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Tyrosine kinase inhibitors: relapse prophylaxis after allogeneic hematopoietic stem cell transplantation in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia

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Summary

The role of prophylactic TKIs after allogeneic stem cell transplantation in Ph-positive acute lymphoblastic leukemia (ALL) remains controversial. We performed a retrospective study in 106 adult patients subjected to allogeneic hematopoietic stem cell transplantation (allo-HSCT) from matched related donors (MRD, 26%), matched unrelated donors (MUD/MMUD, 60%), and haploidentical donors (14%) in complete remission (CR1, 59%), CR2 (14%), and advanced disease (27%). Among them, 60 (57%), received 1st- or 2nd-generation TKIs as prophylaxis after allo-HSCT. In multivariate analysis of RFS, the following factors were associated with reduced risk of relapse or death: allo-HSCT after 2012 (HR=0.46, 95%CI 0.26-0.83, p=0.009), any MRD status of the disease before allo-HSCT except active disease with relatively similar HR in the context of post-transplant TKI prophylaxis. Allo-HSCT from haploidentical donor was associated with increased risk of relapse or death (HR=2.71, 95% CI 1.20-6.13 p=0.016). We were unable to demonstrate the significance of chronic GvHD when performing landmark analysis on day+180 and day+270, as based on available data (HR=0.43, 95% CI 0.13-1.45, p=0.17 and HR=0.5, 95% CI 0.19-1.32; p=0.161, respectively), under the conditions of maintaining TKI therapy after allo-HSCT. This relatively large study in unfavorable group of patients confirms an importance of TKIs prophylaxis for adult patients with Ph-positive ALL after allo-HSCT. A larger group of patients is required to formulate strong clinical recommendations in this cohort.

Keywords

Acute lymphoblastic leukemia, Ph-positive, BCR-ABL1, tyrosine kinase inhibitor, allogeneic hematopoietic stem cell transplantation, relapse, minimal residual disease, chronic GvHD.

Introduction

Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph-positive ALL) is the most common molecular type of B-lineage ALL in adults, characterized by the presence of the Philadelphia chromosome, caused by the reciprocal translocation t(9;22)(q34;q11), leading to BCR-ABL1 fusion gene encoding BCR-ABL oncoprotein, that has abnormal tyrosine kinase activity [1]. Its incidence increases with age and accounts for approximately 25-30% of adult ALL cases and close to 50% of cases in patients after 50 years old [2, 3]. Ph-positive ALL was historically associated with very poor outcomes before the advent of tyrosine kinase inhibitors (TKIs): even though complete response rates in some cases were from 46% to 96%, survival rates remained extremely low with the median overall survival (OS) times typically less than 11 months, mainly due to early relapses [4-6].

The TKIs incorporation into the treatment protocols of Ph-positive ALL has dramatically improved outcomes compared to chemotherapy alone [7-9]. For those patients who were treated by TKIs in combination with chemotherapy followed by allogeneic hematopoietic stem cell transplantation (allo-HSCT), the 5-year overall survival (OS) rates post-transplant have reached 52-61%, according to a donor type [10, 11]. In recent years, an increasing number of studies of 2nd and 3rd generation TKIs in the first-line treatment regardless of monitoring of BCR-ABL1 kinase domain (BCR-ABL1 KD) mutations were performed. The strategy to use more potent TKIs with chemotherapy or immunotherapy, such as bispecific T-cell engager antibody, in order to induce 1st remission leads to very high rates of sustained complete molecular responses (CMR), in about 83-90% of patients, and the 2-year OS rates of 80-88%. Interestingly, that the long-term survival among responding patients in these studies was not affected by allo-HSCT [12, 13]. Despite the impressive results of these recent studies, such therapy is still not uniformly available in real clinical practice in the most centers, due to its cost, lack of official indications, and coverage in the 1st-line therapy. Also, the long-term outcomes of TKIs combined with immunotherapy are still unknown. Thus, Ph-positive ALL patients remain within high-risk group. At the same time, allo-HSCT is still the standard consolidation therapy for young "fit" patients with available donor, according to current international recommendations, such as NCCN (Version 1.2022) and EBMT guidelines [14-16]. Despite all advances, the treatment of Ph-positive ALL is still challenging, especially in cases with relapsed and refractory (r/r) disease after allo-HSCT, thus remaining the main cause of transplant failure in ALL patients [17-19]. With improvement of posttransplant salvage, supportive care and disease monitoring, the 2-year OS after posttransplant relapse increased from 27.8% for patients relapsing between 2000 and 2004 to 54.8% over the period of 2015-2019 (p=0.001), which means that less than a half of the patients may be cured after allo-HSCT [20]. In these r/r cases, there are attempts to achieve further remissions with the use of salvage chemotherapy, second allo-HSCT, or TKIs with broader activity, and monoclonal antibodies, e.g., blinatumomab and inotuzumab [21-28].

