The 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

Running title: TKIs after alloHSCT in Ph+ ALL

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Precis: Tyrosine kinase inhibitor (TKI) maintenance therapy after allogeneic hematopoietic stem cell transplantation (alloHSCT) was demonstrated to reduce the risk of relapse of Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL). In this consensus paper on behalf of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation we present the recommendations on the use of TKIs after alloHSCT in Ph+ ALL regarding the choice of TKI, treatment timing and dosage.

Abstract

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 improved the overall outcome, however, still a significant proportion of patients relapse after alloHSCT. Post-transplant TKI maintenance was demonstrated to reduce the risk of relapse in a large retrospective study and therefore should be considered a valuable option. In this consensus paper on behalf of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation we present the overview of clinical studies on the use of TKIs after alloHSCT and propose practical recommendations regarding the choice of TKI, treatment timing and dosage. We do hope that these recommendations will become the state of art in this field and, more importantly, lead to reduction of Ph-positive ALL relapse post alloHSCT.

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

Introduction

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

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

Although the use of TKIs is associated with better disease control pre-transplant, relapses after alloHSCT remain a major problem being an important reason of treatment failure. Relapse rates are particularly high among patients with *BCR-ABL* transcripts detectable after alloHSCT.[17] Strategies to reduce the incidence of relapse include post-transplant maintenance with the use of TKIs.[10,18-21] Its role, however, remains a subject of uncertainty in view of paucity of prospective studies and conflicting results of retrospective analyses. Furthermore, there are no commonly accepted standards with regard to the choice of TKI, dosage, time of initiation, treatment duration and potential of combination with donor lymphocyte infusions.

In this paper we summarize the clinical experience on the use of TKIs after alloHSCT and present the position statement elaborated by the experts of the EBMT Acute Leukemia Working Party.

Overview of studies on TKI maintenance after alloHSCT

Retrospective studies

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

Burke et al. reported data from the University of Minnesota on 32 patients with Ph-positive ALL treated with alloHSCT.[22] Four patients received imatinib prophylactically post-transplant, 11 patients were treated with imatinib pre-transplant while not after alloHSCT, and 17 patients did not receive imatinib neither pre- nor post-transplantation. A tendency towards improved leukemia-free survival (LFS) ($p=0.12$) was observed for patients treated with imatinib either pre- or post-transplant. Unfortunately, the separate effect of post-alloHSCT imatinib could not be evaluated due to insufficient statistical power.

Nishiwaki at al. performed a multicenter study including 34 patients, among whom seven were treated with imatinib after alloHSCT either prophylactically or pre-emptively i.e. in case of positive status of minimal residual disease (MRD).[23] The post-transplant use of imatinib was associated with significantly improved probability of the OS (67% versus 30%, $p=0.03$).

In the study by Kebriaei et al. conducted on 102 adults and 11 children with Ph-positive ALL, treated with alloHSCT in ether first CR (n=71), second CR (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.[24] AlloHSCT procedures included transplantations from sibling and unrelated donors as well as using cord blood as a source of stem cells. Seven patients stopped TKI due to disease recurrence, while eight patients, because of excess toxicity (fluid retention n=2, nausea n=2, cytopenia n=4). In a univariate analysis the use of TKI post-transplant was not associated with better outcome although in a subgroup of patients treated in CR1 there was a tendency to improved OS (hazard ratio, HR=0.4, 95%CI 0.1-1.3, p=0.1).

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 of relapse. The study population was restricted to patients in CR1, treated with alloHSCT from either matched sibling or unrelated donor. The post-transplant use of TKIs was included in a multviarate analysis as a time-dependent covariate. It was associated with improved OS (HR=0.44, 95%CI 0.26-0.74, p=0.002) and leukemia-free surival (LFS) (HR=0.42, 95%CI 0.23-0.76, p=0.004), as well as reduced risk of relapse (HR=0.4, 95%CI 0.21-0.76, p=0.01) and a tendency to reduced risk of non-relapse mortality (HR=0.46, 95%CI 0.2-1.1, p=0.01). Furthermore, TKI maintenance was significantly associated with lower cumulative incidence of grade II-IV acute graft-versus-host disease (GvHD) (HR=0.21, 95%CI 0.05-0.85, p=0.03). Although the study had some important limitations associated with its retrospective nature, including lack of data on dose and timing of TKIs as well as unknown MRD status, the analyzed population was relatively homogenous. Therefore obtained results provide strong rationale for the use of TKIs as a maintenance after alloHSCT for patients with Ph-positive ALL in first CR.

