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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Short title: AlloSCT for BC CML in the TKI era

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Word counts: abstract: 233, manuscript 3070

ABSTRACT

The prognosis of patients with blast crisis (BC) chronic myeloid leukemia (CML) is still dismal. Allogeneic stem cell transplantation (alloSCT) 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 pre-transplant prognostic factors. A total of 170 patients allografted for BC CML after tyrosine kinase inhibitor pre-treatment between 2004 and 2016 were analyzed. Prior to 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 (OS, HR 1.87, *P*=0.010) and shorter leukemia-free survival (LFS, HR 1.69, *P*=0.017). For patients with BC in remission at transplant, advanced age (≥45 years), lower performance status (≤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 towards improved OS. In summary, survival of patients allografted for BC CML was strongly dependent on the pre-transplant 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 transplantation was associated with prolonged LFS in our study.

INTRODUCTION

The introduction of tyrosine kinase inhibitors (TKI) has profoundly altered the treatment strategy for chronic myeloid leukemia (CML). Targeted therapy with TKI 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, as well as the population of patients undergoing allografting have also changed. In the last two decades, the number of CML patients receiving alloSCT in first chronic phase (CP1) has rapidly declined and nowadays high-risk patients, i.e. 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 one second generation TKI or for patients with blast crisis (BC) CML [1].

The BC of CML fundamentally differs from chronic phase [6,7]. Resembling acute leukemia, the CML BC is characterized by substantial alterations in proliferation, differentiation, and apoptosis which result in drastic changes in treatment response [7]. Although with the advent of TKI the frequency of BC has been greatly reduced compared to 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, EBMT-registry based study, we retrospectively evaluated the outcomes of patients allografted for BC CML focusing on patients with active disease at transplant and pre-transplant prognostic factors.

PATIENTS AND 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 (CMWP). The study was approved by the review board of the CMWP. All patients provided informed consent for data collection and analysis.

Adult patients (≥18 years) reported to have BC CML at transplant (i.e. prior to the start of the 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 the following: exact disease status before start of the conditioning regimen (including blood count, blast count in blood and BM), 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 non-myeloablative regimens, and received methotrexate + calcineurin inhibitor ± other drugs for prophylaxis of graft-*versus*-host disease (GVHD). A total of 170 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 non-relapse mortality (NRM), relapse and GVHD calculated from the date of alloSCT. NRM was defined as death in absence of disease relapse. For all endpoints, patients alive were censored at the date of last contact.

Criteria proposed by the Center for International Blood and Marrow Transplant Research (CIBMTR) and ELN criteria 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 method of Kaplan and Meier (KM); 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. The 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 the competing risks, cumulative incidence functions were implemented and the cumulative incidences were compared using the test of Gray [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 the full models confounding prognostic factors were: patient age, disease status prior to alloSCT, Karnofsky performance status (KPS) prior to 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 prior to transplant, interval from BC diagnosis to transplant, conditioning intensity and donor type.

In order to assess the impact of cGVHD (limited and extensive disease) on LFS, a 6-month post-transplant landmark analysis method was applied, i.e. LFS was analyzed in patients who had cGVHD *versus* without cGVHD and who were alive and free of disease at 6 months after transplantation.

Calculations were done using IBM® SPSS® Statistics, Version 24.0.0, and the statistical software environment R, 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, ‘survival’ version 2.42-6. All statistical tests were two-sided. Hazard ratios (HR) were estimated with 95%CI. Results with *P* values <0.05 were considered to be statistically significant.

RESULTS

Patients

Between 2004 and 2016, 170 patients with reported BC CML at transplant (i.e. prior to the start of the conditioning) met the study eligibility criteria. Type of BC (myeloid or lymphoid) was documented for 135 (79%) patients. Prior to transplantation, all patients received TKI therapy at some point during the course of the disease (**Table 1**). In 76% of the patients TKI was combined with polychemotherapy. *BCR-ABL1* mutations were present in 39 patients; 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 **Table S1** and **Table S2**, respectively. Donor HLA type was available for 74 patients. A total of 19 patients were mismatched with the donor. Information on post-transplant interventions, particularly administration of TKI or donor lymphocyte infusion (DLI) was not available.

