Biology of Blood and Marrow Transplantation

Allogeneic Stem Cell Transplantation for Blast Crisis Chronic Myeloid Leukemia in the Era of Tyrosine Kinase Inhibitors: A Retrospective Study by the EBMT Chronic Malignancies Working Party

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A B S T R A C T

The prognosis of patients with blast crisis (BC) chronic myeloid leukemia (CML) is still dismal. Allogeneic stem cell transplantation represents the only curative treatment option, but data on transplant outcomes are scarce. We therefore conducted a retrospective, registry-based study of adult patients allografted for BC CML, focusing on patients with active disease at transplant and pretransplant prognostic factors. One hundred seventy patients allografted for BC CML after tyrosine kinase inhibitor pretreatment between 2004 and 2016 were analyzed. Before transplant, 95 patients were in remission, whereas 75 patients had active BC. In multivariable analysis of the entire cohort, active BC at transplant was the strongest factor associated with decreased overall survival (hazrd ratio, 1.87; P = .010) and shorter leukemia-free survival (LFS; hazard ratio, 1.69; P = .017). For patients with BC in remission at transplant, advanced age ($\geq$45 years), lower performance status ($\leq$80%), longer interval from diagnosis BC to transplant (>12 months), myeloablative conditioning, and unrelated donor (UD) transplant were risk factors for inferior survival. In patients with active BC, only UD transplant was significantly associated with prolonged LFS and trended toward improved overall survival. In summary, survival of patients allografted for BC

CML was strongly dependent on pretransplant remission status. In patients with remission of BC, conventional prognostic factors remained the major determinants of outcome, whereas in those with active BC at transplant, UD transplant was associated with prolonged LFS in our study.

INTRODUCTION

The introduction of tyrosine kinase inhibitors (TKIs) has profoundly altered the treatment strategy for chronic myeloid leukemia (CML). Targeted therapy with TKIs is now considered the standard first-line approach for CML patients in all disease stages [1−3]. As a consequence, the role and timing of allogeneic stem cell transplantation (alloSCT) in CML and in the populations of patients undergoing allografting have also changed. In the last 2 decades the number of CML patients receiving alloSCT in the first chronic phase (CP1) has rapidly declined, and, today, high-risk patients (ie, at disease stages beyond CP1 or who experienced TKI treatment failure) represent the majority of patients referred to alloSCT [4,5]. This is consistent with current treatment algorithms that recommend alloSCT for eligible patients who are resistant or intolerant to at least 1 second-generation TKI or for patients with blast crisis (BC) CML [1].

The BC of CML fundamentally differs from CP [6,7]. Resembling acute leukemia, CML BC is characterized by substantial alterations in proliferation, differentiation, and apoptosis that result in drastic changes in treatment response [7]. Although with the advent of TKIs the frequency of BC has been greatly reduced compared with the pre-TKI era [8], in patients with overt BC, response to TKI treatment is usually temporary and the prognosis remains dismal despite all efforts and progress in drug development [9]. For this group of patients alloSCT still represents the only curative treatment option, and TKI may provide a therapeutic window that permits allografting [4,8,9]. However, in the current TKI era, data on transplant outcomes in patients with BC CML, particularly those with active BC at transplant, are scarce. Therefore, in the present multicenter, European Society for Blood and Marrow Transplantation (EBMT) registry−based study we retrospectively evaluated the outcomes of patients allografted for BC CML, focusing on patients with active disease at transplant and pretransplant prognostic factors.

METHODS

Data Source, Patient Selection, and Transplant Procedure

This study was based on the registry of the EBMT and was conducted within the Chronic Malignancies Working Party. The study was approved by the review board of the Chronic Malignancies Working Party. All patients provided informed consent for data collection and analysis.

Adult patients (≥18 years) reported to have BC CML at transplant (ie, before the start of conditioning) within the EBMT database and who received their first alloSCT from 2004 through 2016 were identified. Next, study-specific forms were sent to the respective EBMT reporting centers to collect additional information including exact disease status before start of the conditioning regimen (including blood count, blast count in blood and bone marrow), achievement and type of remission with corresponding assessment dates, and the reasons to proceed with alloSCT in BC CML.

Patients were conditioned with myeloablative or nonmyeloablative regimens and received methotrexate + calcineurin inhibitor ± other drugs for prophylaxis of graft-versus-host disease (GVHD). One hundred seventy patients allografted for BC CML between 2004 and 2016 had complete data for analysis. These patients were transplanted in 46 centers in 20 countries.