Prospective studies

The use of TKIs after alloHSCT was a subject of six prospective studies including one randomized trial (Table 1). Five trials examined imatinib and one study nilotinib as post-transplant TKI. Two single arm

studies recruited recipients of both alloHSCT and autologous HSCT (autoHSCT). Two studies included mixed populations of patients with ALL and chronic myeloid leukemia (CML).

In the study by Wassmann et al. imatinib was administered at initial dose of 400 mg/day to patients with detectable MRD after either alloHSCT (n=25) or autoHSCT (n=2).[17] Of note, 22% of patients were beyond CR1 at the time of 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 in first or second relapse or with refractory disease achieved a molecular CR, in contrast to 13 (62%) of 21 patients who underwent transplantation in CR1. Patients achieving molecular remission remained relapse-free during imatinib administration. Three of them relapsed after the treatment discontinuation. Among patients who failed to achieve MRD-negativity relapse rate was 92%. The LFS rate at one year was 91% for patients with early MRD-negativity compared to 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 in whom additional or alternative antileukemic treatment should be initiated.

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

The Spanish group (PETHEMA) conducted a study on newly diagnosed Ph-positive ALL. Among 30 patients included, 21 proceeded to either alloHSCT or autoHSCT.[10] Finally, eight alloHSCT and four 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 two patients were they associated with drug-related toxicities (cytopenia, gastrointestinal complications). Long-term outcome of patients treated with post-transplant imatinib was not reported.

In a Chinese study including both adults and children, imatinib maintenance was scheduled for 3-12 months after alloHSCT, until MRD-negativity confirmed for three consecutive tests or sustained for at least three months.[19] The initial dose for adults was 400 mg/day. Imatinib was administered to 62 out of

82 enrolled patients. Reasons for not starting TKI maintenance were pancytopenia, infections, gut GvHD or personal decisions. Imatinib therapy was initiated at a median time of 70 days post-alloHSCT and the median treatment duration was 90 days. Although 71% of patients experienced possible drug-related complications, they were the cause of treatment termination (cytopenias, edema, nausea/emesis) in only 10 cases (16%). The probabilities of relapse, LFS ad OS at five years for patients receiving imatinib maintenance were 10%, 81.5% and 87%, respectively. Results of the study confirmed feasibility and suggested high efficacy of imatinib prophylaxis after alloHSCT.

The only randomized trial referring to post-transplant use imatinib was performed by the German group (GMALL).[20] The aim was to compare two strategies: prophylactic and MRD-triggered therapy. In the prophylactic treatment arm (n=26) all patients who engrafted, had no uncontrolled GvHD nor infections and had adequate organ function were intended for imatinib. In the pre-emptive treatment arm (n=29) the drug was initiated only after detection of MRD using quantitative real-time PCR, confirmed by nested PCR. The target dose of imatinib was 600 mg/day. The median time to treatment initiation was 48 days and 70 days post-alloHSCT, the median treatment duration was 201 days and 127 days, respectively. Notably, the majority of patients (67% and 71%) in both groups discontinued treatment prematurely. Moreover, only 22% received the intended imatinib dose (600 mg/day), while the majority received 400 mg/day. Although there was a tendency towards 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% versus 75% at five years, p=0.84). The authors concluded that despite unexpectedly low compliance, the use of either prophylactic or pre-emptive treatment with imatinib is associated with low risk of hematologic relapse and contributes to excellent long term-outcome. It was hypothesized that even short-term treatment may be sufficient to prevent hematologic relapse.

The only prospective study on the use of 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 in 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 intention to escalate to 400 mg every 12 hours. Ten episodes of grade 3 or 4 adverse events were reported (liver

toxicites, elevated lipase/amylase, neutropenia, allergy, skin reaction, stroke) leading to treatment discontinuation in 6 cases. Eleven patients achieved or maintained molecular remissions, among whom only one relapsed. Outcomes specific for patients with Ph-positive ALL were not reported.