Given that the prognosis of the patients who relapsed after allo-HCT remains poor, more promising strategy is the relapse prophylaxis or prevention after allo-HSCT using donor lymphocyte infusions (DLI), blinatumomab or posttransplant TKIs. Nonetheless, the need for systematic prolonged use of TKIs after allo-HSCT is still a matter of debate. Several retrospective and prospective comparative analyses were performed aiming to evaluate the impact of TKI usage after allo-HSCT upon clinical outcomes. Noteworthy, most of them found a positive impact of posttransplant TKIs administration despite controversial data obtained in other studies. At the same time, some of these studies had common limitations, due to small number of patients, heterogeneous groups, limited follow-up, variable doses of TKIs, starting date and duration of TKIs after allo-HSCT [29-37]. Another issue concerns the TKIs tolerance after allo-HSCT and need for dose adjustment [38, 39]. Acute Leukemia Working Party (ALWP) of the EBMT recommends to use prophylactic TKIs as soon as possible after engraftment, on the basis of pre- and posttransplant MRD status. However, a precise clinical strategy is still not described [40]. To address the issue if posttransplant TKIs offer a valid therapeutic approach to decrease the relapse rate, we conducted the study aimed for assessing its efficacy in multivariate analysis with respect to the disease- and allo-HSCT-specific factors.

Materials and methods

Patients, inclusion criteria and data collection

This single center study was conducted in the retrospective cohort of 106 Ph-positive ALL patients who received allo-HSCT in R.M. Gorbacheva Research Institute at the First St. Petersburg I.Pavlov State Medical University between 2002 and 2021. All patients had indications for allo-HSCT (complete remission (CR)≥1 or as a "salvage" treatment option if the CR had not been achieved previously) and were without severe cardiac, renal, pulmonary and other comorbidities. Inclusion criteria were: 1. Diagnosis of Ph-positive ALL and age ≥18 years at allo-HSCT; 2. Patients undergoing first allo-HSCT from any type of donor and in any response; 3. Treatment history with or without TKIs before allo-HSCT; 4. Donor bone marrow engraftment (absolute neutrophil counts (ANC) of >0.5×10*9/L without administration of colony-stimulating factor within 3 days with full donor chimerism in bone marrow). Prophylaxis with TKIs was not administrated in cases before introduction of second line TKIs into clinical practice and in cases of poor graft function (two or three cytopenias, >2 weeks after day +28 in the presence of >95% donor chimerism), severe infectious, cytopenias with mixed chimerism and graft rejection (<5% donor chimerism) [41]; 5. Available data about MRD status prior to allo-HSCT, as well as complete clinical data and outcome data. All data were retrieved retrospectively from clinical records according to the policy approved by the Medical Ethics Committee of the University and after obtaining written informed consent from the patients. The study was conducted according to the principles of Helsinki Declaration.

