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Improved Outcome in Patients with Chronic Myelogenous Leukemia after Allogeneic Hematopoietic Stem Cell Transplantation Over the Past 25 Years: A Single-Center Experience

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Although imatinib has become standard first-line therapy in chronic myelogenous leukemia (CML), allogeneic hematopoietic stem cell transplantation (HSCT) is still considered to be an important treatment alternative for patients with drug resistance or advanced disease. We retrospectively analyzed 175 adult CML patients who underwent HSCT at our institution between 1983 and 2007, with the aim to compare outcomes in patient subgroups and to identify prognostic variables. The median follow-up was 65 months. The probability of overall survival (OS) for all patients was 62%, with a significant improvement seen in the imatinib-era (2001-2007) compared to previous time periods ($P < 05$). Furthermore, a significantly better outcome for patients with chronic phase CML compared to patients with accelerated or blast phase could be observed ($P < .05$). Cumulative incidence (CI) of treatment-related mortality (TRM) was 9.7% at 100 days and 1 year after HSCT. CI of relapse was 5% at 1 year and 7.5% at 3 years after HSCT. Post-HSCT outcome was not influenced by pretreatment therapy with imatinib, donor type, or a conditioning regimen with total body irradiation (TBI). These data confirm earlier observations and suggest that allogeneic HSCT is still an important treatment option for high-risk patients with CML, and should thus remain an integral component in current and future treatment algorithms.

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INTRODUCTION

Chronic myelogenous leukemia (CML) is a myeloproliferative stem cell neoplasm, which is defined by the presence of the t(9;22) with the resulting BCR-ABL oncoprotein [1]. The clinical course is divided into a chronic phase (CP), an accelerated phase (AP), and a blast phase (BP) [2,3]. For more than 20 years, the treatment of choice for all eligible patients was allogeneic hematopoietic stem cell transplantation (HSCT), whereas the standard therapy for all ineligible patients was interferon-alpha (IFN-α). During the past 10 years, substantial progress has been made in the treatment of patients with CML. A major breakthrough has been the development and introduction of the BCR-ABL-targeting tyrosine kinase inhibitor (TKI) imatinib and of second-generation TKIs, including dasatinib and nilotinib [3-7]. The majority of all patients in CP CML respond well to imatinib and achieve durable cytogenetic complete remissions (CRs), whereas patients with relapsed disease or advanced phase often show a poor or only transient response to TKIs [3-7]. In addition, imatinib and other currently available TKIs apparently cannot eradicate the disease at the stem cell level, and primary, as well as acquired resistance to imatinib and

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to second-generation TKIs, is an emerging problem in the treatment of patients with CML [8-13].

HSCT is still an important salvage therapy, although the total number of candidates has decreased during the past decade, with a shift toward high-risk patients who still are referred quite frequently for HSCT. Recently, HSCT was also recommended as the preferred second-line option after imatinib failure if a suitable donor is available [14]. Furthermore, with the availability of reduced-intensity conditioning (RIC) [15-17], improvement of antibiotic and antifungal therapy [18,19], donor selection, and prevention and therapy of graft-versus-host disease (GVHD) [20-23], progress could be achieved in reducing morbidity and mortality associated with HSCT.

The present study reports the analysis of 175 patients who received an allogeneic HSCT for CML in our center. In these patients, we evaluated the clinical outcome with overall survival (OS), treatment-related mortality (TRM), relapse rate, and potential prognostic variables.

PATIENTS AND METHODS

Patients

Between 1983 and 2007, a total of 175 adult patients with BCR-ABL-positive CML (females, n = 78; males, n = 97) were referred for allogeneic HSCT to our institution. The median age was 38 years (range: 19-62 years). Disease- and transplant-specific characteristics are shown in Table 1. Stem cell donors were HLA-identical siblings (94 patients), matched unrelated donors (URDs; 64 patients) and 1-allele-mismatched URDs (17 patients). During the last 10 years, HSCT with an URD was performed increasingly, whereas in previous time periods (1983-2000) more sibling donors were used. Histocompatibility typing and donor selection were performed as previously described [24,25]. At the time of HSCT, 122 patients were in first CP of CML, 13 were in second or third CP, 25 were in AP, and 15 patients were in BP. As expected, more patients with advanced phase of the disease were transplanted in recent years (2000 to 2007). Patients were diagnosed according to published criteria [26]. Since 2001, patients have been classified according to the proposal of the World Health Organisation [27].