Study Endpoints and Definitions

Primary endpoints were overall survival (OS) and leukemia-free survival (LFS) calculated from the date of alloSCT to death of any cause or to occurrence of disease relapse or death from any cause, respectively. Secondary endpoints were incidence of nonrelapse mortality (NRM), relapse, and GVHD calculated from the date of alloSCT. NRM was defined as death in absence of disease relapse. For all endpoints, surviving patients were censored at the date of last contact.

Criteria proposed by the Center for International Blood and Marrow Transplant Research and European LeukemiaNet were applied for definition of BC CML [1,10]. Remission and relapse of CML was classified in accordance with previous reports [11,12]. Acute GVHD (aGVHD) and chronic GVHD (cGVHD) were graded and reported according to the standard clinical criteria and in accordance with previous reports [12].

Statistics

Variables related to patient, disease, and transplant characteristics were summarized using descriptive statistics. Categorical and continuous variables were compared using Fisher's exact test and the Mann-Whitney test, respectively. For OS and LFS, survival curves were calculated according to the Kaplan-Meier method; the log-rank test was used to compare survival curves. The confidence interval (CI) estimation was performed using Greenwood's formula for the variance of the survival function. Follow-up times were calculated by the reverse Kaplan-Meier estimate [13].

NRM and recurrence of the underlying malignancy were considered as competing events. To account for competing risks, cumulative incidence functions were implemented and cumulative incidences compared using Gray's test [14−16]. The cumulative incidences of GVHD were calculated with death without GVHD as competing event.

For multivariable analysis of predictors of OS and LFS and NRM and relapse, Cox proportional hazard regression models were performed. Confounding prognostic factors were chosen to reflect main transplant characteristics and factors of the established EBMT score [17] and covariates associated with OS in univariate analysis. For full models confounding prognostic factors were patient age, disease status before alloSCT, Karnofsky performance status (KPS) before transplant, interval from BC diagnosis to transplant, year of transplant, stem cell source, conditioning intensity, donor type, and donor−recipient sex match. The slim models included the covariates patient age, KPS before transplant, interval from BC diagnosis to transplant, conditioning intensity, and donor type.

To assess the impact of cGVHD (limited and extensive disease) on LFS, a 6-month post-transplant landmark analysis method was applied. That is, LFS was analyzed in patients who had cGVHD versus without cGVHD and who were alive and free of disease at 6 months after transplant.

Calculations were done using IBM SPSS (https://www.ibm.com/de-de/products/spss-statistics) Statistics, version 24.0.0, and the statistical software environment R (https://www.r-project.org/), version 3.3.2, together with the R packages maxstat version 0.7-25, knitr version 1.20, survplot version 0.0.7, rms version 5.1-2, cmprsk version 2.2-7, and survival version 2.42-6. All statistical tests were 2-sided. Hazard ratios were estimated with 95% CIs. Results with $P < .05$ were considered to be statistically significant.

RESULTS

Patients

Between 2004 and 2016, 170 patients with reported BC CML at transplant (ie, before the start of conditioning) met the study eligibility criteria. Type of BC (myeloid or lymphoid) was documented for 135 patients (79%). Before transplant, all patients received TKI therapy at some point during the course of the disease (Table 1). In 76% of patients TKI was combined with polychemotherapy. *BCR-ABL1* mutations were present in 39 patients, and T315I was documented in 18 patients. Details on non-T315I mutations and the TKI treatment in patients with *BCR-ABL1* mutations are summarized in Supplementary Tables S1 and S2, respectively. Donor HLA type was available for 74 patients. Nineteen patients were mismatched with the donor. Information on post-transplant interventions, particularly administration of TKI or donor lymphocyte infusion, was not available.

After thorough analysis of parameters relating to disease status before the start of the conditioning treatment, 95 patients (56%) had achieved remission of BC CML before transplant. Sixty-six patients had complete hematologic remission

Table 1
Patient, Disease, and Transplant Characteristics (N = 170)

Parameter	Value
Age at alloSCT, yr, median (range)	44 (18-75)
Patient sex	
Male	119 (70)
Female	51 (30)
Disease status at alloSCT	
BC in remission	95 (56)
BC active	75 (44)
Type of BC	
Myeloid	88 (52)
Lymphoid	47 (28)
Unknown	35 (21)
KPS	
>80%	111 (65)
≤80%	51 (30)
Unknown	8 (5)
TKI pretreatment	
1 TKI	100 (59)
First generation*	73 (43)
Second generation†	26 (15)
Third generation‡	1 (1)
2 TKI	56 (33)
First/second generation	51 (30)
First/third generation	2 (1)
Second/third generation	3 (2)
3 or more TKI	14 (8)
First/second generation	3 (2)
Second/third generation	1 (1)
First/second/third generation	10 (6)
Additional cytogenetic aberrations	
Present	30 (18)
Absent	109 (64)
Unknown	31 (18)
BCR-ABL1 mutations	
T315I	18 (11)
Other than T315I	21 (12)
No	2 (1)
Unknown	129 (76)
Interval diagnosis of BC to transplant	
≤12 months	73 (43)
>12 months	97 (57)
Year of transplant	
≤2010	74 (44)
>2010	96 (56)
Stem cell source	
PB	145 (85)
BM	18 (11)
CB	7 (4)
Conditioning	
MAC	108 (64)
RIC	62 (36)
Donor	
Unrelated	91 (54)
Related	79 (46)
Recipient−donor sex match	
Matched	101 (59)
Male−female	39 (23)

