Challenges for Allogeneic Hematopoietic Stem Cell Transplantation in Chronic Myeloid Leukemia in the Era of Tyrosine Kinase Inhibitors

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Key Words

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Abstract

Following the introduction of the tyrosine kinase inhibitor (TKI) imatinib in the treatment of chronic myeloid leukemia (CML) patients, the allogeneic hematopoietic stem cell transplantation (HSCT) scene in CML has changed dramatically. The number of patients receiving HSCT in first chronic phase (CP) has declined rapidly, as allogeneic HSCT in CP is now performed in these patients only in case of failure or intolerance of TKIs. Second, those CML patients who undergo allogeneic HSCT represent a selection of high-risk patients due to more advanced disease with high rates of accelerated or blast phase (being associated with an increased relapse risk), advanced age and relevant co-morbidities. Efforts at meeting these special challenges are being developed: treatment with TKIs aims to improve the pre-transplant remission status before HSCT. Dose-reduced conditioning protocols were introduced to decrease transplant-related mortality in patients with co-morbidities or older age. In the post-transplant period, TKIs may be administered for prophylaxis and

for treatment of post-transplant relapse. Still, the outcome of patients in advanced CML phases remains guarded, and requires an improvement in current transplant strategies.

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Introduction

The treatment of chronic myeloid leukemia (CML) underwent dramatic changes in recent years. From the 1980s to 2000, allogeneic hematopoietic stem cell transplantation (HSCT) was the treatment of choice for younger patients in first chronic phase (CP) if an HLA-matched donor was available. Before 1999, CML was the most frequent indication for allogeneic HSCT worldwide [1]. With the approval of imatinib by the FDA in 2001 [2], this tyrosine kinase inhibitor (TKI) soon became the front-line therapy for newly diagnosed CML patients. Following the International Randomized Study of Interferon and STI571 (IRIS) trial which clearly demonstrated the superiority of imatinib over a combination of IFN- α and cytarabine in patients with newly diagnosed CML in CP with respect to response rates and toxicity [3–6], transplantation rates in CML dropped quickly worldwide [7].

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As a result of the efficacy of imatinib, and thanks to the introduction of second-generation TKIs such as dasatinib and nilotinib, HSCT shifted from a preferred first-line therapy to a second, third or fourth-line option, and is now reserved for patients with insufficient imatinib response, or with advanced phases of CML [7, 8]. Pre-transplant application of first- or second-generation TKIs allowed patients with accelerated (AP) or blast phase (BP), who previously would not have survived long enough to benefit from transplantation, to become transplantation candidates [7, 9, 10]. Thus, as a result of the selection of patients with unfavorable risk profiles, increasing relapse rates in those patients with CML undergoing HSCT have been reported [11–13]. Intensive pre-treatment, advanced age and co-morbidities are associated with an increased risk of transplant-related morbidity and mortality (TRM).

Thus, comprehensive approaches are needed for those CML patients being selected nowadays for HSCT to improve transplant outcomes. In the pre-transplant period, use of first- or second-generation TKIs has been shown to improve remission rates in patients with advanced disease [14, 15], either alone or in combination with cytotoxic agents [10, 16–18].

Some groups successfully introduced reduced-intensity conditioning (RIC) strategies in patients with CML who otherwise would not have been eligible for transplantation [19–22]. However, the number of RIC studies, specifically in CML, is still limited. With respect to the post-transplant period, imatinib has been explored for its potential for maintenance therapy or for therapy of CML relapse [21, 23–25]. Initial studies suggested acceptable tolerance also for second-generation TKIs in the post-transplant period [26]. Another option is the use of donor lymphocyte infusions (DLI) for adoptive immunotherapy [27–29], but its role should be reassessed in view of the new option of post-transplant TKI treatment. This review discusses recent changes in the indications and timing of HSCT in CML, and summarizes new options and developments of transplantation strategies while paying attention to the pre- and post-transplant periods in patients with CML.