One hundred thirty-one patients received bone marrow (BM) stem cells, and 44 patients received peripheral blood stem cells (PBSCs) mobilized by recombinant human granulocyte colony stimulating factor (rHu G-CSF). Patients were hospitalized in isolation rooms with laminar air flow or reverse isolation. They received antimicrobial prophylaxis with oral nonabsorbable antibiotics and *Pneumocystis jirovecii* prophylaxis with trimethoprim/sulfamethoxazole. For cytomegalovirus (CMV) prophylaxis, patients received acyclovir as described [28]. Packed red blood cells (RBCs) were given to maintain hemoglobin concentrations above 8.0 g/dL, and platelet transfusions were given to keep the platelet count above 20×10^9/L. All patients received CMV-negative blood products. Approved informed consent was obtained from all patients.

Conditioning Regimens and GVHD Prophylaxis

Myeloablative conditioning was performed in 166 patients. Of these, 126 patients received intravenous (i.v.) cyclophosphamide (Cy) at 120 mg/kg body weight plus fractionated total body irradiation (TBI) (12 Gy for related donor HSCT, and 13.2 Gy for URD HSCT). One patient received i.v. etoposid 60 mg/kg body weight and 13.2 Gy TBI. Thirty-nine patients received i.v. Cy in the same dosage plus either oral busulfan at 16 mg/kg body weight or i.v. busulfan at 12.8 mg/kg body weight. RIC was performed in 9 patients and consisted either of the FLAMSA (fludarabine, amsacrine, ARA-C, 4 Gy of TBI, Cy, antithymocyte globulin [ATG]) protocol (4 patients), or fludarabine at 90 mg/m^2 body surface area plus 2 Gy of TBI (5 patients) [29]. RIC was performed in case of an advanced age (≥60 years, n = 4), or because of poor performance status with severe comorbidities (n = 5).

For GVHD prophylaxis, 162 patients received cyclosporine A (CsA) and methotrexate (MTX) according to the Seattle protocol [30], 9 patients received CsA and mycophenolate mofetil [31], 3 patients received only MTX, and 1 patient received CsA and methylprednisolone. The clinical diagnosis of GVHD was confirmed by biopsy and was clinically graded as 0 to IV for acute GVHD (aGVHD), and as "none," "limited," or "extensive" for chronic GVHD (cGVHD) [32,33].

Engraftment and Molecular Response

In all patients PBSC counts were determined on a daily basis, starting 7 days before HSCT until hematopoietic engraftment. Absolute neutrophil counts (ANCs) were calculated from leukocyte and differential counts. BM aspirates/biopsies were performed before HSCT, as well as on days 28 and 1 year after transplantation. Engraftment was defined as the first of 3 days with an ANC of at least 0.5×10^9/L, a stable platelet count of at least 20×10^9/L, and RBC transfusion independence. Engraftment of donor cells was documented by cytogenetic analyses and amplification of highly variable DNA regions (short tandem repeats) of different sex-independent genes by PCR of recipient BM cells before and 28 days after transplantation. Chromosome analyses were performed from short-term BM cell cultures using the G-banding technique. Chromosomal abnormalities were described according to the International System for Human Cytogenetic Nomenclature [34]. For serial chimerism analysis, unseperated PB, $CD3^+$ and $CD33^+$ subsets, and granulocytes were