After thorough analysis of parameters relating to disease status prior to the start of the conditioning treatment, a total of 95 (56%) patients had achieved remission of BC CML prior to transplant. A total of 66 patients had complete hematologic remission and/or no evidence of leukemia, whereas had 29 patients documented complete cytogenetic or major molecular response. This patient cohort was termed as BC in remission. Seventy-five (44%) patients had active BC CML prior to transplant (termed BC active). Main reason for proceeding with alloSCT despite active disease was resistance/refractoriness towards TKI and/or TKI in combination with polychemotherapy. Extramedullary disease was documented in 4 patients. Median follow-up time was 54.7 months (range 0.1-135.2). Patient, disease and transplant characteristics are summarized in **Table 1**.

Outcomes

A total of 54 patients experienced aGVHD of any grade post-transplant. The cumulative incidences of any grade aGVHD and grade 3-4 aGVHD at day+100 were 26.3% (95% CI 19.9-33.2) and 11.0% (95% 6.8-16.3), respectively. A total of 60 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 25.8-40.3).

The response after alloSCT was reported for a total of 157 patients with 91 patients (58%) having documented major molecular response post-transplant. By the time of analysis, a total of 103 patients had died, 41 of NRM and 62 due to disease progression. A total of 84 patients experienced CML relapse post-transplant including both hematologic and molecular relapse only.

For the entire patient cohort, OS at 1 and 3 years after alloSCT was 57.5% (95% CI 50.1-64.9) and 38.5% (95% CI 30.7-46.3), respectively. The estimated probability of LFS was 34.6% (95% CI 27.3-41.9) and 26.1% (95% CI 19.2-33.0) at 1 and 3 years after alloSCT, respectively. The cumulative incidence of relapse at 1 and 3 years after alloSCT was 45.7% (95% CI 38.0-53.1) and 50.7% (95% CI 42.6-58.1), respectively, and the cumulative incidence of NRM at 1 and 3 years after alloSCT was 19.7% (95% CI 14.1-26.1) and 23.3% (95% CI 17.1-30.1), 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 towards 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 (HR 1.87, *P*=0.010) and shorter LFS (HR 1.69, *P*=0.017). 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**.

Accordingly, for patients who received alloSCT in active BC probability of OS and LFS post-transplant was significantly lower as compared to patients allografted for BC in remission (*P*<0.001 and *P*=0.001, respectively) (**Figure 1A and B**). Again, worse survival of patients transplanted in active disease was rather due to a trend towards higher incidence of relapse (*P*=0.076) (**Figure 1C**) than NRM (*P*=0.190) (**Figure 1D**). The incidences of acute and chronic GVHD were similar between the cohorts. The same is true for the documented post-transplant molecular response rates (56% and 60%).

Consequently, prognostic factors for survival were analyzed separately according to disease status at alloSCT. For this purpose, due to 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 UD transplant were risk factors for inferior survival with the latter two being associated with a higher risk of NRM (**Table 4**). In contrast, in patients allografted for active BC, only transplant from an unrelated donor (UD) was significantly associated with prolonged LFS and trended towards 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. A total of 85 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 and 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, however, not reaching statistical significance (**Figure 2C**).

DISCUSSION

The BC remains the major challenge in the management of CML [8]. This is mainly due to the fact that 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 (pre-treatment) era, the definition of prognostic factors for transplant outcomes in BC CML has been hampered by relative 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 overall 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 being the major factors influencing transplant outcome [22]. In the last and so far largest CIBMTR-based registry study published in 2012, a total of 449 patients allografted 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 pre-transplant 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 towards higher risk of relapse rather than NRM. For patients who achieved remission prior to 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 (RIC) 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 RIC 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 RIC, a potential advantage of RIC due to lower early NRM particularly for patients with advanced age and co-morbidities can probably be assumed [4].

For patients with active BC at transplant, UD transplantation 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 since there is no correlation with relapse or NRM. One could hypothesize, that patients with active BC may benefit from an UD transplant because of a stronger graft-*versus*-leukemia (GVL) effect. However, a previous large registry study failed to demonstrate so [25]. Plus, generally, sensitivity to GVL is thought to be more pronounced in patients allografted for chronic phase or rather less advanced CML [26].

It has been long recognized, that GVL is related to cGVHD, which exerts anti-leukemic 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 acute and chronic GVHD were comparable to 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 related to the fact that the GVL 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 was accessible for analysis. Further, since prognostic factors of survival outcomes were the focus of the present study, information on post-transplant interventions (DLI 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, but even so, survival is far worse compared to patients transplanted in CP1. *Therefore, for physicians following CP CML patients under TKI it is of utmost importance to avoid evolution to BC and to consider alloSCT prior to overt disease progression*. This means that patients under TKI should be referred early to a transplant center,

particularly when there is evidence for molecular progression after two or three lines of TKI therapy. In patients with BC CML who achieve remission prior to transplantation, conventional and well-recognized prognostic indicators remain the main determinants of survival outcomes, whereas in those with active BC at transplant, UD transplantation is associated with a survival advantage.