Actual Trends and Developments in HSCT

Annual transplantation rates in first CP (CP1) dropped quickly after the first reports on the efficacy of imatinib in the year 2000 [30]. An EBMT study showed an increase from 559 HSCTs yearly for CML in 1991 to a maximum

of 1,396 in 1999, followed subsequently by a reduction to 802 in 2004 [31]. In 2007, there were a total of 434 HSCTs for CML, 228 in CP1 and 206 in advanced stages of the disease. The German Registry (DRST) reported a decrease in the annual transplantation rate in CML from a total of 357 in 1998 to 98 in 2004 (approx. a 73% drop) [32]. At the same time, annual transplantation rates were increasing in other entities such as acute myeloid leukemia or myelodysplastic syndromes. However, the number of HSCTs for CML did not decline in all countries at the same rate [33].

Shift of Stages in the Allogeneic Transplantation Setting

Higher remission rates were reported due to the use of imatinib and second-generation TKIs in patients with advanced disease [7, 9], leading to a shift in the stage at which CML patients were referred for HSCT. Thus, the proportion of patients with advanced disease (>CP1, AP, BP) increased from 32 to 53% of the annual transplantations in the DRST study [32]. Similarly, a large study of the Center of International Bone Marrow Transplantation Registry (CIBMTR) including 2,436 patients documented an increase in HSCTs for CP2 or AP from 24 to 41% of all transplantations for CML [30]. Here, two different mechanisms have to be assumed. First, the number of HSCTs in initial CML has undergone a more pronounced reduction when compared to those in advanced phase [15]. Second, remission rates could be improved in patients with advanced disease before HSCT. Thus, more patients in advanced disease became eligible for HSCT due to the use of first- or second-generation TKIs before transplant.

Evolution of Prognostic Scoring Systems for HSCT in CML

The first adequate scoring systems for evaluation of risks from Sokal et al. [34] included patient's age, spleen size, thrombocytes level and myeloblasts in peripheral blood as prognostic parameters. Hasford et al. [35] proposed that peripheral basophil and eosinophil counts had additional prognostic significance. With the development of HSCT, the classical stratification scales turned towards the incorporation of some transplant-related parameters such as donor type (related or unrelated), disease stage, donor/patient sex-compatibility, and intervals

Table 1. Outcomes of chronic phase CML reported in 2009–2010

Study	Patients ¹	Disease phase	Donor type/stem cell source	Conditioning	Outcomes for CP patients		
					OS	EFS/DFS	TRM/NRM
Shimoni et al. [17] ²	21 (45 years, 16–59)	CP1 = 5 Adv = 16	Sib 7, UR 13/ PB 64, BM 20	MAC 14, RIC 7	64% (2 years)	46% (2 years)	7% (2 years)
Luo et al. [57]	28 (26 years, 17–49)	CP1 = 28	Sib 13, UR 15/ PB 21, BM 7	RIC 28	81% (3 years)	67% (3 years)	15% (3 years)
Saussele et al. [42]	84 (37 years, 16–62)	CP1 = 56 Adv = 28	Sib 30, UR 54/ PB 64, BM 20	MAC 57, RIC 11, others 16	91% (3 years)	88% CMR	8% (3 years)
Copelan et al. [47]	335 (37 years, 18–58)	CP = 229 Adv = 106	Sib 335/ BM 335	MAC 335	71% (3 years)	69% (3 years)	14% (3 years)
Bacher et al. [32]	1,716 (40 years, 1–68)	CP1 = 1,084 Adv = 542	Rel 773, UR 932/ PB 1,069, BM 640	MAC 724, RIC 147, others 800	70% (5 years)	41% (5 years)	28% (5 years)

OS = Overall survival; EFS/DFS = event-/disease-free survival; TRM/NRM = transplant-related/non-relapse mortality; CP1 = first chronic phase; Adv = advanced (>CP1/>CP); Sib = sibling; Rel = related; UR = unrelated; PB = peripheral blood; BM = bone marrow; MAC = myeloablative conditioning; RIC = reduced-intensity conditioning; CMR = complete molecular remission.

