Review Article

Use of Tyrosine Kinase Inhibitors to Prevent Relapse After Allogeneic Hematopoietic Stem Cell Transplantation for Patients With Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia: A Position Statement of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

Sebastian Giebel, MD[1]; Anna Czyz, MD, PhD[2]; Oliver Ottmann, MD[3]; Frederic Baron, MD[4]; Eolia Brissot, MD, PhD[5]; Fabio Ciceri, MD[6]; Jan J. Cornelissen, MD[7]; Jordi Esteve, MD[8]; Norbert-Claude Gorin, MD[5]; Bipin Savani, MD[9]; Christoph Schmid, MD[10]; Mohamad Mohty, MD[5]; and Arnon Nagler, MD[11,12]

Allogeneic hematopoietic stem cell transplantation (alloHSCT) is a standard of care for patients with Philadelphia chromosome (Ph)–positive acute lymphoblastic leukemia (ALL). The introduction of tyrosine kinase inhibitors (TKIs) to first-line therapy has improved overall outcomes; however, a significant proportion of patients still relapse after alloHSCT. Posttransplant TKI maintenance was demonstrated to reduce the risk of relapse in a large retrospective study and, therefore, should be considered a valuable option. This consensus paper, written on behalf of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation, presents an overview of clinical studies on the use of TKIs after alloHSCT and proposes practical recommendations regarding the choice of TKI, treatment timing, and dosage. It is hoped that these recommendations will become the state of art in this field and, more importantly, lead to a reduction of Ph-positive ALL relapse after alloHSCT. ***Cancer* 2016;000:000–000**. © *2016 American Cancer Society*.

KEYWORDS: allogeneic hematopoietic stem cell transplantation, dasatinib, imatinib, maintenance therapy, nilotinib, Philadelphia chromosome–positive acute lymphoblastic leukemia, recommendations, tyrosine kinase inhibitors.

INTRODUCTION

The presence of the Philadelphia chromosome (Ph) in acute lymphoblastic leukemia (ALL) has been recognized as a quite adverse independent prognostic factor for more than 30 years.[1] This chromosomal abnormality is one of the most common in adult patients with ALL, and the rate increases with age. Translocation (9;22) or the *BCR-ABL* fusion gene is detected in approximately 5% to 15% of adolescents, in 25% to 30% of patients aged 25 to 35 years, and in more than 35% to 40% of patients older than 35 years.[2,3] Historically, treatment results for Ph-positive ALL were very poor, and a patient's prognosis was dismal.[4,5] Although complete remission (CR) was obtained in 60% to 90% of patients after first-line therapy, the relapse rate was very high, and the probability of long-term survival did not exceed 10% in patients treated with standard chemotherapy and 30% to 35% in those undergoing allogeneic hematopoietic stem cell transplantation (alloHSCT).[4,5] Furthermore, a significant proportion of patients could not proceed to alloHSCT because of early relapse.

Corresponding author: Sebastian Giebel, Department of Bone Marrow Transplantation and Onco-Hematology, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, 44-101 Gliwice, Str. Wybrzeze Armii Krajowej 15, Poland; Fax: (011) 48-32-278-9149; sgiebel@io.gliwice.pl

[1]Department of Bone Marrow Transplantation and Onco-Hematology, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland; [2]Department of Hematology and Bone Marrow Transplantation, Poznan University of Medical Sciences, Poznan, Poland; [3]Institute of Cancer and Genetics, Cardiff University School of Medicine, Cardiff, United Kingdom; [4]Department of Hematology, Centre Hospitalier Universitaire Sart-Tilman, University of Liege, Belgium, France; [5]Clinical Hematology and Cellular Therapy Department, Hospital Saint-Antoine, Assistance Publique–Hôpitaux de Paris, Paris, France; [6]Hematology and Bone Marrow Transplantation (BMT) Unit, San Raffaele Scientific Institute, Milan, Italy; [7]Department of Hematology, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, the Netherlands; [8]Hematology Department, August Pi i Sunyer Institute for Biomedical Research, Hospital Clinic, Barcelona, Spain; [9]Department of Hematology and Transplantation, Vanderbilt University, Nashville, Tennessee; [10]Department of Hematology and Oncology, Klinikum Augsburg, Ludwig-Maximilians-Universitaet, Munich, Augsburg, Germany; [11]Division of Hematology and Bone Marrow Transplantation, Chaim Sheba Medical Center, Tel-Hashomer, Israel; [12]European Society for Blood and Marrow Transplantation Acute Leukemia Working Party Office, Hospital Saint-Antoine, Paris, France