Acknowledgments:

The authors acknowledge the cooperation of all participating centers.

Conflict of interest statement:

AR: Jazz pharmaceuticals: travel grant.

PJ: Novartis: travel grant.

JLB: Novartis, Pfizer: advisory board honoraria.

YC: Novartis, BMS, Pfizer, Incyte: advisory board honoraria; Novartis, BMS: travel grant.

All other authors: there are no conflicts of interest to report.

Author contributions:

AR designed the study, contributed and analyzed data. SD and HJB contributed essential data management and analyzed data. YC and NK designed the study and contributed data. All the remaining authors (AN, FA, JF, JT, JM, YK, FS, JP, JLB, PJ, JHV, GS, JM, NS, MS, MIR, ET, MA, VR, PL, IYA) contributed data to the study. Every author critically appraised and approved the final version of the paper.

REFERENCES

1. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood.* 2013;122:872-884.

2. Rosti G, Castagnetti F, Gugliotta G, Baccarani M. Tyrosine kinase inhibitors in chronic myeloid leukaemia: which, when, for whom? *Nat Rev Clin Oncol.* 2017;14:141-154.

3. Radich J. When to Consider Allogeneic Transplantation in CML. *Clin Lymphoma Myeloma Leuk.* 2016;16Suppl:S93-95.

4. Gratwohl A, Heim D. Current role of stem cell transplantation in chronic myeloid leukaemia. *Best Pract Res Clin Haematol.* 2009;22:431-443.

5. Passweg JR, Baldomero H, Gratwohl A, et al. The EBMT activity survey: 1990-2010. *Bone Marrow Transplant.* 2012;47:906-923.

6. Calabretta B, Perrotti D. The biology of CML blast crisis. *Blood.* 2004;103:4010-4022.

7. Radich JP. The Biology of CML blast crisis. *Hematology Am Soc Hematol Educ Program.* 2007:384-391.

8. Hehlmann R. How I treat CML blast crisis. *Blood.* 2012;120:737-747.

9. Saußele S, Silver RT. Management of chronic myeloid leukemia in blast crisis. *Ann Hematol*. 2015; 94Suppl2:S159-165.

10. Speck B, Bortin MM, Champlin R, et al. Allogeneic bone-marrow transplantation for chronic myelogenous leukaemia. *Lancet.* 1984;1:665-668.

11. Jain P, Kantarjian HM, Ghorab A, et al. Prognostic factors and survival outcomes in patients with chronic myeloid leukemia in blast phase in the tyrosine kinase inhibitor era: Cohort study of 477 patients. *Cancer.* 2017;123:4391-4402.

12. Radujkovic A, Guglielmi C, Bergantini S, et al. Donor Lymphocyte Infusions for Chronic Myeloid Leukemia Relapsing after Allogeneic Stem Cell Transplantation: May We Predict Graft-versus-Leukemia Without Graft-versus-Host Disease? *Biol Blood Marrow Transplant.* 2015;21:1230-1236.

13. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials.* 1996;17:343-346

14. Gray RJ. A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. *Annals of Statistics.* 1988;16:1141-1154.

15. Scrucca L, Santucci A, Aversa F. Competing risk analysis using R: an easy guide for clinicians. *Bone Marrow Transplant.* 2007;40:381-387.

16. Scrucca L, Santucci A, Aversa F. Regression modeling of competing risk using R: an in depth guide for clinicians. *Bone Marrow Transplant.* 2010;45:1388-1395.

17. Gratwohl A, Hermans J, Goldman JM, et al. Risk assessment for patients with chronic myeloid leukaemia before allogeneic blood or marrow transplantation. Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Lancet.* 1998;352:1087-1092.

18. Gratwohl A, Brand R, Apperley J, et al. Allogeneic hematopoietic stem cell transplantation for chronic myeloid leukemia in Europe 2006: transplant activity, long-term data and current results. An analysis by the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). *Haematologica.* 2006;91:513-521.

19. Gratwohl A, Brand R, Niederwieser D, et al. Introduction of a quality management system and outcome after hematopoietic stem-cell transplantation. *J Clin Oncol.* 2011;29:1980-1986.