Table 1. Patients' Characteristics I

	All Patients n	Year of Transplantation		
		1983-1994 n	1995-2000 n	2001-2007 n
No. of patients	175	55	78	42
Median age (range) in years	38 (19-62)	35 (19-57)	39 (19-62)	39 (24-60)
Median time from diagnosis to HSCT(months)	14 (2-226)	14 (5-72)	14 (2-226)	14 (4-188)
Sex				
Female	78	24	34	20
Male	97	31	44	22
Conditioning				
Myeloablative with TBI	127	43	58	26
Myeloablative without TBI	39	12	18	9
RIC	9	0	2	7
Disease status at HSCT				
CP 1	122	40	63	19
>CP 1	13	2	2	9
AP	25	10	8	7
BP	15	3	5	7
GVHD-Prophylaxis				
CSA/methylprednisolone	1	1	0	0
MTX	3	3	0	0
CsA/MTX	162	51	76	35
CsA/MMF	9	0	2	7
Imatinib prior to HCT				
Yes	32	0	1	31
No	143	55	77	11
Stem cell source				
BM	131	55	61	15
PB	44	0	17	27
Gratwohl Score*				
1+2	72	35	29	8
3+4	81	17	41	23
5+6	22	3	8	11
Donor HLA-identity				
HLA-match	158	53	69	36
1-allele-mismatch	17	2	9	6
Donor type				
Sibling	94	52	30	12
URD	81	3	48	30

HSCT indicates hematopoietic stem cell transplantation; TBI, total body irradiation; RIC, reduced intensity conditioning; CP, chronic phase; AP, accelerated phase; BP, blast phase; GVHD, graft-versus-host disease; MTX, methotrexate; CsA, cyclosporine A; MMF, mycophenolate mophetil; BM, bone marrow; PB, peripheral blood; HLA, human leukocyte antigen; URD, unrelated donor.
*See [39].

analyzed on days 28, 56, and 84, and then every 6 months in patients receiving RIC. Monitoring of molecular response by measurement of BCR-ABL transcript levels was based on reverse-transcription polymerase chain reaction (RT-PCR) every 3 months until a complete molecular response was documented. After achieving a complete molecular response, monitoring was performed every 6 months. For BCR-ABL analysis, total RNA was extracted after red cell lysis from 20 mL PB or 5 mL BM using the Rneasy® Mini Kit (Quiagen, Hilden, Germany) according to the manufacturer's instructions. cDNA synthesis was performed using random hexamer primers and MultiScribe Reverse Transcriptase (Applied Biosystems, Foster City, CA, USA). Real-time PCR amplification of BCR-ABL using nested primers was performed as described [35]. Since 2001, quantitative real-time qualative (Q-PCR) for BCR-ABL and total ABL transcripts were performed in duplicates using the LightCycler 1.0 or 2.0 apparatus (Roche, Indianapolis, IN, USA) and the M-bcr FusionQuant® Kit for the RT-QPCR analysis of M-bcr transcripts (Ipsogen, Marseille, France), according to the manufacturer's instructions.

Statistical Analysis

OS was calculated from the day of HSCT until death from any cause. Patients who were alive or lost for follow-up were censored. The probability of OS was estimated using the Kaplan-Meier method. Potential prognostic factors for survival were examined in univariate and multivariate analysis by Cox's regression. TRM was defined as mortality after HSCT not occurring because of relapse. The software package SPSS 10.0 (SPSS Inc., Chicago, IL, USA) was used for all these statistical analyses.

For outcome analysis, the proportional subdistribution hazards' regression model of Fine and Gray was used [36]. To investigate the relation of relevant covariables on GVHD, univariate competing risk regressions were calculated. The incidence of GVHD before day 100 after HSCT was defined as "acute"

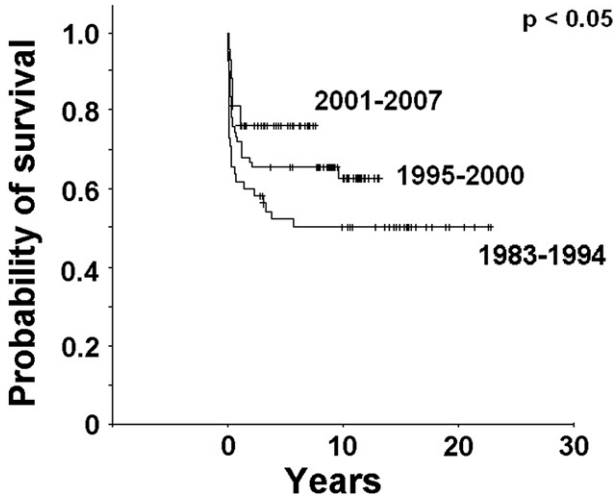

Figure 1. Probability of overall survival (OS) for all CML patients (n = 175) performed in the years 1983-1994, 1995-2000, and 2001-2007 (P <05).