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The introduction of the *BCR-ABL*–directed tyrosine kinase inhibitors (TKIs) to the front-line therapy for Ph-positive ALL has improved CR rates, the quality of responses, and the duration of remission.[6,7] The combination of imatinib or second-generation TKIs (eg, dasatinib and nilotinib) with either corticosteroids or multi-agent chemotherapy results in 90% to 100% CR rates along with deep molecular response rates of 38% to 72%.[8-12] However, without alloHSCT, most patients ultimately relapse, so transplantation from either related or unrelated donors remains a standard of care and should be considered for all eligible patients.[12] Moreover, with upfront use of TKIs, up to 77% of transplant-eligible patients are able to proceed to alloHSCT during their first complete remission (CR1).[8] Treatment strategies that are based on TKIs combined with chemotherapy or corticosteroids for front-line treatment followed by alloHSCT during CR1 facilitate long-term survival in 30% to 65% of patients.[10-12] According to retrospective analyses, the results of alloHSCT with myeloablative and reduced-intensity conditioning for Ph-positive ALL are comparable in terms of overall survival (OS).[13,14] The availability of TKIs also enables bridging a Ph-positive ALL patient without a related donor or with a major infection to alloHSCT and allows sufficient time for the allocation of an unrelated donor or recovery from an invasive fungal infection, respectively.[15,16]

Although the use of TKIs is associated with better disease control before transplantation, relapses after alloHSCT remain a major reason for treatment failure. Relapse rates are particularly high among patients in whom *BCR-ABL* transcripts are detectable after alloHSCT.[17] Strategies to reduce the incidence of relapse include posttransplant maintenance with the use of TKIs.[10,18-21] Their role, however, remains a subject of uncertainty because of the paucity of prospective studies and the conflicting results of retrospective analyses. Furthermore, there are no commonly accepted standards with respect to the choice of TKI, dosage, time of initiation, treatment duration, or potential of a combination with donor lymphocyte infusions (DLIs).

In this article, we summarize the clinical experience with the use of TKIs after alloHSCT and present the position statement elaborated by the experts of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT).

OVERVIEW OF STUDIES ON TKI MAINTENANCE AFTER ALLOHSCT

Retrospective Studies

Several retrospective, comparative analyses were performed with the aim of evaluating the impact of the use of TKIs after alloHSCT on outcomes. Most of them included rather small groups of patients.

Nishiwaki et al[22] performed a multicenter study that included 34 patients; 7 of these patients were treated with imatinib after alloHSCT either prophylactically or preemptively (ie, in the case of a positive minimal residual disease [MRD] status).[22] The posttransplant use of imatinib was associated with a significantly improved probability of OS (67% vs 30% at 2 years; $P = .03$). The probabilities of leukemia-free survival (LFS) were 56% and 30%, respectively ($P = .29$).

In the study by Kebriaei et al,[23] which involved 102 adults and 11 children with Ph-positive ALL who were treated with alloHSCT during CR1 (n = 71), the second complete remission (CR2; n = 11), or active disease (n = 31), 32 individuals received TKI maintenance with either imatinib (n = 31) or dasatinib (n = 1) for a median of 10.6 months. AlloHSCT procedures included transplants from sibling and unrelated donors and the use of cord blood as a source of stem cells. Seven patients stopped TKIs because of disease recurrence, whereas 8 patients stopped because of excess toxicity (fluid retention, n = 2; nausea, n = 2; and cytopenia, n = 4). In a univariate analysis, the use of a TKI after transplantation was not associated with a better outcome, although in a subgroup of patients treated during CR1, there was a tendency toward improved OS (hazard ratio [HR], 0.4; 95% confidence interval [CI], 0.1-1.3; $P = .1$). On the other hand, among patients with detectable MRD before alloHSCT, the rate of progression was 31%, regardless of the posttransplant use of TKIs.

The largest analysis, including 473 alloHSCT recipients, has been recently published on behalf of the EBMT Acute Leukemia Working Party.[13] One hundred fifty-seven adult patients received TKIs, most frequently imatinib (n = 124) and dasatinib (n = 26), for primary prophylaxis against relapse. The study population was restricted to patients in CR1 who had been treated with alloHSCT involving either a matched sibling or an unrelated donor. The posttransplant use of TKIs was included in a multivariate analysis as a time-dependent covariate. It was associated with improved OS (HR, 0.44; 95% CI, 0.26-0.74; $P = .002$) and LFS (HR, 0.42; 95% CI, 0.23-0.76; $P = .004$) as well as a reduced risk of relapse (HR, 0.4; 95% CI, 0.21-0.76; $P = .01$) and a tendency toward a reduced risk of nonrelapse mortality (HR, 0.46; 95% CI, 0.2-1.1; $P = .01$). Furthermore, TKI maintenance was significantly associated with a lower cumulative incidence of grade 2 to 4 acute graft-versus-host disease (GVHD; HR, 0.21; 95% CI, 0.05-0.85; $P = .03$).