20. Gratwohl A, Pfirrmann M, Zander A, et al. Long-term outcome of patients with newly diagnosed chronic myeloid leukemia: a randomized comparison of stem cell transplantation with drug treatment. *Leukemia.* 2016;30:562-569.

21. Oyekunle A, Zander AR, Binder M, et al. Outcome of allogeneic SCT in patients with chronic myeloid leukemia in the era of tyrosine kinase inhibitor therapy. *Ann Hematol.* 2013;92:487-496.

22. Nicolini F, Modolo L, Raus N, et al. Allogeneic stem cell transplantation for blast crisis (BC) chronic myelogenous leukemia (CML) in the tyrosine kinase inhibitors (TKIs) era. Analysis of pre-transplant variables on transplant outcome. On behalf of the Societe Française de Greffe de Moelle et de Therapie Cellulaire and the French Group of CML. *Blood.* 2010;116(abstract 2266).

23. Khoury HJ, Kukreja M, Goldman JM, et al. Prognostic factors for outcomes in allogeneic transplantation for CML in the imatinib era: a CIBMTR analysis. *Bone Marrow Transplant.* 2012;47:810-816.

24. Crawley C, Szydlo R, Lalancette M, et al. Outcomes of reduced-intensity transplantation for chronic myeloid leukemia: an analysis of prognostic factors from the Chronic Leukemia Working Party of the EBMT. *Blood.* 2005;106:2969-2976.

25. Ringdén O, Pavletic SZ, Anasetti C, et al. The graft-versus-leukemia effect using matched unrelated donors is not superior to HLA-identical siblings for hematopoietic stem cell transplantation. *Blood.* 2009;113:3110-3118.

26. Barrett J. Allogeneic stem cell transplantation for chronic myeloid leukemia. *Semin Hematol.* 2003;40:59-71.

27. Weiden PL, Sullivan KM, Flournoy N, Storb R, Thomas ED; Seattle Marrow Transplant Team. Antileukemic effect of chronic graft-versus-host disease: contribution to improved survival after allogeneic marrow transplantation. *N Engl J Med.* 1981;304:1529-1533.

28. Boyiadzis M, Arora M, Klein JP, et al. Impact of Chronic Graft-versus-Host Disease on Late Relapse and Survival on 7,489 Patients after Myeloablative Allogeneic Hematopoietic Cell Transplantation for Leukemia. *Clin Cancer Res.* 2015;21:2020-2028.

29. Radich JP, Dai H, Mao M, et al. Gene expression changes associated with progression and response in chronic myeloid leukemia. *Proc Natl Acad Sci U S A* 2006;103:2794-2799.

Table 1. Patient, disease and transplant characteristics.

	N=170
Parameter	
Age [years] at alloSCT (median, range)	44 (18-75)
Patient sex, n (%)	
Male	119 (70)
Female	51 (30)
Disease status at alloSCT, n (%)	
BC in remission	95 (56)
BC active	75 (44)
Type of BC, n (%)	
Myeloid	88 (52)
Lymphoid	47 (28)
Unknown	35 (21)
Karnofsky performance status, n (%)	
>80%	111 (65)
≤80%	51 (30)
Unknown	8 (5)
TKI pre-treatment, n (%)	
1 TKI	100 (59)
1st generation*	73 (43)
2nd generation†	26 (15)
3rd generation‡	1 (1)
2 TKI	56 (33)
1st / 2nd generation	51 (30)
1st / 3rd generation	2 (1)
2nd / 3rd generation	3 (2)
3 or more TKI	14 (8)
1st / 2nd generation	3 (2)
2nd / 3rd generation	1 (1)
1st / 2nd / 3rd generation	10 (6)
Additional cytogenetic aberrations, n (%)	
Present	30 (18)
Absent	109 (64)
Unknown	31 (18)
***BCR-ABL1* mutations, n (%)**	
T315I	18 (11)
Other than T315I	21 (12)
No	2 (1)
Unknown	129 (76)
Interval diagnosis of BC to transplant, n (%)	
≤12 months	73 (43)
>12 months	97 (57)
Year of transplant, n (%)	
≤2010	74 (44)
>2010	96 (56)

Table 1. continued	
	N=170
Parameter	
Stem cell source, n (%)	
PB	145 (85)
BM	18 (11)
CB	7 (4)
Conditioning, n (%)	
MAC	108 (64)
RIC	62 (36)
Donor, n (%)	
Unrelated	91 (54)
Related	79 (46)
Recipient – donor sex match, n (%)	
Matched	101 (59)
Male – female	39 (23)
Female – male	27 (16)
Unknown	3 (2)

Abbreviations: CB, cord blood; BC, blast crisis; BM, bone marrow; CI, confidence interval; HR, hazard ratio; MAC, myeloablative conditioning; OS, overall survival; PB, peripheral blood; PFS, progression-free survival; RIC, reduced intensity conditioning; TKI, tyrosine kinase inhibitor.
* imatinib, † dasatinib or nilotinib or bosutinib, ‡ ponatinib.