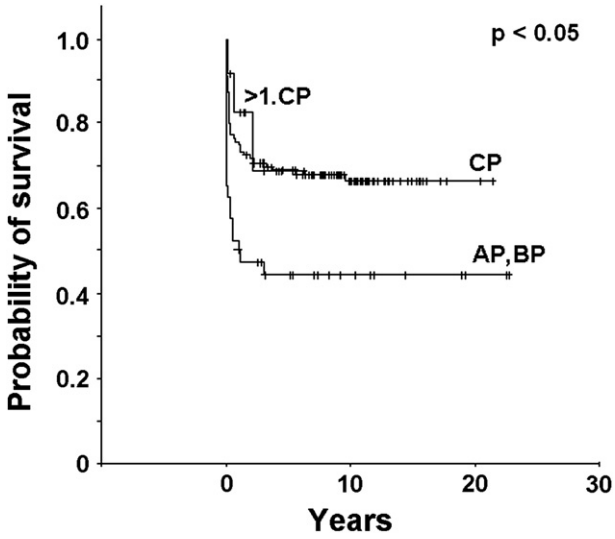

Figure 2. Probability of overall survival (OS) for all CML patients (n = 175) according to the phase of the disease (P <.05).

and after day 100 as "chronic." All risk factors with a P-value <.05 were further applied in a multivariate competing risk regression. For the outcome analysis of relapse, the same covariables were studied and additionally, the previous incidence of GVHD (aGVHD and, cGVHD, or 1 of them) was tested. These analyses were performed using SAS 9.1 (SAS Institute, Inc., Cary, NC, USA) and R 2.8.1. (using cmprsk package). Values of P <.05 were considered to be statistical significant.

Definition of Relapse and Imatinib Failure or Resistance

Relapse was defined as recurrence of Ph+ metaphases/BCR-ABL transcripts by cytogenetic/molecular analysis or hematologic signs of CML in PB or BM after achievement of complete remission. Relapse was defined as molecular if it occurred without hematologic or clinical signs of disease. Relapse was defined as hematologic if hematologic signs of CML preceded or accompanied molecular evidence of relapse. Treatment failure or resistance to imatinib were defined according to institutional guidelines that are based on the recommendations by the European Leukemia Net (ELN) [37].

RESULTS

Outcome and Survival

Apart from 1 patient, all engrafted, and currently 108 of the 175 patients (62%) are alive with a median follow-up of 65 (range: 1-273) months. Significant improvement of OS was observed when comparing time intervals over the last 25 years. For transplantations performed in the years 1983-1994, 1995-2000, and 2001-2007, OS was 50%, 63%, and 76%, respectively (Figure 1, P <.05). OS for patients in different phases of CML is shown in Figure 2. Significantly better OS in patients with CP, compared to patients in AP or BP, was observed. Between 1983 and 1994, 24% of all CML patients were in AP or BP, between 1995 and 2000 17%, and between 2001 and 2007 33%. No difference of OS was found for patients with a sibling compared to a URD. The cumulative incidence (CI) for relapse was 5% 1 year after HSCT (Table 2), and 8% 3 and 5 years after HSCT (Table 2). Twenty-three patients died as a consequence of cGVHD, 15 patients died from severe infections without cGVHD, 10 patients died because of toxicity and multiorgan failure, 1 patient died from myocardial infarction, and in 2 patients the exact cause of death remains unknown. The cumulative incidence for TRM at 100 days and 1 year after HSCT was considerably low and amounted to 10%. The cumulative incidence for GVHD at 100 days after HSCT was 53%, and at 1 year and at 5 years 66% (Table 2).

Outcome of Patients with Imatinib Prior to HSCT

In the years 2000 to 2007, 32 patients received imatinib prior to HSCT (Table 3). Imatinib treatment ranged from 1 to 48 months, and patients were

Table 2. Cumulative Incidences (CIs) of TRM, GVHD, and Relapse Rate

	100 Days	1 Year	3 Years	5 Years after HCT
TRM	0.097	0.097	0.097	0.103
GVHD	0.526	0.663	0.663	0.663
Relapse	0.011	0.051	0.075	0.075

TRM indicates treatment-related mortality; GVHD, graft-versus-host disease.