TABLE 1. Prospective Studies of the Use of TKIs After Allogeneic Hematopoietic Stem Cell Transplantation

Study	Type of TKI	Strategy	No.[a]	Median Treatment Duration, mo	Treatment Stop Due to Adverse Events	Relapse Rate	LFS	OS
Single-arm								
Wassmann 2005[17]	Imatinib	Preemptive	27 (including 2 autoHSCTs)	Not reported	Not reported	55% (8 mo)	Not reported	Not reported
Carpenter 2007[18]	Imatinib	Prophylactic	22 (ALL +CML)	11 (ALL)	9% (ALL + CML)	13% (ALL)	Not reported	80% (1.3 y, ALL)
Ribera 2010[10]	Imatinib	Prophylactic	13 (including 4 autoHSCTs)	9	20%	33%	Not reported	Not reported
Chen 2012[19]	Imatinib	Prophylactic	62	3	16%	10% (5 y)	82% (5 y)	87% (5 y)
Shimoni 2015[21]	Nilotinib	Prophylactic	16 (ALL + CML)	6 (ALL + CML)	37.5% (ALL + CML)	Not reported	Not reported	Not reported
Randomized								
Pfeifer 2013[20]	Imatinib	Prophylactic	26	7	67%[b]	8% (30 mo)	69% (5 y, all patients)	77% (5 y, all patients)
		Preemptive	29	4	71%[b]	17% (32 mo)		

Abbreviations: ALL, acute lymphoblastic leukemia; autoHSCT, autologous hematopoietic stem cell transplantation; CML, chronic myeloid leukemia; LFS, leukemia-free survival; OS, overall survival; TKI, tyrosine kinase inhibitor.
[a] For single-arm studies, only patients effectively treated with TKIs were considered.
[b] Treatment discontinuation for any reason.

Although the study had some important limitations associated with its retrospective nature, including a lack of data on the dose and timing of TKIs as well as the MRD status, the analyzed population was relatively homogeneous. Therefore, the obtained results provide a strong rationale for the use of TKIs as maintenance after alloHSCT for patients with Ph-positive ALL in CR1.

Prospective Studies

The use of TKIs after alloHSCT was a subject of 6 prospective studies, including 1 randomized trial (Table 1). Five trials examined imatinib and 1 study examined nilotinib as posttransplant TKIs. Two single-arm studies recruited recipients of both alloHSCT and autologous hematopoietic stem cell transplantation (autoHSCT). Two studies included mixed populations of patients with ALL and chronic myeloid leukemia (CML).

In the study by Wassmann et al,[17] imatinib was administered at an initial dose of 400 mg/d to patients with detectable MRD after either alloHSCT (n = 25) or autoHSCT (n = 2). Notably, 22% of the patients were beyond CR1 at the time of hematopoietic stem cell transplantation (HSCT). In 14 patients (52%), the BCR-ABL transcript became undetectable after a median of 1.5 months. None of the 5 patients who had received transplants during their first or second relapse or had refractory disease achieved molecular CR, whereas 13 of 21 patients (62%) who underwent transplantation during CR1 did. Patients achieving molecular remission remained relapse-free during imatinib administration. Three of them relapsed after the treatment discontinuation. Among the patients who failed to achieve MRD negativity, the relapse rate was 92%. The LFS rate at 1 year was 91% for patients with early MRD negativity and 9% for those who remained MRD-positive. The authors concluded that continued detection of BCR-ABL transcripts after 2 to 3 months on imatinib identifies patients who will ultimately experience relapse and for whom additional or alternative antileukemic treatment should be initiated.

Carpenter et al[18] administered imatinib after alloHSCT prophylactically, regardless of the MRD status. The study population included 22 patients, 11 with ALL and 11 with CML. Among patients with Ph-positive ALL, with a median follow-up of 1.3 years, the relapse rate was 9%, whereas the probability of OS was 80%. The posttransplant use of imatinib was found to be feasible.

The Spanish group Programa Español de Tratamientos en Hematología (PETHEMA) conducted a study on newly diagnosed Ph-positive ALL. Among the 30 patients, 21 proceeded to either alloHSCT or autoHSCT.[10] Finally, 8 alloHSCT recipients and 4 autoHSCT recipients were treated with imatinib maintenance. The reasons for not initiating imatinib treatment were mainly transplant-related complications. Furthermore, treatment interruptions were reported in 10 cases, although only in 2 patients were they associated with drug-related toxicities (cytopenia and gastrointestinal complications). The long-term outcomes of patients treated with posttransplant imatinib were not reported.

In a Chinese study including both adults and children, imatinib maintenance was scheduled for 3 to 12 months after alloHSCT until MRD negativity was

confirmed by 3 consecutive tests or was sustained for at least 3 months.[19] The initial dose for adults was 400 mg/d. Imatinib was administered to 62 of 82 enrolled patients. Reasons for not starting TKI maintenance were pancytopenia, infections, gut GVHD, and personal decisions. Imatinib therapy was initiated at a median time of 70 days after alloHSCT, and the median treatment duration was 90 days. Although 71% of the patients experienced possible drug-related complications, they were the cause of treatment termination (cytopenias, edema, and nausea/emesis) in only 10 cases (16%). The probabilities of relapse, LFS, and OS at 5 years for patients receiving imatinib maintenance were 10%, 81.5%, and 87%, respectively. The results of the study confirmed the feasibility and suggested high efficacy of imatinib prophylaxis after alloHSCT.