(continued)

Table 1 (*Continued*)

Parameter	Value
Female−male	27 (16)
Unknown	3 (2)

Values are n (%) unless otherwise defined. CB indicates cord blood; BM, bone marrow; MAC, myeloablative conditioning; PB, peripheral blood; RIC, reduced intensity conditioning.

* Imatinib
† Dasatinib or nilotinib or bosutinib
‡ Ponatinib

and/or no evidence of leukemia, whereas 29 patients had documented complete cytogenetic or major molecular response. This patient cohort was termed "BC in remission." Seventy-five patients (44%) had active BC CML before transplant and were termed "BC active." The main reason for proceeding with alloSCT despite active disease was resistance/refractoriness toward TKIs and/or TKIs in combination with polychemotherapy. Extramedullary disease was documented in 4 patients. Median follow-up time was 54.7 months (range, .1 to 135.2). Patient, disease, and transplant characteristics are summarized in Table 1.

Outcomes

Fifty-four patients experienced aGVHD of any grade posttransplant. The cumulative incidences of any grade aGVHD and grades III to IV aGVHD at day +100 were 26.3% (95% CI, 19.9 to 33.2) and 11.0% (95% CI, 6.8 to 16.3), respectively. Sixty patients experienced cGVHD after alloSCT (limited and extensive in 30 patients each). Cumulative incidence of cGVHD (limited and extensive) at 1 year was 32.9% (95% CI, 25.8 to 40.3).

The response after alloSCT was reported in 157 patients, with 91 patients (58%) having documented major molecular response post-transplant. By the time of analysis 103 patients had died, 41 of NRM and 62 due to disease progression. Eighty-four patients experienced CML relapse post-transplant including both hematologic and molecular relapse only.

For the entire patient cohort, OS after alloSCT was 57.5% (95% CI, 50.1 to 64.9) at 1 year and 38.5% (95% CI, 30.7 to 46.3) at 3 years. The estimated probability of LFS was 34.6% (95% CI, 27.3 to 41.9) and 26.1% (95% CI, 19.2 to 33.0) at 1 and 3 years after alloSCT, respectively. The cumulative incidences of relapse at 1 and 3 years after alloSCT were 45.7% (95% CI, 38.0 to 53.1) and 50.7% (95% CI, 42.6 to 58.1), respectively, and the cumulative incidences of NRM at 1 and 3 years after alloSCT were 19.7% (95% CI, 14.1 to 26.1) and 23.3% (95% CI, 17.1 to 30.1), respectively.

Prognostic Factors

With regard to the primary endpoints, in univariable analyses of the entire cohort, only low KPS (≤80%) and active BC at transplant were significantly associated with both worse OS and shorter LFS after alloSCT. For both covariates the adverse impact on survival was based on a trend toward higher risk or relapse rather than NRM. Results of the univariate analyses are summarized in Table 2.

In multivariable analyses, active BC at transplant was significantly associated with both decreased OS (hazard ratio, 1.87; *P* = .010) and shorter LFS (hazard ratio, 1.69; *P* = .017). Other covariates showing associations with outcome were low KPS (shorter OS and LFS) and early year of transplant (≤2010, higher risk of NRM). Results of the multivariable analyses of the entire patient cohort are given in Table 3.

Table 2
Prognostic Factors of OS and LFS and Relapse and NRM (Entire Cohort, Univariate Analysis)