¹ Figures in parentheses are median age and range. ² This study includes 2 Ph+ ALL patients.

between diagnosis and transplant (more or less than 12 months). This has eventually led to the Gratwohl score [36]. Moreover, some additional elements known to influence TRM (captured in an HSCT co-morbidity score) have been shown to be helpful [37, 38]. Additionally, novel prognostically relevant markers have been suggested. For instance, increased expression of the polycomb group gene *BMI-1* (the gene is essential for the maintenance of the stem cell pool and enhances self-renewal of human stem and progenitor cells) was shown to be associated with lower TRM in patients with CML [39]. Likewise, the possession of one (C1 or C2) KIR2DS5 (natural killer immunoglobulin-like receptor) ligand, as opposed to both, has been shown to be associated with improved leukemia-free survival after HSCT [40].

Indications for HSCT in CML

Allogeneic HSCT remains a confirmed curative approach for CML patients, but is associated with a significant TRM risk. Nevertheless, due to improvements of supportive care and HLA typing methods, the results of HSCT have been substantially improved over the time, especially for those patients with unrelated donors.

According to the updated guidelines of the European LeukemiaNet (ELN) [41], indications for HSCT in CML

are: at diagnosis for patients presenting in AP or BP after TKI pre-treatment, at imatinib failure for patients progressing to AP or BP (after second-generation TKI pre-treatment) or with the T315I mutation, or for all patients failing second-generation TKI treatment. These categories are clearly defined by hematological, cytogenetic and molecular criteria: failure of imatinib means failure to achieve complete hematological remission (CHR) at 3 months, or failure to achieve any cytogenetic response at 6 months. Also, persistence of $\geq 35\%$ Ph+ metaphases at 12 months, or less than complete cytogenetic response (CCR) at 18 months is defined as imatinib failure. Resistance is defined as loss of CHR or CCR; or development of highly resistant ABL kinase domain mutations during imatinib treatment [41].

Saussele et al. [42] published the results of an interim analysis of a large randomized study (German CML study IV) including 1,242 CML patients, which was very instructive regarding the current role of allogeneic HSCT. A total of 84 patients underwent allogeneic HSCT, 56 of them in CP (19 in early CP and 37 after imatinib failure). The 3-year overall survival (OS) probability of the patients in CP was 91%. Interestingly, in matched pair analysis, the 3-year disease OS of 53 patients who underwent transplantation was not different from that of 106 matched patients who did not (92 vs. 96%). Saussele et al. [42] concluded that allogeneic HSCT

might become the preferred second-line approach in case of imatinib failure for suitable patients in CP, with a donor. However, considering the relatively young age of the patients reported (median age of 36 years) this assertion deserves further investigation by additional randomized studies.

Advanced CML

According to the ELN recommendations, allogeneic HSCT is indicated for all patients in AP or BP as first- or second-line option. In both cases, it is recommended that HSCT should be preceded by TKIs; for first-line, high-dose imatinib (600 or 800 mg), and for second-line, second-generation TKIs (dasatinib or nilotinib) [41]. In the study from Saussele et al. [42], a total of 28 patients in advanced disease received allogeneic HSCT following pretransplant application of TKIs. Following HSCT, these patients experienced a 3-year OS of 59% (CI: 39–76%). Therefore, Saussele et al. [42] agreed with earlier suggestions that the best long-term survival results in blast phase are achieved by allogeneic HSCT and that most long-term survivors in blast phase have received an allogeneic HSCT, mostly in CP2.

Recent Results of HSCT in CML

From 1980 to 1990, more than 2,600 allogeneic HSCT were performed in CML patients in Europe. The probability of survival at 20 years after stem cell transplantation was about 40, 20 and 10% for patients in CP1, AP and BP, respectively [43, 44]. Subsequently, better supportive care, risk stratification strategies and better HLA typing methods allowed a reduction of TRM from 41 to 8% for all transplanted patients with CML. Nevertheless, the risks, especially for older patients, still remain high [42, 44].