The only randomized trial referring to the posttransplant use of imatinib was performed by a German group German multicenter study group for adult acute lymphoblastic leukemia (GMALL).[20] Their aim was to compare 2 strategies: prophylactic and MRD-triggered therapy. In the prophylactic treatment arm (n = 26), all patients who underwent engraftment, had no uncontrolled GVHD or infections, and had adequate organ function were intended to receive imatinib. In the preemptive treatment arm (n = 29), the drug was initiated only after the detection of MRD by quantitative real-time polymerase chain reaction (PCR); this was confirmed by nested PCR. The target dose of imatinib was 600 mg/d. The median times to treatment initiation were 48 and 70 days after alloHSCT, respectively, and the median treatment durations were 201 and 127 days, respectively. Notably, a majority of patients (67% and 71%) in both groups discontinued treatment prematurely. Moreover, only 22% received the intended imatinib dose (600 mg/d), whereas the majority received 400 mg/d. Although there was a tendency toward a longer duration of molecular remission in the prophylactic treatment arm, the probabilities of LFS and event-free survival did not differ significantly, and the OS rates were essentially superimposable (80% vs 75% at 5 years; $P = .84$). The authors concluded that despite unexpectedly low compliance, the use of either prophylactic or preemptive treatment with imatinib is associated with a low risk of hematologic relapse and contributes to excellent long-term outcomes. It was hypothesized that even short-term treatment may be sufficient to prevent hematologic relapse. The results of the GMALL study appear superior to those of other prospective trials conducted in the era of TKIs without posttransplant maintenance. In a recently published study by a French group,[12] the reported LFS rates after alloHSCT with human leukocyte antigen–identical siblings and unrelated donors were 42% and 57%, respectively, at 5 years.

The only prospective study of the use of the second-generation TKI nilotinib was performed by Shimoni et al.[21] Among 22 alloHSCT recipients with CML (n = 15) or Ph-positive ALL (n = 7), nilotinib maintenance was introduced for 16 individuals. The treatment was initiated at a median of 38 days after alloHSCT. The maximum tolerated dose was 200 mg every 12 hours, although there was an intention to escalate the dose to 400 mg every 12 hours. Ten episodes of grade 3 or 4 adverse events were reported (liver toxicities, elevated lipase/amylase levels, neutropenia, allergy, skin reaction, and stroke), and they led to treatment discontinuation in 6 cases. Eleven patients achieved or maintained molecular remission, and only 1 of these patients relapsed. Outcomes specific for patients with Ph-positive ALL were not reported.

CHOICE OF TKI FOR POSTTRANSPLANT MAINTENANCE

Almost all prospective and retrospective studies of posttransplant TKI maintenance have examined the use of imatinib and indicated its efficacy in preventing relapse and eradicating Ph-positive leukemic cells. Its safety profile has been relatively well defined. Treatment with nilotinib has been tested in a single prospective phase 1/2 trial,[21] whereas therapy with dasatinib has been the subject of case reports and small retrospective cohorts, the largest including 8 alloHSCT recipients.[24-28] Reports on dasatinib indicate the possibility of eradicating MRD after imatinib failure along with acceptable tolerance of the treatment. It should be mentioned, however, that 1 case series report showed a high incidence of extramedullary relapse, which was detected in 3 of 6 patients on posttransplant dasatinib therapy.[28] The use of third-generation TKIs such as ponatinib as maintenance after alloHSCT has not been reported so far. Altogether, on the basis of available data, imatinib should be considered the first-choice TKI for posttransplant maintenance. However, there are several clinical scenarios in which an alternative TKI may be considered from the outset after alloHSCT. Similarly, the reappearance or persistence of BCR-ABL transcripts during imatinib treatment or its poor tolerability may mandate a change in TKI.

The results of the randomized GMALL study of imatinib given prophylactically or as MRD-triggered therapy demonstrated a high probability of maintaining hematologic remission in the whole study group.[20]

However, a detailed analysis revealed that the early reappearance of the BCR-ABL transcript (ie, within the 3 months after alloHSCT) and/or its reappearance at a high level ($>10^{-4}$) was associated with a high risk of relapse and a low probability of LFS despite imatinib administration. The authors suggested that these adverse factors could allow the identification of a population of patients for whom second-generation TKIs may be beneficial.