Covariate	Effect	OS(n = 103)[†]			LFS(n = 125)[‡]			Relapse(n = 84)[¶]			NRM(n = 41)[§]		
		HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Patient age	≥45 yr	1.23	.84-1.82	.286	1.20	.84-1.70	.318	1.32	.86-2.02	.201	.92	.50-1.68	.770
Patient sex	Female	1.02	.67-1.54	.941	1.13	.78-1.65	.522	1.46	.93-2.29	.097	.68	.34-1.37	.280
Disease status	BC active	2.00	1.35-2.96	.001	1.80	1.27-2.57	.001	1.48	.97-2.27	.068	1.50	.82-2.75	.191
Type of BC	Myeloid	1.05	.66-1.66	.844	1.15	.75-1.74	.528	1.88	1.12-3.16	.017	.49	.24-.98	.044
KPS	≤80%	1.96	1.30-2.98	.001	1.95	1.34-2.86	.001	1.58	.98-2.56	.061	1.33	.70-2.55	.392
TKI pretreatment	>1 TKI	.65	.41-1.03	.067	.79	.52-1.20	.261	1.35	.82-2.23	.250	.32	.14-.74	.008
Additional cytogenetic aberrations	Absent	1.26	.72-2.22	.416	.82	.51-1.30	.392	.57	.34-.99	.046	1.87	.68-3.50	.221
T315I mutation	Absent	.43	.18-1.02	.055	.55	.27-1.12	.101	.81	.37-1.81	.620	.44	.11-1.75	.240
Interval diagnosis of BC to transplant	≤12 months	.81	.55-1.21	.302	.86	.60-1.23	.408	.93	.61-1.43	.761	.86	.46-1.59	.630
Year of transplant	≤2010	1.64	1.11-2.43	.013	1.39	.97-1.97	.073	.84	.54-1.29	.420	2.92	1.53-5.59	.001
Stem cell source	PB	.76	.45-1.27	.292	1.05	.64-1.73	.852	1.46	.78-2.77	.240	.65	.30-1.43	.292
Conditioning	RIC	.88	.59-1.32	.530	.99	.69-1.43	.963	1.39	.91-2.14	.131	.52	.25-1.05	.069
Donor	Unrelated	1.08	.73-1.59	.701	.92	.65-1.31	.634	.95	.62-1.46	.822	.99	.54-1.81	.960
Recipient−donor sex match	RMDF	1.04	.65-1.66	.860	.92	.60-1.41	.698	.83	.49-1.41	.490	1.16	.57-2.36	.680

Abbreviations: BC, blast crisis; CI, confidence interval; HR, hazard ratio; LFS, leukemia-free survival; NRM, non-relapse-mortality; OS, overall survival; PB, peripheral blood; RIC, reduced intensity conditioning; RMDF, recipient male − donor female; TKI, tyrosine kinase inhibitor.

[†] Number of events: 103;
[‡] Number of events: 125
[¶] Number of events: 84
[§] Number of events: 41.

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Table 3
Multivariable analysis overall and leukemia-free survival and relapse and non-relapse mortality (entire cohort, complete case analysis, n = 159).

Covariate	Effect	OS[†]			LFS[‡]			Relapse[¶]			NRM[§]		
		HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Patient age	≥45 years	1.25	.79-1.99	.345	1.09	.71-1.68	.690	1.13	.65-1.95	.660	1.16	.51-2.61	.730
Disease status	BC active	1.87	1.16-3.00	.010	1.69	1.10-2.59	.017	1.33	.75-.81	.260	1.69	.73-3.91	.220
Karnofsky performance status	<80%	1.82	1.10-3.01	.019	1.65	1.05-2.59	.029	1.50	.85-2.63	.160	1.23	.54-2.80	.630
Interval diagnosis of BC to transplant	≤12 months	.79	.51-1.22	.290	.78	.52-1.17	.231	.82	.50-1.35	.440	.95	.48-1.88	.880
Year of transplant	≤2010	1.27	.83-1.95	.276	1.09	.73-1.61	.687	.70	.42-1.18	.180	2.59	1.33-5.06	.005
Stem cell source	PB	.67	.37-1.22	.189	.99	.57-1.72	.970	1.41	.66-2.99	.380	.60	.22-1.64	.320
Conditioning	RIC	.65	.39-1.07	.092	.83	.52-1.30	.410	1.12	.65-1.94	.680	.53	.78-4.65	.160
Donor	Unrelated	1.13	.71-1.82	.605	.86	.57-1.31	.486	.94	.57-1.56	.820	1.04	.46-2.36	.930
Recipient − donor sex match	RMDF	1.07	.66-1.76	.778	.96	.61-1.51	.855	.92	.51-1.68	.790	.94	.44-2.02	.880

Abbreviations: BC, blast crisis; CI, confidence interval; HR, hazard ratio; LFS, leukemia-free survival; NRM, non-relapse-mortality; OS, overall survival; PB, peripheral blood; RIC, reduced intensity conditioning; RMDF, recipient male − donor female.

[†] Number of events: 93
[‡] Number of events: 115
[¶] Number of events: 78
[§] Number of events: 37.