Table 2. Prognostic factors of overall and leukemia-free survival and relapse and non-relapse mortality (entire cohort, univariate analysis).

		OS†			LFS‡			Relapse¶			NRM§		
Covariate	**Effect**	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Patient age	≥45 years	1.23	0.84-1.82	0.286	1.20	0.84-1.70	0.318	1.32	0.86-2.02	0.201	0.92	0.50-1.68	0.770
Patient sex	Female	1.02	0.67-1.54	0.941	1.13	0.78-1.65	0.522	1.46	0.93-2.29	0.097	0.68	0.34-1.37	0.280
Disease status	BC active	2.00	1.35-2.96	0.001	1.80	1.27-2.57	0.001	1.48	0.97-2.27	0.068	1.50	0.82-2.75	0.191
Type of BC	Myeloid	1.05	0.66-1.66	0.844	1.15	0.75-1.74	0.528	1.88	1.12-3.16	0.017	0.49	0.24-0.98	0.044
Karnofsky performance status	≤80%	1.96	1.30-2.98	0.001	1.95	1.34-2.86	0.001	1.58	0.98-2.56	0.061	1.33	0.70-2.55	0.392
TKI pre-treatment	>1 TKI	0.65	0.41-1.03	0.067	0.79	0.52-1.20	0.261	1.35	0.82-2.23	0.250	0.32	0.14-0.74	0.008
Additional cytogenetic aberrations	Absent	1.26	0.72-2.22	0.416	0.82	0.51-1.30	0.392	0.57	0.34-0.99	0.046	1.87	0.68-3.50	0.221
T315I mutation	Absent	0.43	0.18-1.02	0.055	0.55	0.27-1.12	0.101	0.81	0.37-1.81	0.620	0.44	0.11-1.75	0.240
Interval diagnosis of BC to transplant	≤12 months	0.81	0.55-1.21	0.302	0.86	0.60-1.23	0.408	0.93	0.61-1.43	0.761	0.86	0.46-1.59	0.630
Year of transplant	≤2010	1.64	1.11-2.43	0.013	1.39	0.97-1.97	0.073	0.84	0.54-1.29	0.420	2.92	1.53-5.59	0.001
Stem cell source	PB	0.76	0.45-1.27	0.292	1.05	0.64-1.73	0.852	1.46	0.78-2.77	0.240	0.65	0.30-1.43	0.292
Conditioning	RIC	0.88	0.59-1.32	0.530	0.99	0.69-1.43	0.963	1.39	0.91-2.14	0.131	0.52	0.25-1.05	0.069
Donor	Unrelated	1.08	0.73-1.59	0.701	0.92	0.65-1.31	0.634	0.95	0.62-1.46	0.822	0.99	0.54-1.81	0.960
Recipient – donor sex match	RMDF	1.04	0.65-1.66	0.860	0.92	0.60-1.41	0.698	0.83	0.49-1.41	0.490	1.16	0.57-2.36	0.680

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

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.

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

		OS†			LFS‡			Relapse¶			NRM§		
Covariate	**Effect**	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Patient age	≥45 years	1.25	0.79-1.99	0.345	1.09	0.71-1.68	0.690	1.13	0.65-1.95	0.660	1.16	0.51-2.61	0.730
Disease status	BC active	1.87	1.16-3.00	0.010	1.69	1.10-2.59	0.017	1.33	0.75-0.81	0.260	1.69	0.73-3.91	0.220
Karnofsky performance status	≤80%	1.82	1.10-3.01	0.019	1.65	1.05-2.59	0.029	1.50	0.85-2.63	0.160	1.23	0.54-2.80	0.630
Interval diagnosis of BC to transplant	≤12 months	0.79	0.51-1.22	0.290	0.78	0.52-1.17	0.231	0.82	0.50-1.35	0.440	0.95	0.48-1.88	0.880
Year of transplant	≤2010	1.27	0.83-1.95	0.276	1.09	0.73-1.61	0.687	0.70	0.42-1.18	0.180	2.59	1.33-5.06	0.005
Stem cell source	PB	0.67	0.37-1.22	0.189	0.99	0.57-1.72	0.970	1.41	0.66-2.99	0.380	0.60	0.22-1.64	0.320
Conditioning	RIC	0.65	0.39-1.07	0.092	0.83	0.52-1.30	0.410	1.12	0.65-1.94	0.680	0.53	0.78-4.65	0.160
Donor	Unrelated	1.13	0.71-1.82	0.605	0.86	0.57-1.31	0.486	0.94	0.57-1.56	0.820	1.04	0.46-2.36	0.930
Recipient – donor sex match	RMDF	1.07	0.66-1.76	0.778	0.96	0.61-1.51	0.855	0.92	0.51-1.68	0.790	0.94	0.44-2.02	0.880