Response and clinical definitions

Complete remission (CR) before and after allo-HSCT was defined as blast cell ratio < 5% at the ANC counts of > 1×10*9/L,

and platelet numbers of >100×10*9/L. CR with incomplete recovery (CRi) was defined as platelet count <100×10*9/L and/or absolute neutrophil count <1×10*9/L. Molecular response (MR) or minimal residual disease (MRD) negativity was defined as undetectable BCR-ABL1 transcript p210 or p190 level determined by real time quantitative polymerase chain reaction (qPCR) with an ABL1 level at least 10000 copies number in a sample after remission induction or relapse treatment. MRD was defined as detectable BCR-ABL1 p210 or p190 transcript level after remission induction or relapse treatment and was assessed for patients in CR only. We provided MRD data at the time of allo-HSCT (within 30 days before the procedure) and after allo-HSCT. Molecular relapse was defined as any detectable BCR-ABL1 transcript level by real time qPCR confirmed by, at least, two consecutive tests after previous molecular response. qPCR monitoring of BCR-ABL1 was carried out according to NCCN Guidelines every 3 months for patients with complete molecular remission (undetectable levels) at least for 2 years, the frequency could be increased if MRD levels were detectable [42]. Relapse was defined as a presence of >5% blasts in bone marrow or any extramedullary site in the patients with previously documented CR. The Consensus Conference criteria were used for acute GvHD grading and National Institutes of Health criteria were used for chronic GvHD grading [43, 44].

Laboratory tests

Conventional cytogenetic analysis was used for evaluation of chromosome aberrations at diagnosis, or assessment of therapeutic response during follow-up. Cytogenetic studies were carried out on G-banded chromosomes obtained from the non-stimulated 24-hr bone marrow cultures. Karyotypes were described according to an International System for Human Cytogenomic Nomenclature [45]. When the standard cytogenetics was not available, the interphase blast cells were evaluated using fluorescence *in situ* hybridization (FISH) probes designed for detection of (9;22) translocation (Dual Fusion Probe, Cytocell, UK). For molecular analysis at diagnosis, assessment of response and MRD status, relative expression levels of BCR-ABL1 were measured using standard qPCR approach. The ABL1 gene was used for normalization of the results. ABL1 kinase domain mutations were determined by direct Sanger sequencing [46]. To assess relative expression of e1a2 variant of the BCR-ABL1 chimeric transcript, total RNA was isolated from blood or bone marrow samples by means of phenol-chloroform extraction. The reverse transcription reaction and real-time qPCR were performed using the BCR-ABL1mbcr RQ Kit (Inogene, Russia) according to the manufacturer's instructions. The samples with, at least, >10,000 copies of the reference ABL1 gene *per* a reaction were considered valid when assessing MRD levels.

Statistical analysis

Primary endpoints in the present study were as follows: OS, relapse incidence (RI), non-relapse mortality (NRM), relapse-free survival (RFS) and GvHD incidence. OS was defined as the probability of survival, irrespective of the disease status at any point in time after allo-HSCT. OS time duration was estimated from the time of allo-HSCT to the date of last contact or the date of death. The RFS was estimated as a period from allo-HSCT to the last contact date, death, or relapse. Probabilities of OS and RFS were calculated using the Kaplan-Meier Method. The comparisons were made using the log-rank test. P-values are two-sided with type 1 error rate fixed at 0.05. The RI was defined as the probability to develop a disease relapse after allo-HSCT. NRM was defined as probability of death without a relapse after allo-HSCT. Analysis of time-dependent variables, such as RI, NRM, GvHD incidence were calculated using cumulative incidence estimates with a competing risk setting using Fine and Grey test: death in remission as a competing event to relapse, relapse as a competing risk to NRM, death before 100 days without acute GvHD after allo-HSCT to the cases of acute GvHD; death without chronic GvHD to lethal cases with chronic GvHD, respectively. Patients alive at the end of the follow-up were censored at this date. Patients who reached D+100 after allo-HSCT were included into the analysis to assess the impact of prophylaxis with TKIs on the risk of chronic GvHD. Patients who presented with chronic GvHD prior to TKIs prophylaxis were excluded from this analysis.