Table 3. Patients' Characteristics II

	Imatinib Prior to HSCT n	No Imatinib Prior to HSCT n
No. of patients	32	143
Median age (range) in years	42 (24-60)	38 (19-62)
Median time from diagnosis to HSCT(months)	15 (4-188)	13 (2-226)
Imatinib duration (months)	8 (1-48)	—
Gender		
Female	15	63
Male	17	80
Conditioning		
Myeloablative with TBI	21	106
Myeloablative without TBI	4	35
RIC	7	2
Disease status at HSCT		
CP 1	12	110
>CP 1	7	6
AP	7	18
BP	6	9
GVHD-Prophylaxis		
CSA/methylprednisolone	0	1
MTX	0	3
CsA/MTX	25	137
CsA/MMF	7	2
Stem cell source		
BM	6	125
PB	26	18
Gratwohl Score*		
1+2	3	69
3+4	13	68
5+6	16	6
Donor HLA-identity		
HLA-match	26	132
1-allele-mismatch	6	11
Donor type		
Sibling	7	87
URD	25	56

HSCT indicates hematopoietic stem cell transplantation; TBI, total body irradiation; RIC, reduced-intensity conditioning; CP, chronic phase; AP, accelerated phase; BP, blast phase; GVHD, graft-versus-host disease; MTX, methotrexate; CsA, cyclosporine A; MMF, mycophenolate mophetil; BM, bone marrow; PB, peripheral blood; HLA, human leukocyte antigen; URD, unrelated donor.

transplanted at a median of 15 months after diagnosis. The reasons for referral for HSCT were imatinib failure (n = 24), imatinib toxicity (n = 2), and high-risk disease with an available HLA-matched donor (n = 6). Twenty-one of 32 patients (66%) are still alive with a median follow-up of 19 (range: 1-74) months. Three patients died because of relapse, and 8 patients died because of TRM (GVHD with or without infection). OS (Figure 3), and TRM were not different from patients who did not receive imatinib, whereas the incidence of GVHD was significantly increased in the imatinib group (hazard ratio [HR] = 2.21 [1.22;3,99], $P = .009$), as assessed with multivariate competing risk regression. The median Karnofsky performance score for all patients alive at 1 year after HSCT was 80% (range: 70%-100%).

Analysis of Patients with Relapse after HCT

Twenty-eight of 175 patients (17%) relapsed after allogeneic HSCT at a median of 15 months (range: 3-144) after HSCT, and 2 patients had persistent disease. Fifteen patients had hematologic relapse, 5 patients had molecular relapse, and 8 patients had extramedullary relapse, 1 of these with involvement of the central nervous system (CNS). Thirteen of the patients with hematologic relapse were transplanted in the years 1983 to 2000; thus, these patients had no quantitative monitoring of BCR-ABL. Further therapy consisted of donor lymphocyte infusion (DLI) in 12 patients, 3 patients received a second HSCT, 10 patients received imatinib, 1 patient had local radiation, and 4 patients did not receive further treatment. The patient with CNS relapse received intrathecal cytarabine and dasatinib and entered a cytogenetic CR. Fifteen patients with relapse died; univariate analysis revealed the presence of BP at the time of HSCT as a significant prognostic factor for the risk of relapse. No significant influence of GVHD was found; however, the previous incidence of aGVHD and/or cGVHD showed a tendency to protect from relapse (HR = 0.52 [0.25; 1.09], $P = .0842$).

Outcome of Patients with Reduced-Intensity Conditioning

Nine patients received RIC; 5 of these patients were in first (n = 3) or second (n = 2) CP of the disease, 1 was in AP, and 3 patients were in BP. Five patients died, 2 because of persistent disease, 2 because of relapse and 1 had an infection with severe cGVHD. Four patients alive have been in continuous molecular CR, for a median of 51 (range: 37-65) months after HSCT. Of note, all achieved a complete donor chimerism that has been sustained.

Analysis of BM versus PBSCs

As depicted in Table 1, 131 patients received BM and 44 PBSCs. We could find a slight but not statistically significant difference in OS (Figure 4). In further outcome analysis with competing risk regressions, no significant influence of the stem cell source on the occurrence of GVHD or the risk of relapse was found.