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

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.

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).

		OS†			LFS‡			Relapse¶			NRM§		
Covariate	**Effect**	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Patient age	≥45 years	2.42	1.13-5.14	0.022	2.51	1.30-4.83	0.006	1.40	0.67-2.95	0.370	2.72	0.93-7.94	0.067
Karnofsky performance status	≤80%	2.69	1.26-5.76	0.011	2.83	1.46-5.49	0.002	2.18	0.98-4.87	0.057	0.94	0.22-3.94	0.930
Interval diagnosis of BC to transplant	≤12 months	0.48	0.24-0.94	0.033	0.57	0.32-1.00	0.052	0.67	0.33-1.36	0.270	0.90	0.31-2.61	0.850
Conditioning	RIC	0.26	0.11-0.65	0.004	0.40	0.19-0.84	0.016	1.25	0.57-2.75	0.570	0.09	0.02-0.44	0.003
Donor	Unrelated	3.61	1.72-7.58	0.001	1.81	0.99-3.31	0.053	0.78	0.39-1.54	0.470	4.41	1.51-12.86	0.007

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

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.

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†			LFS‡			Relapse¶			NRM§		
		HR	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Patient age	≥45 years	0.85	0.46-1.55	0.589	0.59	0.33-1.04	0.068	0.98	0.51-1.90	0.960	0.75	0.28-2.02	0.571
Karnofsky performance status	≤80%	1.47	0.78-2.79	0.233	1.35	0.76-2.37	0.305	1.03	0.54-1.96	0.918	1.25	0.43-3.65	0.680
Interval diagnosis of BC to transplant	≤12 months	0.84	0.48-1.46	0.530	0.84	0.48-1.45	0.528	1.03	0.53-1.98	0.938	0.75	0.32-1.79	0.522
Conditioning	RIC	0.75	0.41-1.35	0.338	1.03	0.58-1.82	0.931	1.22	0.59-2.52	0.600	0.71	0.29-1.78	0.473
Donor	Unrelated	0.56	0.31-1.01	0.055	0.47	0.27-0.81	0.007	1.07	0.53-2.15	0.850	0.48	0.19-1.24	0.130

†Number of events: 57; ‡Number of events: 64; ¶Number of events: 42; §Number of events: 22.

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.

FIGURE LEGENDS

Figure 1. Overall survival (OS), leukemia-free survival (LFS) and cumulative incidences of relapse and non-relapse mortality (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 13.6-34.0) as compared to 51.1% (95%CI 40.5-61.7) for patients who received alloSCT in remission of BC CML (P<0.001, 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 3.0-20.2) *versus* 33.8% (95% CI 23.6-44.0), respectively (P=0.001, 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 44.1-66.9) as compared to 45.9% (95% CI 35.1-56.1) for patients who were allografted for BC in remission (P=0.076, 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 17.4-37.7) and 20.2% (95% CI 12.5-29.3), respectively (P=0.190, Gray's test).

Figure 2. Kaplan-Meier estimates of leukemia-free survival based on a landmark analysis at 6 months post-transplant, grouping patients according to prior history of chronic GVHD.

(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 35.6-75.2 *versus* 48.0% 95% CI 34.7-61.3).

(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 5.7-55.9) and 43.2% (95% CI 19.9-66.5), 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 62.1-100.0) and 49.8% (95% CI 33.3-66.3), respectively.

Supplementary Material for Online Publication

Table S1. *BCR-ABL1* mutations in patients with non-T315I mutations.

Table S2. Specification of the TKI treatment in patients with *BCR-ABL1* mutations.