Accordingly, for patients who received alloSCT in active BC, the probability of OS and LFS post-transplant was significantly lower as compared with patients allografted for BC in remission (*P* < .001 and *P* = .001, respectively) (Figure 1**A,B**). Again, worse survival of patients transplanted in active disease was because of a trend toward higher incidence of relapse (*P* = .076) (Figure 1C) than NRM (*P* = .190) (Figure 1D). The incidences of aGVHD and cGVHD were similar between cohorts. The same was true for the documented post-transplant molecular response rates (56% and 60%, respectively).

Consequently, prognostic factors for survival were analyzed separately according to disease status at alloSCT. For this purpose, because of the lower number of events in each cohort, slim models were applied. For patients with BC in remission at transplant advanced age, lower KPS, longer interval from diagnosis of BC to transplant, myeloablative conditioning, and unrelated donor (UD) transplant were risk factors for inferior survival, with the latter 2 associated with a higher risk of NRM (Table 4). In contrast, in patients allografted for active BC, only transplant from a UD was significantly associated with prolonged LFS and trended toward improved OS (Table 5).

Impact of cGVHD on Outcome

To evaluate the impact of cGVHD (both extensive and limited disease) on LFS (entire cohort and in the subgroups according to the disease status at alloSCT) a 6-month landmark analysis was performed, grouping patients with respect to prior history of cGVHD. Eighty-five patients fulfilled the conditions of being alive and in remission at 6 months post-transplant. There was no significant association of prior cGVHD with LFS in all cohorts analyzed. Specifically, in the entire cohort and the subgroup of patients with active BC at transplant, survival rates of patients with and without prior history of cGVHD were very similar (Figure 2A,B). In contrast, in patients allografted for BC in remission, the 3-year LFS rates of patients with and without prior history of cGVHD were 83% and 50%, respectively, but did not reach statistical significance (Figure 2C).

DISCUSSION

BC remains a major challenge in the management of CML [8]. This is mainly because in patients with BC CML, even after alloSCT long-term outcomes are rarely achieved [18]. For CML in general, the disease and transplant risks that primarily influence patient outcome are well defined and can be captured by the EBMT score [17]. The assessment of both has become standard and with improved supportive care and patient selection NRM has substantially declined over time [4]. However, this is not true for patients with high transplant risk [19], and survival outcomes of patients with high transplant risk allografted for advanced and/or refractory CML remains particularly poor [20].