Analysis of Prognostic Variables for OS, Incidence of GVHD, and Risk of Relapse

To determine the influence on OS, several possible and known prognostic factors were investigated in univariate and multivariate analyses. In detail, we evaluated sex, age at HSCT, TKI prior to HCT, phase of the disease at HSCT, donor type, HLA-match, Gratwohl score, stem cell source, TBI for conditioning therapy, and aGVHD. In our group of CML patients, we could not identify an independent risk factor indicating a favorable outcome concerning OS.

Furthermore, we determined the influence of the same covariates on the occurrence of aGVHD/cGVHD or the risk of relapse. A TKI prior to HSCT, the presence of a later than first CP at HSCT and a sibling donor increased the risk of GVHD, but

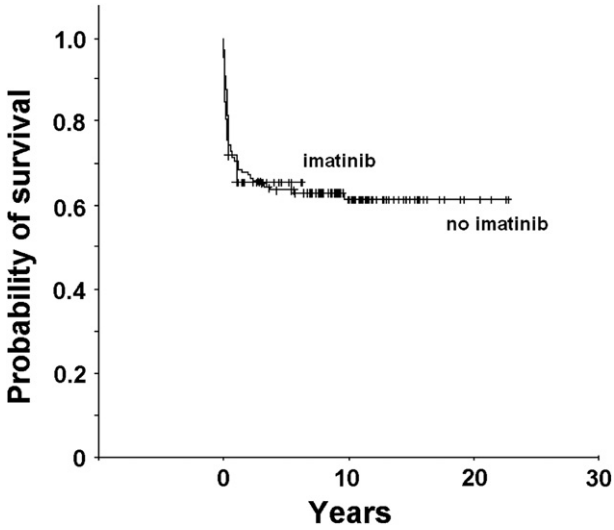

Figure 3. Cumulative incidence probability of overall survival (OS) for CML patients with (n = 32) or without (n = 143) imatinib prior to HCT.

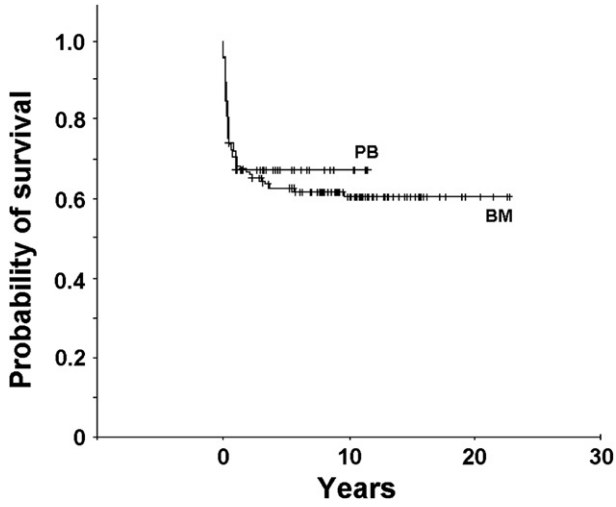

Figure 4. Probability of overall survival (OS) for CML patients with bone marrow derived stem cells (n = 131) or peripheral blood derived stem cells (n = 44).

only a TKI prior to HSCT remained significant in the multivariate model (HR = 2.21 [1.22; 3.99], $P = .009$). Concerning the risk of relapse, no significant influence of GVHD was found, although the previous incidence of aGVHD and/or cGVHD showed a tendency to protect from relapse (HR = 0.52 [0.25; 1.09], $P = .0842$). Only BP at HSCT increased the risk of relapse significantly in univariate analysis.

In a subanalysis of 57 consecutive patients between 2001 and 2007, based on a previously published study [38], we also investigated the prognostic impact of serum β-2-microglobulin levels and ferritin on outcome and survival; no statistically significant effect could be found.

DISCUSSION

Allogeneic HSCT is still considered to be the only curative treatment for CML, although the total number of eligible patients has decreased since the introduction of TKIs. We analyzed 175 patients with CML who were transplanted at a single center between 1983 and 2007 with a median follow-up of 65 (range: 1-273) months. We assessed OS, CI of GVHD, TRM, relapse rate, and possible prognostic variables, to define the potential role of HSCT in the TKI era.