Recent HSCT data showed the following results for patients with CML: EBMT data from 2000 to 2003 reported 2-year OS rates of 74% for sibling and 63% for unrelated allogeneic HSCT in patients in CP1 [44]. The CIBMTR documented survival rates of 79 and 72% at 1 and 2 years, respectively, for the transplant period 1999 to 2004 for patients in all phases of CML [45]. The German CML Study III documented 5-year survival rates of 72% in low-risk, 62% in intermediate-risk, and 49% in high-risk patients [46]. Recently published results of the German CML study IV showed remarkable improvements of al-

logeneic HSCT, with the 3-year OS of patients in first CP being higher than 90% in spite of the fact that the majority of these patients underwent transplantation with an EBMT score equal to or higher than 3 [42].

Myeloablative Conditioning

Copelan et al. [47] reported on myeloablative conditioning with busulfan/cyclophosphamide (BuCy) in 335 CML patients (CP, n = 229; >CP, n = 106) who underwent allogeneic HSCT from HLA-matched related donors from 1984 to 1995, with >14 years median follow-up. The estimated probability of 18-year leukemia-free survival was 56 and 11% for CP and >CP patients, respectively. Late relapses (p = 0.039) and late nonrelapse mortality (NRM, p = 0.008) occurred at higher rates in patients beyond CP at transplantation. Occasional relapses were seen as late as 18 years after HSCT [47].

In an attempt to minimize regimen-related toxicity while preserving antileukemic effects in myeloablative conditioning, Radich et al. [48] used an intravenous BuCy preparative regimen with busulfan dose targeted to achieve a steady-state plasma concentration of ≥ 900 ng/ml. This strategy was based on reports of lower relapse and better survival rates when serum levels of busulfan were ≥ 917 ng/l [49]. This approach resulted in an estimated 3-year OS and a disease-free survival (DFS) of 86 and 78%, respectively, and low relapse and NRM rates of 8 and 14%, respectively, were reported.

Reduced Intensity Conditioning

In view of the modified selection criteria for HSCT with the afore-mentioned shift to poor-risk patients and patients having experienced more intensive pretreatment, RIC was introduced in CML [50–52]. In the study by Kerbaux et al. [53], low-dose TBI (2 Gy) with or without fludarabine (90 mg/m²) was used in 24 CML patients in CP1/2 or AP who were ineligible for myeloablative conditioning (MAC). A 3-year OS rate of 54% was obtained. The 2-year survival estimates obtained for patients in CP1 and >CP1 were 70 and 56%, respectively, with an NRM of 21%. It thus appears that this RIC strategy is promising for such patients. Faber et al. [54] compared the results of RIC- and MAC-HSCT in 55 CML patients. Median OS was better in the RIC than the MAC cohort (26 vs. 9 months; p = 0.036) even though the relapse rate was significantly higher in the RIC patients (45 vs. 0%).

In one large EBMT study by Crawley et al. [20], outcomes of 186 patients with CML at a median age of 50 years predominantly in CP (63% of patients) and receiving RIC-HSCT, were analyzed. The regimen consisted of busulfan (cumulative, ≤ 8 mg/kg) and TBI (≤ 6 Gy). The 2-year NRM was 23%, while the 3-year OS and relapse-free survival were 58 and 37%, respectively. A complete molecular response (CMR) was achieved in 40% of patients, and CCR in 62% [20, 55]. Overall response rates were affected by the stages of disease, being >90 and 67% in CP and AP, respectively, but only 22% in BP. Also, the risk of relapse was $>65\%$ in patients in AP/BP, compared to 35% in those in CP1. Thus, advanced disease remains poorly controlled with current RIC regimens, while outcomes seem favorable for CP patients.