The choice of TKI for post-transplant maintenance

Almost all prospective and retrospective studies on post-transplant TKI maintenance examined the use of imatinib, indicating its efficacy in preventing relapse and eradicating Ph-positive leukemic cells. Its safety profile has been relatively well defined. Treatment with nilotinib was tested in a single prospective phase I/II trial,[21] while therapy with dasatinib was a subject of case reports or small retrospective cohorts, the largest including 8 alloHSCT recipients.[25-29] Reports on dasatinib indicated the possibility to eradicate MRD after imatinib failure, with acceptable tolerance of the treatment. It should be mentioned however, that one case-series report showed high incidence of extramedullary relapse, which was detected in three out of six patients on post-transplant dasatinib therapy.[29] The use of third generation TKIs, like ponatinib, as maintenance after alloHSCT has not been reported so far. Altogether, based on available data imatinib should be considered the first choice TKI for post-transplant maintenance. However, there are several clinical scenarios, in which an alternative TKI may be considered from the outset after alloHSCT. Similarly, reappearance or persistence of BCR-ABL transcripts during imatinib treatment or its poor tolerability may mandate a change of TKI.

Results of the randomized GMALL study on imatinib given prophylactically or MRD-triggered demonstrated high probability of maintaining hematologic remission in the whole study group.[20] However, detailed analysis revealed that reappearance of BCR–ABL transcript early, within 3 months after alloHSCT and/or at high level ($>10^{-3}$) was associated with high risk of relapse and low probability of LFS. The authors suggested that these adverse factors allow to identify 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 post-transplant maintenance therapy are those who experienced resistance to pre-transplant treatment with imatinib. Soverini et al. demonstrated that approximately 70% of patients with resistance to imatinib are

characterized by point mutations within ABL kinase domain, with T315I, E255K, and Y253H being the most common ones.[30] Moreover, there are data indicating that Ph-positive ALL patients with detectable BCR-ABL transcript and kinase domain mutation before alloHSCT relapse after transplant with the same mutation. Egan et al. analyzed ABL kinase domain mutations in patients with CML and Ph-positive ALL who had detectable BCR-ABL transcript before alloHSCT.[31] Pre-transplant ABL kinase domain mutations were found in 14 patients, including 4 patients with Ph-positive ALL. Seven of those patients had relapsed or remained with refractory disease after alloHSCT. These data suggest that the choice of TKI for post-transplant maintenance therapy in patients with resistance to imatinib or with detectable BCR-ABL transcript before transplantation should be based on mutation analysis with taking into consideration resistance profiles of TKIs.

Prior leukemic involvement of the central nervous system (CNS) is another specific clinical situation, which should be taken into consideration when choosing TKI. Imatinib poorly penetrates into the CNS and does not reach adequate concentration for kinase inhibition.[32] Moreover, isolated CNS relapse occurs in up to 20% of patients with Ph-positive ALL during imatinib monotherapy.[33,34] In contrast, dasatinib penetration into the CNS was demonstrated in cerebrospinal fluid pharmacokinetic study performed by Porrka et al.[35] Its clinical activity in CNS was documented by several case reports.[36-38] Based on these data, dasatinib maintenance therapy after alloHSCT should be considered as rational strategy in patients with the history of CNS involvement.

Tolerability of TKIs after alloHSCT is another important issue that may impact on the choice of drug. Imatinib therapy in early period after alloHSCT is associated with high incidence of gastrointestinal intolerance and hematological side effects leading to dose reduction or withholding therapy.[10,18,20] During dasatinib maintenance therapy grade 2 hematologic toxicity, diarrhea and pleural effusion requiring dose reduction were reported.[26] Nilotinib given at the standard dose was not well tolerated due to gastrointestinal and liver side effects, however, grade 2-4 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, guided by comorbidities and post-transplant complications.

Timing and dosage of TKIs after alloHSCT

According to the GMALL study, both prophylactic and pre-emptive use of imatinib are equally effective in preventing relapse after alloHSCT.[20] Pre-emptive strategy should be applied only if adequate monitoring of BCR-ABL transcript is available with the use of real time quantitative polymerase chain reaction (RT-qPCR) confirmed by nested PCR.[39] The first evaluation should be done after engraftment, preferably within one month after alloHSCT. By pre-emptive strategy, a significant proportion of patients may avoid potentially toxic treatment with TKIs. Patients who cannot be monitored for 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.