Another group of patients who should be considered for the use of second-generation TKIs in posttransplant maintenance therapy are those who have experienced resistance to pretransplant treatment with imatinib. Soverini et al[29] demonstrated that approximately 70% of patients with resistance to imatinib are characterized by point mutations within the ABL kinase domain, with T315I, E255K, and Y253H being the most common ones. Moreover, there are data indicating that Ph-positive ALL patients with detectable BCR-ABL transcripts and kinase domain mutations before alloHSCT relapse after transplantation with the same mutation. Egan et al[30] analyzed ABL kinase domain mutations in patients with CML and Ph-positive ALL who had detectable BCR-ABL transcripts before alloHSCT. Pretransplant ABL kinase domain mutations were found in 14 patients, including 4 patients with Ph-positive ALL. Seven of those patients had relapsed or continued to have refractory disease after alloHSCT. These data suggest that the choice of TKI for posttransplant maintenance therapy in patients with resistance to imatinib or with detectable BCR-ABL transcripts before transplantation should be based on a mutation analysis taking into consideration resistance profiles of TKIs. Unfortunately, an analysis of the mutation status for patients with low levels of MRD is difficult because of the limited sensitivity of the methods. The most commonly used bidirectional Sanger sequencing of the entire BCR-ABL1 tyrosine kinase domain amplified by PCR does not reveal the presence of mutant subclones representing less than 10% to 20% of the Ph-positive cell pool.[31] Other techniques such as long-range, next-generation sequencing are more sensitive; however, so far they are not widely available.[32]

Prior leukemic involvement of the central nervous system (CNS) is another specific clinical situation that should be taken into consideration when a TKI is being chosen. Imatinib poorly penetrates the CNS and does not reach adequate concentration for kinase inhibition.[33] Moreover, isolated CNS relapse occurs in up to 20% of patients with Ph-positive ALL during imatinib monotherapy.[34,35] In contrast, dasatinib penetration into the CNS was demonstrated in a cerebrospinal fluid pharmacokinetic study performed by Porkka et al.[36] Its clinical activity in the CNS has been documented in several case reports.[37-39] On the basis of these data, dasatinib maintenance therapy after alloHSCT should be considered a rational strategy for patients with a history of CNS involvement.

The tolerability of TKIs after alloHSCT is another important issue that may affect the choice of drug. Imatinib therapy in the early period after alloHSCT is associated with a high incidence of gastrointestinal intolerance and hematological side effects leading to dose reductions or the withholding of therapy.[10,18,20] During dasatinib maintenance therapy, grade 2 hematologic toxicity, diarrhea, and pleural effusion requiring dose reductions were reported.[25] Nilotinib given at the standard dose was not well tolerated because of gastrointestinal and liver side effects; however, grade 2 to 4 hematologic toxicities were infrequent.[21] In conclusion, the available data are insufficient to determine which TKI is better tolerated in the early period after alloHSCT. The decision has to be made individually and be guided by comorbidities and posttransplant complications.

TKI TIMING AND DOSAGE AFTER ALLOHSCT

According to the GMALL study, prophylactic use and preemptive use of imatinib are equally effective in preventing relapse after alloHSCT.[20] A preemptive strategy should be applied only if adequate monitoring of BCR-ABL transcripts is available with the use of real-time quantitative PCR (confirmed by nested PCR).[40] The first evaluation should be performed after engraftment, preferably within the month after alloHSCT. In the GMALL study, 22% of the patients were already PCR-positive within the 3 months after stem cell transplantation (median, 34 days; range, 23-81 days), and the median time to the first detection of BCR-ABL1 transcripts among all patients who became MRD-positive was 4.1 months (range, 0.9-26.5 months).[20] Therefore, a high monitoring frequency, as in this study, with a bone marrow evaluation every 6 weeks and an assessment in peripheral blood every 3 weeks appears prudent.

With a preemptive strategy, a significant proportion of patients may avoid potentially toxic treatment with TKIs. Patients who cannot be rigorously monitored for the MRD status should be treated prophylactically. According to the design of prospective studies, treatment should be started as soon as possible after engraftment in the absence of uncontrolled GVHD or infections.

The optimal treatment duration has not been defined so far. According to the study by Chen et al,[19] the treatment should be continued until MRD negativity is confirmed by 3 consecutive tests or sustained for at least 3 months. Relapses occurring relatively late after imatinib discontinuation were observed in the study by Wassmann et al,[17] and this suggests that too early discontinuation of TKIs may carry risks for some patients and should be balanced against tolerability. In the GMALL study, imatinib administration was scheduled for 1 year of continuous PCR negativity, with a single positive result resetting the treatment period.[20] In view of the poor compliance in this study with respect to prolonged treatment, the potential advantages of better disease control may in clinical practice be offset by drug-related toxicities. At present, there is no conclusive evidence showing that these considerations do not apply to second-generation TKIs.