In the current TKI (pretreatment) era, the definition of prognostic factors for transplant outcomes in BC CML has been hampered by relatively small patient numbers. In the study of Oyekunle et al. [21], which evaluated the outcomes of 68 patients (including 8 with BC), advanced phase (>CP1) disease was associated with adverse OS and relapse-free survival (47% and 32% at 2 years, respectively). In another smaller study on 63 patients (28 with active disease at transplant), the 2-year incidence of relapse was 38%, with disease status at transplant together with the EBMT score major factors influencing transplant outcome [22]. In the last and so far largest Center for International Blood and Marrow Transplant Research−based registry study published in 2012, 449 patients allografted
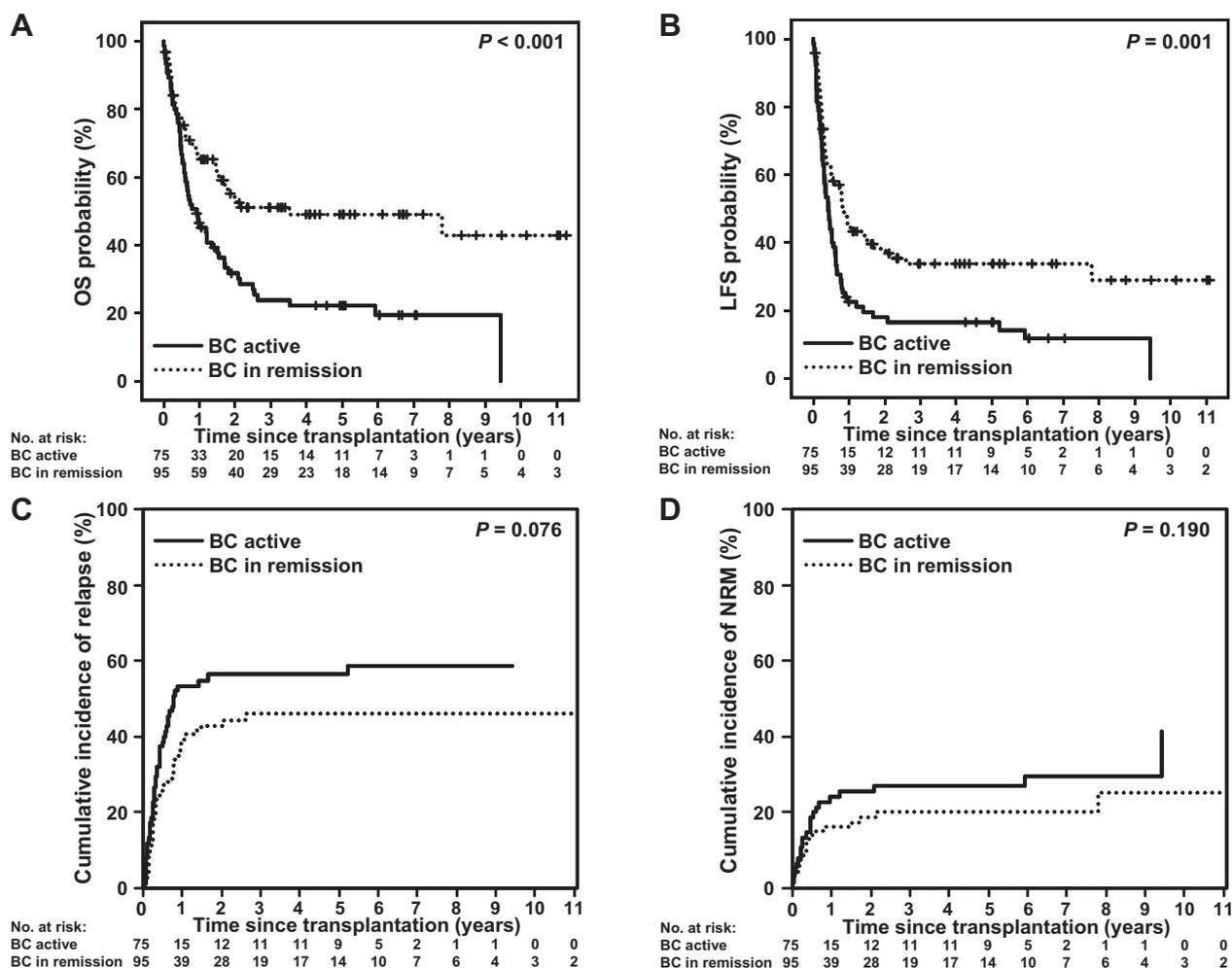
Figure 1. OS, LFS, and cumulative incidences of relapse and NRM in patients transplanted in active BC CML (n = 75) versus patients allografted for BC CML in remission (n = 95). (A) For patients who were allografted for active BC, the 3-year estimated probability of post-transplant OS was 23.8% (95% CI, 13.6 to 34.0) as compared with 51.1% (95% CI, 40.5 to 61.7) for patients who received alloSCT in remission of BC CML (*P* < .001, log-rank test for the total observation time). (B) The estimated probability of LFS at 3 years post-transplant in patients transplanted for active BC versus BC in remission was 11.6% (95% CI, 3.0 to 20.2) versus 33.8% (95% CI, 23.6 to 44.0), respectively (*P* = .001, log-rank test for the total observation time). (C) For patients who received allografts in active BC, the 3-year cumulative incidence of relapse after alloSCT was 56.4% (95% CI, 44.1 to 66.9) as compared with 45.9% (95% CI, 35.1 to 56.1) for patients who were allografted for BC in remission (*P* = .076, Gray's test). (D) The 3-year cumulative incidence of NRM post-transplant in the active BC cohort versus the BC in remission cohort was 27.1% (95% CI, 17.4 to 37.7) and 20.2% (95% CI, 12.5 to 29.3), respectively (*P* = .190, Gray's test).

between 1999 and 2004 were analyzed, including 80 patients with documented BC at the start of conditioning, 37 of whom had previous TKI treatment [23]. With an estimated 1- and 3-year OS of 30% and <20%, respectively, the post-transplant outcome for this group of patients was particularly poor. By comparison, in the 23 patients with prior history of BC who achieved remission after TKI therapy, survival rates of 61% and 41% (at 1 and 3 years, respectively) could be estimated [23]. Prognostic factors significantly associated with both OS and LFS in this study were lower KPS (<80%) and longer interval from diagnosis to transplant (>12 months), whereas no impact of pretransplant imatinib use was observed [23].

In our study, and in accordance with previous reports [21,22], active disease at transplant was the strongest factor associated with worse post-transplant survival. This was based on a trend toward higher risk of relapse rather than NRM. For patients who achieved remission before alloSCT, previously reported [23] and well-recognized [17] prognostic factors were the main determinants of post-transplant survival. Interestingly, in this group of patients, reduced-intensity conditioning was associated with

improved outcome due to lower risk of NRM as revealed by the multivariable models. This contrasts with previous studies that show comparable transplant outcomes after myeloablative conditioning and reduced-intensity conditioning in patients with advanced phase CML [23] and overall post-transplant survival to be primarily influenced by the EBMT score and less by the choice of the conditioning regimen [24]. However, although larger retrospective series failed to confirm superiority of reduced-intensity conditioning, a potential advantage of reduced-intensity conditioning due to lower early NRM, particularly for patients with advanced age and comorbidities, can probably be assumed [4].