To analyze the development of outcome and survival, we divided our cohort into 3 groups, depending on the time period HSCT was performed: 1983-1994, 1995-2000, and 2001-2007. OS showed a distinct improvement over time ranging from 50% in the early group to 76% ($P < .05$) in the recently transplanted group even though the number of transplant candidates with the AP of the disease increased during the past decade. This development in the outcome may be attributable to a number of different factors, including improvements in high-resolution HLA-typing, less toxicity of pretransplantation treatment, improvement of supportive care, better antiinfectious therapy, and improved overall management of GVHD.

In our cohort we had 32 patients who received imatinib prior to HSCT. The median time interval from diagnosis to HSCT was 15 months. These patients were transplanted primarily because of imatinib failure with loss of molecular response or cytogenetic remission. Six patients were referred to our institution because of high-risk disease according to the Gratwohl score [39] ranging between 4 and 6. Outcome and TRM did not differ when comparing patients who had received imatinib prior to HSCT with all other patients. However, in further outcome analysis, we found that imatinib prior to HSCT increased the CI of GVHD but had no negative influence on OS. This data are only in parts consistent with previously published results [40], but interpretation is limited because of the small cohort of imatinib pretreated patients in our group. One possible explanation for this discrepancy is a higher rate of skin only GVHD in patients with imatinib (5 of 32 patients = 16%) compared to patients without imatinib prior to HSCT (3 of 143 = 2% patients), which shows a better response to treatment, thereby not affecting survival. Further immunologic investigations were not performed. With regard to the fact that imatinib has become the standard first-line treatment for CML patients, it seems rather important to emphasize that prior therapy with a TKI does not increase TRM. Also, provocative results have been published by Oehler et al. [41], who showed that the best transplant results may be obtained in patients responding to imatinib compared to non- or suboptimal responders prior to transplantation. These findings clearly show that close molecular monitoring is necessary and that rapid changes of therapeutic strategies (eg, performing

HSCT) might improve patients' outcome. Also, interesting results showed a recent report published by Saussele et al. [14], who found an OS at 3 years after allogeneic HSCT for patients with imatinib failure in first CP of 94%. These are excellent results, and in their group of patients with advanced phase of CML OS was still 59%. If these results can be confirmed, allogeneic HSCT will clearly be recommended as the preferred second-line treatment option after failure of first-line TKI therapy. Also, subclones resistant to imatinib may be eradicated with HSCT more effectively at an earlier time point because of the plasticity of CML stem cells with rapid outgrowth of more malignant subclones.The next step was to focus on different prognostic factors concerning OS. In our group of patients, we could not find a statistical significant predictor of favorable survival, additionally we were unable to show a prognostic impact of elevated β2-microglobulin, a parameter that has recently been described to be prognostic in non-transplant patients treated with imatinib [38]. It also seems that the Gratwohl Score [39] is more applicable for "historic" patients who did not receive any TKIs prior to HSCT because of changes in patients' selection for HSCT. Therefore, it will be necessary for the future to establish new prognostic scores for CML patients.

With the introduction of RIC in the last years toxicity and the risk of TRM could be decreased for patients with substantial comorbidity and/or higher age and/or high-risk disease. To focus on the selection of the ideal conditioning therapy, our number of patients was too small for any solid conclusion. Nevertheless, with the availability of RIC, HSCT can be offered to a broader spectrum of patients.

Regarding stem cell source and donor type (related versus unrelated donor) our results for OS, TRM, and occurrence of GVHD were comparable.

The CI of recurrence of CML after transplantation was 5% at 1 year after HSCT and 8% at 3 years. Fifty percent of relapsed patients had hematologic relapse, 23% had molecular, and 27% had extramedullary relapse. Further systemic therapy consisted either of imatinib or DLIs, or imatinib and DLIs. Fifteen patients died all in all, with a trend toward better survival of patients who received a TKI.

Finally, according to these observations, we conclude that HSCT remains an important treatment option for patients with failure/resistance (especially in patients with poor-risk mutations, eg, T315I mutation) to TKIs, primary advanced phase of the disease or progression to AP/BP under TKI treatment.

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