Secondary endpoint concerned assessment of efficacy of TKIs prophylaxis on RFS, in view of the disease- and HSCT-specific factors. To this purpose, multivariate analysis was performed with the use of Cox proportional hazard model. Landmark analysis for day+180, +270, +360 was used to assess the impact of chronic GvHD on RFS. Fisher's exact test and Pearson's Chi-square were used to find difference between two groups of categorial factors. Non-parametric Mann-Whitney U-test was used to compare the quantitative attributes between groups. Statistical analyses were performed with SPSS 26.0 (IBM Corp., Armonk, NY, USA), R programming language version 4.0.5. software packages (R Development Core Team, Vienna, Austria), EZR free statistical environment, version 2.15.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients and allo-HSCT characteristics

A total of 106 Ph-positive ALL patients with median age of 30 (range 18-59) years were included into the study. The median follow-up time was 40.0 (range 5.0-150.4) months for the patients enrolled who were still alive at the end of the study. According to the current indications for allo-HSCT most of the patients (63 cases, 60%)) were transplanted in CR1; 15 (14%), in CR2; 11 (10%), in ≥CR3 and 17 (16%), in active disease ("salvage" allo-HSCT). There were no significant differences in gender, MRD status, extramedullary disease, BCR-ABL1 type of protein, cytogenetics, TKIs treatment prior to allo-HSCT, year of allo-HSCT, donor's gender, ABO-combability, busulfan dosage, graft source, GvHD prophylaxis between patients in CR1, and advanced stage of the disease. At the same time, matched/mismatched unrelated donor type (MUD/MMUD) was the most frequent type of donors in all groups (60% *vs* 26% *vs* 14%). Busulfan-based conditioning was used in most cases for the both groups (85% *vs* 10% *vs* 5%). Median time from allo-HSCT to first relapse was 262 (range 14-1926) days, and 8 (30%) of cases had relapse during 100 days after allo-HSCT. Relapses developed in 42 (40%) of the patients: bone marrow relapse