For patients with active BC at transplant, UD transplant showed an association with improved LFS in our series. In this patient cohort, data on donor HLA type were available for 31 patients, of whom only 8 patients were mismatched with the donor. Therefore, further analyses with regard to HLA matching were precluded by the small sample size. The reasons for this association are not clear, particularly because there is no correlation with relapse or NRM. One could hypothesize that patients with active BC may benefit from an UD transplant

Table 4
Multivariable analysis overall and leukemia-free survival and relapse and non-relapse mortality in patients with CML blast crisis in remission at transplant (slim model, complete case analysis, n = 88).

| Covariate	Effect	OS[†] HR	95% CI	P	LFS[‡] HR	95% CI	P	Relapse[¶] HR	95% CI	P	NRM[§] HR	95% CI	P
Patient age	≥45 years	2.42	1.13-5.14	.022	2.51	1.30-4.83	.006	1.40	.67-2.95	.370	2.72	.93-7.94	.067
Karnofsky performance status	≤80%	2.69	1.26-5.76	.011	2.83	1.46-5.49	.002	2.18	.98-4.87	.057	.94	.22-3.94	.930
Interval diagnosis of BC to transplant	≤12 months	.48	.24-.94	.033	.57	.32-1.00	.052	.67	.33-1.36	.270	.90	.31-2.61	.850
Conditioning	RIC	.26	.11-.65	.004	.40	.19-.84	.016	1.25	.57-2.75	.570	.09	.02-.44	.003
Donor	Unrelated	3.61	1.72-7.58	.001	1.81	.99-3.31	.053	.78	.39-1.54	.470	4.41	1.51-12.86	.007

Abbreviations: BC, blast crisis; CI, confidence interval; CML, chronic myeloid leukemia; HR, hazard ratio; LFS, leukemia-free survival; NRM, non-relapse-mortality; OS, overall survival; PB, peripheral blood; RIC, reduced intensity conditioning; RMDF, recipient male − donor female.

[†] Number of events: 39
[‡] Number of events: 54
[¶] Number of events: 37
[§] Number of events: 17.

Table 5
Multivariable analysis overall and leukemia-free survival and relapse and non-relapse mortality in patients with active blast crisis CML at transplant (slim model, complete case analysis, n = 74).

Covariate	Effect	OS[†] HR	95% CI	P	LFS[‡] HR	95% CI	P	Relapse[¶] HR	95% CI	P	NRM[§] HR	95% CI	P
Patient age	≥45 years	.85	.46-1.55	.589	.59	.33-1.04	.068	.98	.51-1.90	.960	.75	.28-2.02	.571
Karnofsky performance status	≤80%	1.47	.78-2.79	.233	1.35	.76-2.37	.305	1.03	.54-1.96	.918	1.25	.43-3.65	.680
Interval diagnosis of BC to transplant	≤12 months	.84	.48-1.46	.530	.84	.48-1.45	.528	1.03	.53-1.98	.938	.75	.32-1.79	.522
Conditioning	RIC	.75	.41-1.35	.338	1.03	.58-1.82	.931	1.22	.59-2.52	.600	.71	.29-1.78	.473
Donor	Unrelated	.56	.31-1.01	.055	.47	.27-.81	.007	1.07	.53-2.15	.850	.48	.19-1.24	.130

Abbreviations: BC, blast crisis; CI, confidence interval; CML, chronic myeloid leukemia; HR, hazard ratio; LFS, leukemia-free survival; NRM, non-relapse-mortality; OS, overall survival; PB, peripheral blood; RIC, reduced intensity conditioning; RMDF, recipient male − donor female.