A combination of treosulfan (3×14 g/m²) and fludarabine (5×30 mg/m²) used by Holowiecki et al. [56] resulted in OS, DFS and NRM (at 2 years) of 85, 82 and 15%, respectively. Or et al. [51] explored the role of DLIs following RIC-HSCT (using fludarabine, low-dose busulfan and ATG) in 24 adult and pediatric patients in CP1. Six patients experienced mixed chimerism. Withdrawal of post-transplant immunosuppression with cyclosporin A resulted in molecular remission in 3 of the 6 patients. The remaining 3 patients received DLIs as post-transplant adoptive strategy and achieved complete donor chimerism [51].

Regarding the use of RIC-HSCT in younger patients, Luo et al. [57] reported on 28 CP1 CML patients (median age 26 years) who received busulfan (8 mg/kg per os or equivalent intravenously), fludarabine (150 mg/m²) and ATG (20 mg/kg). Twenty-five patients received grafts from HLA-matched, 3 patients from HLA-mismatched donors. Although all patients had received pre-transplant imatinib therapy (and were resistant to imatinib), the 3-year estimated OS and DFS were 81 and 67%, respectively. Following HSCT, 91% of patients achieved a molecular remission, but there was a high relapse rate of 32%. Early and cumulative 3-year TRM were 3.6 and 15.4%, respectively [57].

The Use of TKIs before Allogeneic HSCT

Tolerance of Pre-Transplant Imatinib

Several studies explored the application of pre-HSCT imatinib (at doses of 400–600 mg/day) in patients who were later referred to HSCT [14, 58]. In the study by Zaucha et al. [58], the median time of imatinib administration before HSCT was 8 months, but some patients re-

ceived imatinib pre-transplant for more than 2 years. Others confirmed that pre-transplant imatinib did not increase the toxicity of subsequent allogeneic HSCT [59, 60]. Neutrophil and thrombocyte engraftment were not affected. Thus, pre-transplant application of imatinib does not appear to increase the toxicity of subsequent conditioning and has no influence on engraftment.

Contrarily, discussions have developed around the suspected immunosuppressive effects of imatinib. Oehler et al. [60] evaluated outcomes for 145 patients (CP 50%, AP 41%, BP 9%) who received pre-transplant imatinib at a median dose of 500 mg and 231 patients (CP 79%, AP 17%, BP 4%) who did not. The authors found that the risk to develop extensive chronic graft-versus-host disease (cGvHD) post-transplant was significantly lower in patients who received imatinib compared with those who did not ($p < 0.001$), while that of acute GvHD (aGvHD) was similar [60]. Other investigators showed efficacy of the compound in the treatment of refractory cGvHD associated with fibrotic features [61, 62]. Imatinib has been shown to inhibit T cell proliferation and activation as well as T cell responses to herpes viruses [63]. Other reports indicate that imatinib may be immunosuppressive by inhibiting dendritic cell development and function, or T cell responses [64]. However, it is unclear how long these effects might persist after imatinib is stopped, and whether pre-transplant imatinib might have such prolonged effects in the post-transplant period.

Efficacy of Pre-Transplant Imatinib

A recent CIBMTR study by Lee et al. [45] in 1,309 CML patients (CP1, $n = 860$; $>CP$, $n = 449$) showed a trend for improved OS rates for patients in CP1 who received imatinib before HSCT. The OS estimates for patients in CP1 who received imatinib and those who did not were 79 vs. 74% at 1 year ($p = 0.08$) and 72 vs. 65% at 3 years ($p = 0.07$), respectively. In contrast, in patients with advanced CML, post-transplant survival did not differ significantly, whether patients received imatinib prior to HSCT or not: adjusted OS for imatinib and non-imatinib patients were both 48% at 1 year and 36 vs. 34% at 3 years, respectively [45]. Others found no difference in outcomes between the imatinib-treated and historical cohorts. For instance, Oehler et al. [60] reported a 3-year OS in CP and AP/CP2 patients of 74 and 54%, respectively, in the imatinib-treated patients, which was very similar to 78 and 48%, respectively, in the nonimatinib patients.