Optimal treatment duration has not been defined so far. According to the study by Chen et al. the treatment should be continued until MRD-negativity confirmed for three consecutive tests or sustained for at least three months.[19] Relapse occurring relatively late after imatinib discontinuation were observed in the study by Wassmann et al, suggesting that too early discontinuation of TKI may carry risks for some patients and should be balanced against tolerability.[17] In the GMALL study imatinib administration was scheduled for one 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 regard 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 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/day, however, the vast majority of patients do not tolerate it after alloHSCT. It appears reasonable to start with the dose of 400 mg/day and to try to escalate in case of good tolerance. On the other hand, the risk of the occurrence of severe adverse events is high and even 400 mg/day may be intolerable. Therefore, decisions on the dose of imatinib should be made individually.

Based on 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 appropriate dose of dasatinib

administered after alloHSCT is 100 mg/day although in the cohort reported by Caocci et al. in five out of eight patients the dose was reduced to 50 mg/day.[26,29]

Summary of the position statement

1. All patients with Ph-positive ALL are candidates for post-transplant use of TKIs in order to reduce the risk of relapse.
2. Patients should be evaluated for the presence of BCR-ABL transcript and for the presence of ABL kinase domain mutations prior to alloHSCT and after engraftment (Figure 1).
3. Patients with undetectable MRD after alloHSCT may be treated prophylactically or alternatively may be monitored and administered TKI only after detection of MRD (pre-emptive strategy).
4. Patients with detectable MRD after alloHSCT should be started on TKI treatment as soon as possible.
5. Imatinib at initial dose of 400 mg/day is the first choice of TKI. Second generation TKIs (nilotinib 200 mg every 12 hours or dasatinib 50-100 mg/day) should be used in case of resistance to imatinib or the presence of ABL kinase domain mutations either prior to alloHSCT or after alloHSCT. In addition, they should be considered in case of MRD-positivity detected within 3 months after alloHSCT or at level $>10^{-3}$, or if BCR-ABL1 transcript levels remain detectable after 6-8 weeks of post-transplant imatinib
6. Patients with the history of CNS involvement should be treated with dasatinib.
7. The treatment should be given for at least 3-12 months of continuous MRD-negativity. Individual adjustments may be needed in case of severe toxicity.
8. Both, hematologic and nonhematologic adverse events should be monitored periodically, according to TKI toxicity profile (Table 2).

Future directions

The issue of TKI treatment following alloHSCT remains a relatively poorly explored area of investigation with many open questions requiring further research. Both, prospective and retrospective studies included mostly patients treated with myeloablative alloHSCT. However, it may be hypothesized that the optimal treatment schedule should differ according to the intensity of preparative regimens. As demonstrated by Bachanova et al., the risk of relapse is higher after reduced-intensity compared to myeloablative conditioning, especially if MRD status was positive prior to alloHSCT.[13] In such a situation a significant proportion of relapses occur later than one year after transplantation suggesting the need for more intensive and prolonged TKI maintenance. For patients with persisting MRD-positivity the use of donor lymphocyte infusion could be an additional intervention to reduce the risk of relapse. Although the synergistic effect of donor lymphocyte infusion and imatinib treatment was reported in a setting of CML, such data for Ph-positive ALL are not yet available.[40]

Rigorous monitoring of MRD allows to identify patients who benefit most from the TKI treatment after alloHSCT. However, the sensitivity of methods used for MRD detection varies and, in contrast to p210 in case of CML, the quantification of p190, typical for ALL, by RT-qPCR is still insufficiently standardized. New approach based on microfluidic digital PCR using Taqman chemistry, allowing for detection of rare copies of BCR-ABL1 in Ph-positive ALL has been proposed.[41] Its application might allow for more accurate discrimination between patients being in need or not requiring TKI maintenance.

The issue of poor TKI tolerance after alloHSCT remains a major concern. It could be speculated that intermittent administration or alternate use of different TKIs might reduce 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.[42,43] Imatinib treatment was found effective as a salvage treatment of steroid-refractory chronic GvHD.[44,45] In a single retrospective analysis on patients with Ph-positive ALL the use of post-transplant imatinib maintenance is associated with both reduced incidence and severity of this complication.[46] Significant differences were demonstrated with regard to

gut and oral mucosa as target organs. Therefore, it may be speculated that in some patients treatment with TKIs after alloHSCT may contribute to improved quality of life.