In terms of treatment efficacy, the optimal dose of imatinib for patients with Ph-positive ALL is 600 mg/d; however, the vast majority of patients do not tolerate it after alloHSCT. It appears reasonable to start with the dose of 400 mg/d and to try to increase it in cases of good tolerance. On the other hand, the risk of the occurrence of severe adverse events is high, and even 400 mg/d may be intolerable. Therefore, decisions on the dose of imatinib should be made individually.

According to the results of the prospective study, the maximum tolerated dose of nilotinib is 200 mg every 12 hours.[21] Results of retrospective case series studies suggest that the appropriate dose of dasatinib after alloHSCT is 100 mg/d, although in the cohort reported by Caocci et al,[25] in 5 of 8 patients, the dose was reduced to 50 mg/d.[28]

SUMMARY OF THE POSITION STATEMENT

There is a lack of grade 1 evidence for the use of posttransplant TKIs, and all the subsequent recommendations are based on a consensus of experts:

1. All patients with Ph-positive ALL are candidates for the posttransplant use of TKIs to reduce the risk of relapse.
2. Patients should be evaluated for the presence of BCR-ABL transcripts and for whether they are positive for the presence of ABL kinase domain mutations before alloHSCT and after engraftment (Fig. 1).
3. MRD monitoring should start 4 weeks after alloHSCT. During the first year of treatment, the analysis should be continued every 6 to 8 weeks in bone marrow and every 3 to 4 weeks in peripheral blood. The detection of MRD should prompt rapid confirmatory testing.
4. Patients with undetectable MRD after alloHSCT may be treated prophylactically or, alternatively, may be monitored and administered a TKI only after the detection of MRD (preemptive strategy).
5. Patients with detectable MRD after alloHSCT should be started on TKI treatment as soon as possible.
6. Imatinib at an initial dose of 400 mg/d is the first-choice TKI. Patients with early molecular recurrence (ie, within the 3 months after HSCT) or BCR-ABL transcripts at a level higher than 10^4 at any time after HSCT appear to derive little benefit from intervention with imatinib and should be started on a second-generation TKI instead (nilotinib at 200 mg every 12 hours or dasatinib at 50-100 mg/d). It should be recognized that nilotinib is not licensed for use in patients with Ph-positive ALL. Second-generation TKIs should be used in cases of resistance to imatinib or if ABL kinase domain mutations are present either before alloHSCT or after alloHSCT. In addition, switching to a second-generation TKI is recommended if BCR-ABL transcript levels remain detectable after 6 to 8 weeks of posttransplant imatinib.
7. Patients with a history of CNS involvement should be treated with dasatinib.
8. For patients undergoing transplantation during CR1, TKI treatment should be given for 12 months of continuous MRD negativity. For patients undergoing HSCT during CR2 or a later remission, treatment should be given indefinitely unless this is precluded by poor tolerability or safety concerns. Individual adjustments may be needed in cases of severe toxicity.
9. Both hematologic and nonhematologic adverse events should be monitored periodically according to the TKI toxicity profile (Table 2).

FUTURE DIRECTIONS

The issue of TKI treatment after alloHSCT remains a relatively poorly explored area of investigation with many open questions requiring further research. Both prospective and retrospective studies included mostly patients undergoing allografting during CR1 and receiving myeloablative alloHSCT. It is plausible but as yet untested that the optimal posttransplant choice of TKI and treatment schedule should differ according to the intensity of the preparative regimens. As demonstrated by Bachanova et al,[13] the risk of relapse is higher after reduced-intensity conditioning versus myeloablative conditioning,