Combination Therapies before HSCT

The use of imatinib in combination with other medications or novel agents in the pre-transplant period is another interesting approach in patients with advanced disease. Fruehauf et al. [16] studied 16 patients with CML-BP who received a combination of mitoxantrone/etoposide and imatinib. This combination was tolerated and was claimed to result in a more effective reduction of the leukemia cell load and to improve the outcome after HSCT. CHR resulted from the combination of imatinib with mitoxantrone/etoposide in 81% of patients [16]. In the MD Anderson study, imatinib was combined with low-dose cytarabine and idarubicin in patients in BP. A second CP or CHR was achieved in 74% of the patients, and HSCT was then possible in 32% of cases [18]. Deenik et al. [65] assessed the efficacy and tolerance of escalated imatinib in combination with 2 cycles of intravenous cytarabine (200 mg/m² or 1 g/m² on days 1–7) in 162 CML patients, the majority of whom had low/intermediate Sokal or Euro risk scores. They observed the 5-year cumulative incidences of a complete cytogenetic, major molecular and complete molecular response in 89, 71 and 53% of patients, respectively. Importantly, a higher Sokal risk score was inversely associated with CCR (hazard ratio of 0.63; $p < 0.001$). A higher dose of imatinib and a higher dose of cytarabine were associated with increased complete molecular response. OS and progression-free survival at 5 years were 96 and 92%, respectively [65].

Management of Post-Transplant Relapse of CML

Minimal Residual Disease Monitoring in the Post-Transplant Period

Considering the increased risk of relapse in patients with advanced disease and, eventually, RIC-HSCT, measurement of the minimal residual disease (MRD) load has become particularly important following HSCT. Several authors [66–68] have demonstrated that the kinetics of *BCR-ABL1* expression levels in transplanted CML patients was prognostically relevant. Lange et al. [68] showed that slow reduction of the *BCR-ABL1* expression levels early after transplantation (days +28 and +56) was predictive for an increased relapse rate. A total of 19 CML patients were evaluated (CP1, $n = 9$; >CP1, $n = 5$; AP, $n = 4$; BP, $n = 1$) who underwent RIC-HSCT. Eleven had positive *BCR-ABL1* levels (<0.01%, $n = 4$; >0.01%, $n = 7$). Five patients (1 with *BCR-ABL1* expression of <0.01% and 4 with expression of >0.01%) experienced hematological relapse

within a median of 1 month (range 1–6 months) from the first positive *BCR-ABL1* expression level post-transplant. Asnafi et al. [66] evaluated the prognostic importance of the MRD levels in 38 CML patients (CP, $n = 34$, AP, $n = 4$). Patients who experienced increased *BCR-ABL1* expression levels ($\geq 10^{-4}$) experienced higher relapse rates when compared to those with MRD levels <10⁻⁴ on day 100 after HSCT (79 vs. 29%, $p = 0.009$).

TKI-based Post-Transplant Strategies

Before the introduction of TKIs, adoptive immunotherapy with DLIs was the most frequently used therapeutic strategy in CML patients with post-transplant relapse [69–72]. Following the introduction of TKIs, the role of DLI therapy needs to be reviewed. In a recent study, Carpenter et al. [23] performed prophylactic administration of imatinib after HSCT in Ph+ leukemias. In that study, 22 patients with *BCR-ABL1*-positive ALL and 7 with high-risk CML were recruited and given imatinib from the time of engraftment until 1 year after HSCT. They observed a 2-year relapse rate of 18%. The authors concluded that the use of post-transplant imatinib with DLIs might prevent relapse through synergistic immunological effects.