[†] Number of events: 57
[‡] Number of events: 64
[¶] Number of events: 42
[§] Number of events: 22.
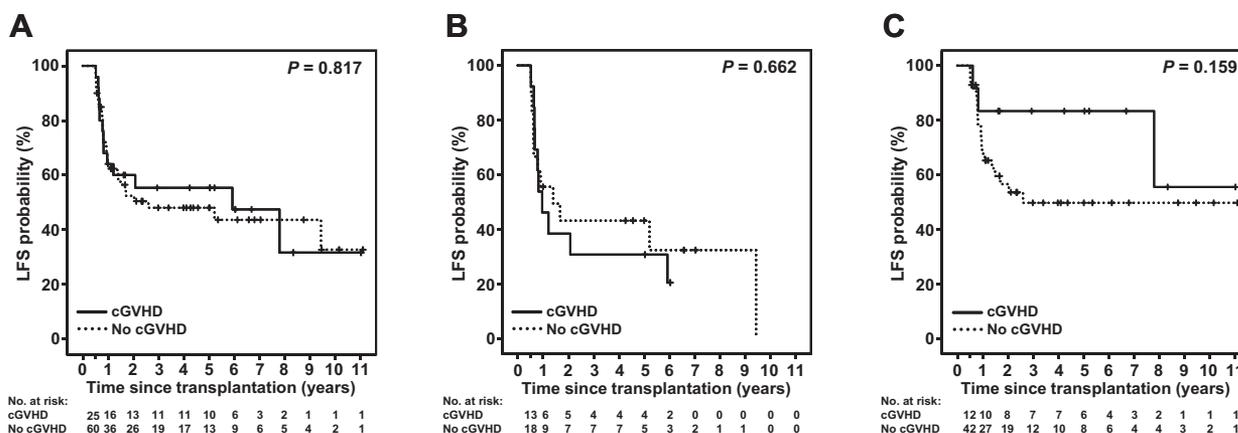
Figure 2. Kaplan-Meier estimates of LFS based on a landmark analysis at 6 months post-transplant, grouping patients according to prior history of cGVHD. (A) In the entire cohort (n = 85), the survival rates of patients with and without prior history of cGVHD were similar (at 3 years: 55.4% [95% CI, 35.6 to 75.2] versus 48.0% [95% CI, 34.7 to 61.3]). (B) When regarding the subgroup of patients with active BC at transplant (n = 31), the 3-year LFS rates of patients with and without prior history were 30.8% (95% CI, 5.7 to 55.9) and 43.2% (95% CI, 19.9 to 66.5), respectively. (C) In the subgroup of patients with BC in remission at alloSCT (n = 54), the 3-year LFS rates of patients with and without prior history were 83.3% (95% CI, 62.1 to 100.0) and 49.8% (95% CI, 33.3 to 66.3), respectively.

because of a stronger graft-versus-leukemia effect. However, a previous large registry study failed to demonstrate any benefit [25]. In addition, generally, sensitivity to the graft-versus-leukemia effect is believed to be more pronounced in patients allografted for CP or rather less advanced CML [26].

It has been long recognized that the graft-versus-leukemia effect is related to cGVHD, which exerts antileukemic effects and thus contributes to improved survival after alloSCT [27]. This is particularly true for patients allografted for CML [28]. In our patients the incidences of aGVHD and cGVHD were comparable with previous reports [22,23]. However, in all cohorts analyzed no significant association of prior cGVHD with LFS was observed. As already stated above, the reason is probably because the graft-versus-leukemia effect is rather weak in BC CML [26]. This also might explain that, albeit not significant, effects of prior cGVHD on LFS were only detectable in patients allografted in remission of BC CML.

Our study has several limitations that need to be addressed. First, as with all registry-based retrospective cohort studies, a selection bias cannot be ruled out. Second, there was a considerable proportion of missing values in the EBMT database and incomplete reporting of requested data, particularly in terms of presence of *BCR-ABL1* mutations, type of BC, and reasons to proceed with alloSCT despite active disease. In addition, no data on the clinical CML scores at diagnosis and the duration of previous disease stages and treatment were accessible for analysis. Further, because prognostic factors of survival outcomes were the focus of the present study, information on post-transplant interventions (donor lymphocyte infusion and particularly post-transplant TKI treatment) was also not available. Finally, one could argue that most patients in our study were in disease remission, which may not necessarily reflect actual BC of CML. However, with regard to the latter, it should be noted that even in remission the gene expression signatures of the BC and hence the adverse biology are retained [7,29]. In the transplant setting this might explain why long-term outcomes are only rarely achieved [18,23]. It can be expected that in the near future, eligible patients with BC CML will continue to be considered candidates for alloSCT. Based, to the best of our knowledge, on one of the largest cohort of patients with BC, the present study provides an update on the efficacy of alloSCT for BC CML in the TKI era and may help select patients most likely to benefit from this treatment approach.

In conclusion, survival of patients allografted for BC CML remains poor in the TKI era unless disease remission could be achieved; however, survival is far worse compared with patients transplanted in CP1. *Therefore, for physicians following CP CML patients under TKI treatment, it is of the utmost importance to avoid evolution to BC and consider alloSCT before overt disease progression.* This means that patients under TKI treatment should be referred early to a transplant center, particularly when there is evidence for molecular progression after 2 or 3 lines of TKI therapy. In patients with BC CML who achieve remission before transplant, conventional and well-recognized prognostic indicators remain the main determinants of survival outcomes, whereas in those with active BC at transplant, UD transplant is associated with a survival advantage.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2019.06.028.

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