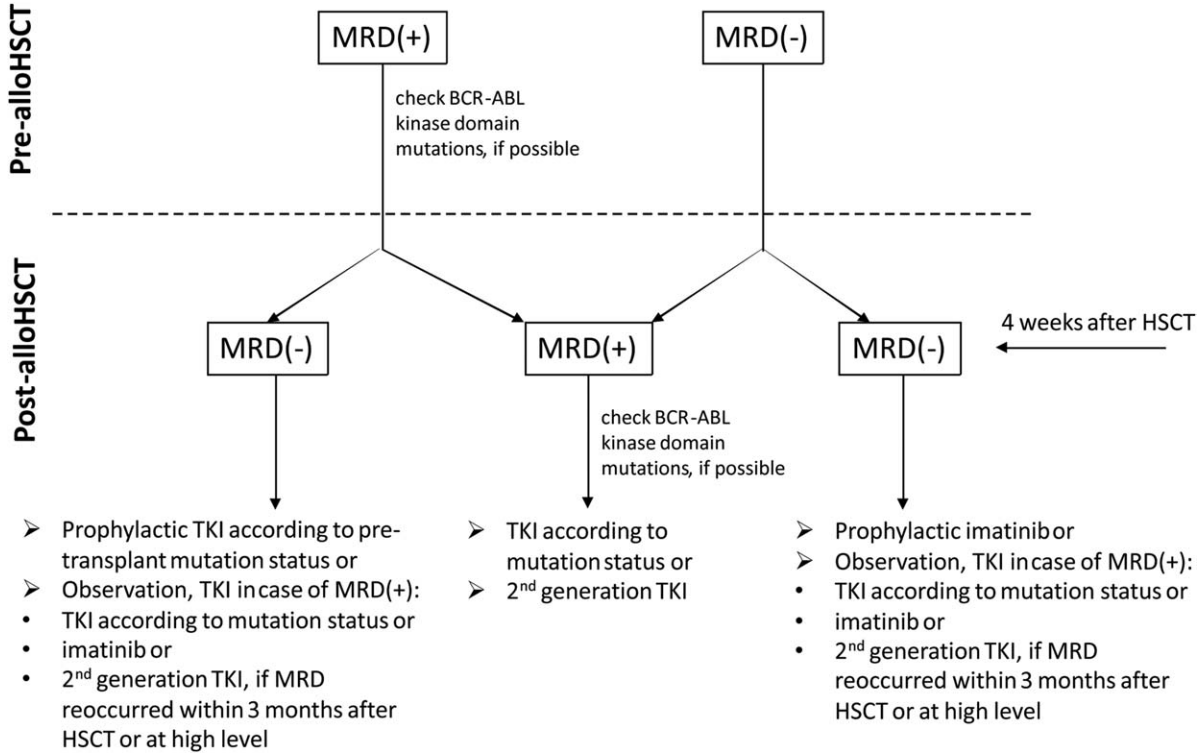

Figure 1. Recommendations for the use of TKIs according to the pre- and posttransplant MRD status. The MRD status should be checked before alloHSCT and monitored after transplantation; the posttransplant monitoring should start early after engraftment. In the case of MRD positivity, as defined by detectable BCR-ABL transcripts, the status of BCR-ABL domain mutations should be checked if possible. Imatinib is the first-choice TKI for posttransplant maintenance. Second- or third-generation TKIs should be used in case of kinase domain mutations conferring resistance to imatinib. Second-generation TKIs should also be considered if there is early reoccurrence of MRD (within 3 months) or if BCR-ABL transcripts are detected at a level higher than 10^4. Detailed recommendations are described in the text. AlloHSCT indicates allogeneic hematopoietic stem cell transplantation; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease; TKI, tyrosine kinase inhibitor.

especially if the MRD status is positive before alloHSCT. In such a situation, a significant proportion of relapses occur later than 1 year after transplantation, and this suggests the need to administer a more potent TKI for more prolonged TKI maintenance. For patients on a TKI in whom BCR-ABL1 transcripts remain detectable, a DLI could be an additional intervention to reduce the risk of relapse. Although a synergistic effect of DLIs and imatinib treatment has been reported in a setting of CML, such data for Ph-positive ALL are not yet available.[41] In view of the delayed onset of clinical activity and the uncertain efficacy of DLIs, switching to a more potent TKI should be the preferred option even when DLIs are being considered. The third-generation TKI ponatinib has been used in the posttransplant setting in the 2 initial phase 1 and 2 studies and a recent case report by Hirschbuehl et al.[42-44] Although only a minority of these patients had Ph-positive ALL, the studies demonstrated the feasibility and efficacy of ponatinib in the posttransplant setting but also indicated the need to be cognizant of adverse events. Additional novel options attractive for clinical trials because of their favorable risk-benefit ratio in the setting of relapsed B-cell precursor ALL include monoclonal antibodies such as inotuzumab ozogamicin and the bispecific T-cell engager antibody blinatumomab, although data on Ph-positive ALL are limited, and only a few of these patients have been treated in the setting of MRD.[45,46]

Rigorous monitoring of MRD allows the identification of the patients who will benefit most from TKI treatment after alloHSCT. However, the sensitivity of the methods used for MRD detection varies, and in contrast to p210 in the case of CML, the quantification of p190, typical for ALL, by real-time quantitative PCR is still insufficiently standardized. A new approach based on microfluidic digital PCR with TaqMan chemistry and allowing the detection of rare copies of BCR-ABL1 in Ph-positive ALL has been proposed.[47] Its application might allow more accurate discrimination between patients in need and those not requiring TKI maintenance.

TABLE 2. Monitoring of Hematologic and Nonhematologic Adverse Events During TKI Maintenance Therapy After Allogeneic Haematopoietic Stem Cell Transplantation

TKI	TKI-Associated Hematologic Adverse Events	Monitoring
All TKIs	Cytopenias	Routine, frequent complete blood counts: • Every 2–4 wk during initial treatment • Every 6–8 wk thereafter