Olavarria et al. [73] reported on the outcomes for 22 CML patients in CP, in whom imatinib 300 mg daily was given from day +35 up to 12 months from RIC-HSCT. Twenty-one patients completed 11 months of imatinib, all remaining in remission. After the discontinuation of imatinib, 15 patients (71%) experienced molecular relapse at a median of 17 months (range 13–29 months) post-transplant and were treated with DLIs. With a median follow-up of 36 months (range 12–64 months), 19 patients were alive (OS 87%). Fifteen (68%) have achieved molecular remission. Thus, post-transplant imatinib can be used to manipulate the kinetics of CML relapse after RIC-HSCT and reduce the risk of early relapse [73].

In the study by DeAngelo et al. [24], 15 CML patients in CP ($n = 10$) or advanced phases ($n = 5$) with post-transplant relapse were treated with imatinib (400 – 600 mg daily). At 6 months from the beginning of the treatment of the patients in CP relapse, CMR ($n = 7$) or at least CCR ($n = 2$) were achieved in 9 of the 10 CP patients, but only one of the 5 patients in advanced phase achieved CCR. Imatinib was well tolerated in all patients. Responses in patients relapsed in CP were rapid, durable and associated with conversion to full donor chimerism without GvHD [24].

Kantarjian et al. [25] reported an overall response rate of 79% in 28 adults with CML (CP, n = 5; AP, n = 15; and BP, n = 8) who received imatinib (400–1,000 mg daily) due to post-transplant relapse. Nineteen of the patients (68%) were alive after a median follow-up of 15 months, 9 in CCR. Therefore, imatinib seemed to effectively control CML recurring after HSCT.

Recently, Wright et al. [74] reviewed 22 patients (8 in CP and 14 advanced) treated for post-HSCT CML relapse with TKIs (imatinib, n = 20, and/or dasatinib, n = 6). They observed that 14 patients (64%) achieved CMR, 8 of whom had advanced disease. The authors concluded that TKI therapy is capable of inducing durable molecular responses for CML relapsing after HSCT, both in chronic and advanced phases.

Although few studies still have examined the role of second-generation TKIs (dasatinib or nilotinib) in the management of CML relapse post-transplant, current guidelines recommend escalating the dose of imatinib or switching to new TKIs in CML patients with relapse or resistance [75]. Data on the use of second generation TKIs in the post-transplant period [26] are still limited.

Conclusion

Due to the new selection criteria for allogeneic HSCT in patients with CML, more patients with co-morbidities and at later phases of disease are being transplanted, resulting in a higher risk of post-transplant relapse [11, 13, 12] and a higher risk for TRM during allogeneic HSCT. Therefore, novel strategies have to be developed for patients with CML undergoing HSCT. Diverse studies dem-

onstrated that pre-transplant therapy with imatinib has no negative effects on subsequent transplantation [14, 45, 58, 59]. Second-generation TKIs such as dasatinib or nilotinib have also successfully been used in advanced phases of CML before HSCT [8]. Other promising modification strategies for patients in advanced disease include the addition of imatinib to diverse combination chemotherapy regimens, for example mitoxantrone/etoposide pre-transplant [16], or combinations with low-dose cytarabine and idarubicin in patients with blast phase [18]. Additionally, various RIC regimens are being tried, for instance based on low-dose TBI with or without fludarabine [53, 76]. With these protocols, patients in CP who are not eligible for MAC-HSCT seem to have acceptable outcomes, while those in advanced disease seem to do less well. The use of DLI in the post-transplant period after RIC-HSCT might need to be further investigated [51].

In patients with post-transplant relapse, imatinib can as well be successfully used with acceptable tolerance [23]. However, it should be noted that many patients undergoing allogeneic HSCT have a history of imatinib resistance. Therefore, studies on larger cohorts regarding the use of second-generation TKIs in the post-transplant period are needed [26]. However, despite these combined approaches to improve pre- and post-transplant therapy, and to develop less toxic conditioning regimens, prognosis of patients in advanced CML remains guarded. Therefore, despite the low numbers of patients with CML undergoing allogeneic HSCT nowadays, efforts should continue to develop new transplant strategies aiming at improving the safety and the chance of cure for these patients with CML.

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