Table 1. Characteristics of the patients and allo-HSCT

Clinical characteristics		N (%)	CR1	Other disease statuses	P value
Total patients		106 (100)	63 (59)	43 (41)	-
Gender	Male	68 (64)	42 (67)	26 (60)	0.5
	Female	38 (36)	21 (33)	17 (40)	
Age	<39	84 (79)	46 (73)	38 (88)	0.08
	≥39	22 (21)	17 (27)	5 (12)	
Disease status	CR2	15 (14)	–	15 (14)	-
	≥CR3	11 (11)		11 (11)	
	Active disease	17 (16)		17 (16)	
MRD status	MRD-positive	45 (51)	29 (46)	16 (62)	0.1
	MRD-negative	44 (49)	34 (54)	10 (38)	
Extramedullary disease	Yes	20 (19)	9 (14)	11 (26)	0.2
	No	86 (81)	54 (86)	32 (74)	
BCR-ABL1	p210	25 (24)	15 (24)	10 (23)	0.3
	p190	67 (63)	42 (67)	25 (58)	
	Unknown	14 (13)	6 (9)	8 (19)	
Cytogenetics at diagnosis	Ph+ alone	45 (42)	26 (41)	19 (44)	0.7
	Ph+ plus other cytogenetic abnormalities	39 (37)	25 (40)	14 (33)	
	Unknown	22 (21)	12 (19)	10 (23)	
TKIs pre allo-HSCT	Yes	99 (93)	61 (97)	38 (88)	0.1
	No	7 (7)	2 (3)	5 (12)	
Type of TKIs pre allo-HSCT	Imatinib	59 (60)	42 (68)	17 (44)	0.09
	Dasatinib	7 (7)	3 (5)	4 (11)	
	Switch from imatinib to dasatinib	29 (29)	15 (25)	14 (37)	
	Nilotinib	1 (1)	1 (2)	0 (0)	
	Swith from dasatinib to nilotinib	1 (1)	0 (0)	1 (3)	
	Other combinations	2 (2)	0 (0)	2 (5)	
Allo-HSCT year	2002-2012	34 (32)	17 (27)	17 (40)	0.1
	2013-2021	72 (68)	46 (73)	26 (60)	
Donor	MRD	27 (26)	14 (22)	13 (30)	0.005
	MUD/MMUD	64 (60)	45 (71)	19 (44)	
	Haploidentical	15 (14)	4 (7)	11 (26)	
Female donor for male recipient	Yes	22 (21)	11 (17)	11 (26)	0.3
	No	84 (79)	52 (83)	32 (74)	
ABO-combability	Matched	51 (48)	32 (51)	19 (44)	0.3
	Minor	22 (21)	14 (22)	8 (19)	
	Major	23 (22)	10 (16)	13 (30)	
	Mixed	10 (9)	7 (11)	3 (7)	
Graft source	Bone marrow	32 (30)	15 (24)	17 (40)	0.09
	PBSC	74 (70)	48 (76)	26 (60)	
Median number of CD34+ cells x 10*6/kg, (range)	Bone marrow	-	2.65 (0.54-4.8)	2.8 (0.9-8.2)	0.02
	PBSC	-	6.15 (1.84-10.4)	5.1 (2.4-10)	
Conditioning regimen	Busulfan-based	90 (85)	55 (87)	35 (81)	0.01
	Melphalan-based	11 (10)	8 (13)	3 (7)	
	Other	5 (5)	0 (0)	5 (12)	
Busulfan dosage	8 mg/kg	30 (28)	21 (38)	9 (26)	0.3
	10 mg/kg	15 (14)	8 (15)	7 (20)	
	≥12 mg/kg	45 (42)	26 (47)	19 (54)	
GvHD prophylaxis	PtCy-based	61 (58)	40 (63)	21 (49)	0.1
	ATG-based	27 (25)	15 (24)	12 (28)	
	TCR αβ-depletion	4 (4)	3 (5)	1 (2)	
	Other	14 (13)	5 (8)	9 (21)	

Notes: CR=complete remission, MRD=minimal residual disease, TKIs=tyrosine kinase inhibitors, allo-HSCT=allogeneic hematopoietic stem cell transplantation; MRD=matched related donor, MUD=matched unrelated donor, MMUD=mismatched unrelated donor, PBSC=peripheral blood stem cells, PtCy=posttransplant cyclophosphamide, ATG=Anti-thymocyte globulin, GvHD=graft-versus-host disease, TCR αβ-depletion=T cell receptor alpha/beta-depletion

was registered in 34 cases (81%); neuroleukemia, in 3 (7%); extramedullary relapse, in 2 (5%); combined (CNS+bone marrow+other extramedullary) relapse, in 3 patients (7%). Nineteen patients experienced more than 1 relapse. By the end of analysis, 60 patients (57%) were alive, 46 (43%) of the patients died. Noteworthy, relapse was the main cause of death (n=27, 59%). Other causes of death were as follows: infection, 11 cases (24%), GvHD, 6 (13%), toxicity, 1 (2%), unknown reasons, 1 (2%). Other baseline characteristics for these patients and transplant procedure are presented in Table 1.