TKI	TKI-Associated Nonhematologic Adverse Events	Monitoring
Imatinib	Abdominal pain, nausea, diarrhea, edema, muscle cramps, musculoskeletal pain, rash, fatigue, and headache	Physical examination: • Every 2–4 wk during initial treatment • Every 6–8 wk thereafter
	Hypophosphatemia and liver toxicity	Monitoring of electrolyte, phosphate, transaminase, and bilirubin levels: • Every 2–4 wk during initial treatment • Every 6–8 wk thereafter
Nilotinib	Gastrointestinal disturbances, rash, and headache	Physical examination: • Every 2–4 wk during initial treatment • Every 6–8 wk thereafter
	Elevation of bilirubin, transaminases, lipase, and amylase; electrolyte abnormalities; and hyperglycemia	Monitoring of electrolyte, glucose, lipase, amylase, transaminase, and bilirubin levels: • Every 2–4 wk during initial treatment • Every 6–8 wk thereafter
	QTc interval prolongation	Electrocardiogram at baseline, 7 days after initiation, and periodically thereafter
Dasatinib	Pleural effusion, dyspnea, gastrointestinal disturbances, rash, headache, and fatigue	Physical examination: • Every 2–4 wk during initial treatment • Every 6–8 wk thereafter
	Hypocalcemia and elevation of transaminases and bilirubin	Monitoring of electrolyte, transaminase, and bilirubin levels: • Every 2–4 wk during initial treatment • Every 6–8 wk thereafter
	QTc interval prolongation	Electrocardiogram at baseline and periodically thereafter for patients who are at risk for QTc prolongation (patients who are taking anti-arrhythmic medicines, patients with congenital long QT syndrome, and patients with hypokalemia or hypomagnesemia)
Ponatinib	Vascular occlusion, hypertension, congestive heart failure, and hemorrhage	Cardiovascular assessment at baseline Physical examination: • Every 2–4 wk during initial treatment • Every 6–8 wk thereafter
	Pancreatitis	Monitoring of serum lipase: • Every 2 wk for first 2 mo • Periodically thereafter
	Elevation of bilirubin, transaminases, and alkaline phosphatase	Monitoring of bilirubin, transaminase, and alkaline phosphatase levels: • Every 2–4 wk during initial treatment • Every 6–8 wk thereafter

Abbreviation: TKI, tyrosine kinase inhibitor.

The issue of poor TKI tolerance after alloHSCT remains a major concern. It can be speculated that the intermittent administration or alternating use of different TKIs might reduce the toxicity of the treatment. Such approaches, however, require verification in prospective trials. On the other hand, imatinib is known to inhibit pathways related to transforming growth factor β and platelet-derived growth factor receptor, which play a role in the pathogenesis of chronic GVHD.[48,49] Imatinib treatment was found to be effective as a salvage treatment for steroid-refractory chronic GVHD.[50,51] In a single retrospective analysis of patients with Ph-positive ALL, the use of posttransplant imatinib maintenance was associated with reductions in both the incidence and severity of this complication.[52] Significant differences were demonstrated with respect to the gut and oral mucosa as target organs. Therefore, it is worth examining whether treatment with TKIs after alloHSCT may overall contribute to an improved quality of life.

As suggested by the results of 2 prospective studies, autologous HSCT may be a valuable option for patients lacking a donor.[12,53] In a retrospective analysis by the

EBMT, the results of autologous HSCT improved markedly in the era of TKIs with a 3-year LFS rate of 60%. Among 32 patients pretreated with TKIs, 29 also received posttransplant maintenance with either imatinib or dasatinib. This promising strategy requires further prospective evaluation.[54]

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Sebastian Giebel: Writing of the article, contribution to the content by proposing and/or agreeing to the position statement, and approval of the overall content. **Anna Czyz:** Writing of the article, contribution to the content by proposing and/or agreeing to the position statement, and approval of the overall content. **Oliver Ottmann:** Writing of the article, contribution to the content by proposing and/or agreeing to the position statement, and approval of the overall content. **Frederic Baron:** Review of the article, contribution to the content by proposing and/or agreeing to the position statement, and approval of the overall content. **Eolia Brissot:** Review of the article, contribution to the content by proposing and/or agreeing to the position statement, and approval of the overall content. **Fabio Ciceri:** Review of the article, contribution to the content by proposing and/or agreeing to the position statement, and approval of the overall content. **Jan J. Cornelissen:** Review of the article, contribution to the content by proposing and/or agreeing to the position statement, and approval of the overall content. **Jordi Esteve:** Review of the article, contribution to the content by proposing and/or agreeing to the position statement, and approval of the overall content. **Norbert-Claude Gorin:** Review of the article, contribution to the content by proposing and/or agreeing to the position statement, and approval of the overall content. **Bipin Savani:** Review of the article, contribution to the content by proposing and/or agreeing to the position statement, and approval of the overall content. **Christoph Schmid:** Review of the article, contribution to the content by proposing and/or agreeing to the position statement, and approval of the overall content. **Mohamad Mohty:** Review of the article, contribution to the content by proposing and/or agreeing to the position statement, and approval of the overall content. **Arnon Nagler:** Writing of the article, contribution to the content by proposing and/or agreeing to the position statement, and approval of the overall content.

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