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Figure 1. Recommendations for the use of tyrosine kinase inhibitors according to pre- and post-transplant status of minimal residual disease

The status of minimal residual disease (MRD) should be checked before allogeneic hematopoietic stem cell transplantation (alloHSCT) and monitored after the transplantation, starting early after engraftment. In case of MRD-positivity, as defined by detectable *BCR-ABL* transcripts, the status of *BCR-ABL* domain mutations should be checked. Imatinib is the first choice tyrosine kinase inhibitor (TKI) for post-transplant maintenance. Second generation TKIs should be used in case of kinase domain mutations conferring resistance to imatinib.

Table 1. Prospective studies on the use of tyrosine kinase inhibitors after alloHSCT

Study	Type of TKI	Strategy	N*	Treatment duration (median months)	Treatment stop due to AE	Relapse rates	LFS	OS
Single arm								
Wassmann 2005 [17]	Imatinib	pre-emtive	27 (incl. 2 autoHSCT)	Not reported	Not reported	55% (8m)	Not reported	Not reported
Carpenter 2007 [18]	Imatinib	prophylactic	22 (ALL +CML)	11 (ALL)	9% (ALL+CML)	13% (ALL)	Not reported	80% (1.3y, ALL)
Ribera 2010 [9]	Imatinib	prophylactic	13 (incl. 4 autoHSCT)	9	20%	33%	Not reported	Not reported
Chen 2012 [19]	Imatinib	prophylactic	62	3	16%	10% (5y)	82% (5y)	87% (5y)
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 preemptive	26 29	7 4	67%** 71%**	8% (30m) 17% (32m)	69% (5y, all patients)	77% (5y, all patients)

alloHSCT, allogeneic hematopoietic stem cell transplantation; TKI, tyrosine kinase inhibitor; LFS, leukemia-free survival; OS, overall survival ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; AE, adverse events

*for single arm studies only patients effectively treated with TKIs are considered

**treatment discontinuation from any reason

Table 2. Monitoring hematologic and nonhematologic adverse events during tyrosine kinase inhibitor maintenance therapy after allogeneic haematopoietic stem cell transplantation

TKI	TKI-associated adverse events	Monitoring
	Hematologic AEs	
All TKIs	Cytopenias	Routine, frequent complete blood counts - every 2-4 weeks during initial treatment - every 6-8 weeks thereafter
	Nonhematologic AEs	
Imatinib	Abdominal pain, nausea, diarrhea, edema, muscle cramps, musculoskeletal pain, rash, fatigue, headache	Physical examination - every 2-4 weeks during initial treatment - every 6-8 thereafter
	Hypophosphatemia, liver toxicity	Monitoring of electrolyte, phosphate, transaminases and bilirubin levels - every 2-4 weeks during initial treatment - every 6-8 weeks thereafter
Nilotinib	Gastrointestinal disturbances, rash, headache	Physical examination - every 2-4 weeks during initial treatment - every 6-8 weeks thereafter
	Elevation of bilirubin, transaminases, lipase and amylase; electrolyte abnormalities, hyperglycemia	Monitoring of electrolyte, glucose, lipase, amylase, transaminases and bilirubin levels - every 2-4 weeks during initial treatment - every 6-8 weeks thereafter
	QTc interval prolongation	Electrocardiogram at baseline, 7 days after initiation, and periodically thereafter
Dasatinib	Pleural effusion, dsyponea, gastrointestinal disturbances, rash, haedache, fatigue	Physical examination - every 2-4 weeks during initial treatment - every 6-8 weeks thereafter
	Hypocalcemia, elevations of transaminases and bilirubin	Monitoring of electrolyte, transaminases and bilirubin levels - every 2-4 weeks during initial treatment - every 6-8 weeks thereafter
	QTc interval prolongation	Electrocardiogram at baseline and periodically thereafter in patients who are at risk for QTc prolongation (patients who are taking antiarrhythmic medicines, patients with congenital long QT syndrome, patients with hypokalemia or hypomagnesemia)

TKI, tyrosine kinase inhibitor; AE, adverse event