Survival and relapse rates

At 5 years, the cumulative incidence of relapse (RI) and non-relapse mortality (NRM) were 49.1% (37.74-60.46) and 20.2% (95% CI 11.58-28.82), respectively. The Kaplan-Meier OS estimate at 5 years was 55.0% (95% CI 44.62–65.38), and the estimate of RFS at 5 years was 40.4% (95% CI 30.41-50.39). Median time from allo-HSCT to first relapse was 262.5 (range, 14-1926) days. Five-year RFS values was influenced by status of the disease, i.e., RFS was 52.9% (95% CI 39.58-66.22%) when transplanted in CR1; 18.2% (95% CI 3.31-33.09%), if transplanted in CR≥3, and 0% following allo-HSCT in active disease (p<0.001), as seen from Fig. 1A. Moreover, the disease status was a significant risk factor for NRM: patients in advanced-disease phase experienced higher 2-year NRM rates: 64.7% (95% CI 36.87-92.53) compared to 42.7% (95% CI 9.38-76.02%) in CR3 *versus* 12.5% (95% CI 4.47-20.53%) in CR1-2 (p=0.001). At the same time, there was no difference in 5-year OS, RFS, NRM and RI when performing allo-HSCT in CR1 or CR2 (p>0.05). Interestingly, 16 of 17 patients who underwent allo-HSCT in active disease died by 14 months after allo-HSCT. Of them, 11 patients died due to the disease progression; 2 patients due to infectious complications; 2 patients, due to severe acute and chronic GvHD; 1 patient, due to toxicity (multiorgan failure). Median time from MRD assessment to allo-HSCT was 16 (range 6-134) days. One should be noted that, despite the fact that MRD-positive status before allo-HSCT did not affect OS, RFS and NRM, the relapse rate was 22.8% higher in MRD-positive group (p=0.03), as shown in Fig. 1B. In univariate cumulative incidence analysis, we have shown that the 5-year RI for the patients who reached 100 days after allo-HSCT, was twice lower in the TKIs prophylaxis group compared with non-prophylaxis group, i.e., 30.08% (95% CI 17. 7-43.5) *vs* 62.85% (95% CI 44.8-76.5) (Fig. 1C). Univariate analysis for survival and RI of the patients, transplanted in CR are presented in Table 2. Allo-HSCT from haploidentical donors was the factor, which led to significantly worse RFS (p=0.05) and NRM (p=0.01), while there is no difference in other types of donors. Intensity of conditioning regimen (busulfan dose) did not influence the 1-, 2- and 5-year OS, RFS, NRM and RI rates (p>0.05). Simultaneously, exploratory analysis showed that patients after GvHD prophylaxis with posttransplant cyclophosphamide had a significantly higher 5-year OS, RFS and lower NRM and RI likelihood than those treated with other regimens of GvHD prophylaxis (classical, or TCR αβ-depletion). The cumulative incidence frequencies of grades 2-4 acute GvHD at day 100 was 27.57% (95% CI 19.4-36.3%), with the median onset time of 27 (range 7-99) days. The proportion of patients with moderate chronic GvHD was 13 (32.5%), severe chronic GvHD, in 16 cases (40%). Cumulative incidence of NIH-defined chronic GVHD was 41.92% (95% CI 31.7-51.8%), with the median onset time of 199.5 (range, 100 to 1172) days. Experience of chronic GvHD was significantly associated with reduced risk of relapse: 31.4% (95% CI 14.94-47.86%) *vs* 53.7% (95% CI 35.87-71.53%), p=0.04 in univariate analysis.

Treatment with TKIs after allo-HSCT

A total of 80 (75.8%) patients received posttransplant TKIs maintenance therapy used with the prophylactic aim (60 cases, 75%); at the first MRD positivity or molecular relapse post allo-HSCT as pre-emptive treatment (11 cases, 13.8%), or as relapse treatment (9 patients, 11.2%) (Table 3). Median time from allo-HSCT to initiation of prophylactic TKIs was 87 days (range, 19-378). TKI drug was changed in 15 patients, i.e., due to relapse (n=1); due to toxicity/intolerance (n=4) in prophylaxis group; in 5 patients due to relapse (n=3), due to toxicity/intolerance (n=2) in preemptive group, and in 1 patient with disease progression in the relapse treatment group. Frequency of chronic GvHD in the TKIs prophylaxis group was 48.2% *vs* 21.1% in non-prophylaxis group (p=0.05).

