Innovative treatment approaches with targeted drugs will be crucial to further improve this scenario, reducing the risk of post-transplantation relapse and NRM. In addition, prophylactic or preemptive post-transplantation therapy with TKIs should be adopted, according to the recent EBMT recommendations, to minimize the risk of leukemia relapse [44]. Future prospective clinical trials comparing postremission strategy with or without HSCT are urgently needed to define the best evidence-based consolidation for Ph^+ ALL patients achieving a deep molecular remission through the incorporation of innovative drugs into frontline treatment. For the time being, while awaiting newer and more consolidated data, we suggest that HSCT be offered to suitable patients with Ph^+ ALL in CR1, taking the mEBMT risk score and patient preference into consideration.

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SUPPLEMENTARY MATERIALS

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2019.07.037.

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