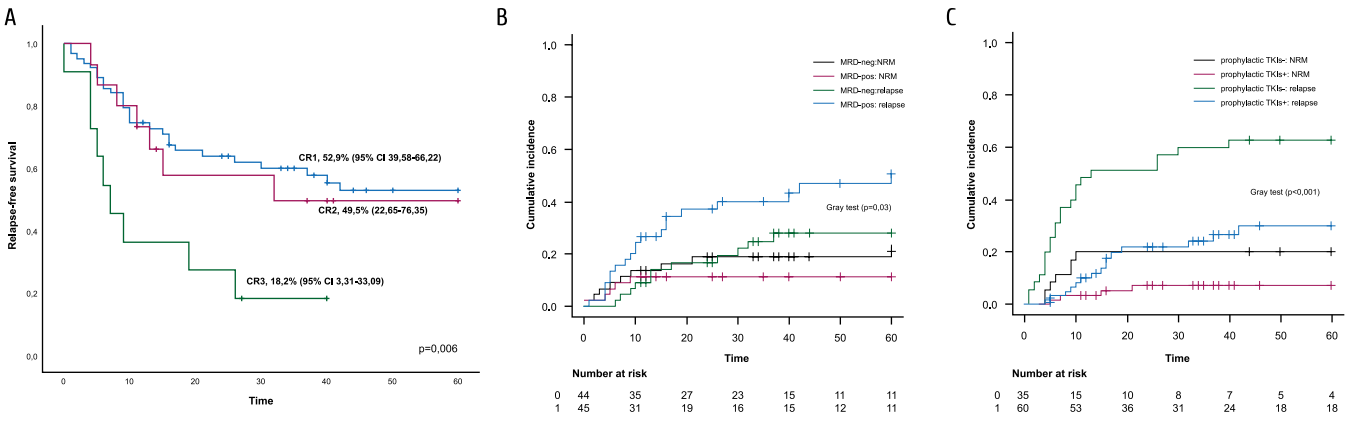

Figure 1. A. Relapse-free survival (RFS) according to CR status prior to allo-HSCT; B. Relapse incidence (RI) according to MRD status prior to allo-HSCT; C. RI according to prophylactic TKIs after allo-HSCT

Prophylaxis with TKIs was associated with increased risk of chronic GvHD: OR 3.47 (95% CI 1.03-11.84), at relative risk of 2.28 (95% CI 5.71-11.7). We did not find any difference in relapse risk according to the type of prophylactic TKIs (imatinib *vs* dasatinib, p=0.1).

To assess the impact of prophylactic TKIs after allo-HSCT upon RFS rates, we performed multivariate analysis including the factors associated with disease and allo-HSCT procedure. The following independent covariates were used: the year of allo-HSCT (2002-2012 vs. 2013-2021, separated by significant change in clinical practice), donor type, the fact of TKIs prophylaxis after transplant, and MRD status of the disease at transplant (Fig. 2). We performed the analysis using different classifications of donor type and status of the disease. The first one included haploidentical (n=15) *vs* other donor types (n=91), the second approach concerned matched (n=76) *vs* other donors (n=30).

Table 2. Univariate analysis of predictors for OS, RFS, NRM and RI at 5 years after allo-HSCT for CR patients

Factor		N (%)	5-year OS (95% CI)	p	5-year RFS (95% CI)	p	5-year NRM (95% CI)	p	5-year RI CI)	p
Status	CR1	63	65.9 (52.58-79.22)	0.06	52.9 (39.58-66.22)	0.006	14 (4.79-23.21)	0.03	38.4 (24.29-52.51)	0.1
	CR2	15	70.9 (46.6-95.2)		49.5 (22.65-76.35)		12.5 (6.43-18.57)		43.4 (16.36-70.44)	
	≥CR3	11	40.9 (8.96-72.84)		18.2 (3.31-33.09)		42.7 (9.38-76.02)		67.9 (40.27-95.53)	
MRD status	MRD-positive	45	67.7 (52.81-82.59)	0.7	53.7 (38.22-69.18)	0.3	19.9 (7.36-32.44)	0.7	50.62 (33.5-65.5)	0.03
	MRD-negative	44	59.0 (42.15-75.85)		40.8 (24.93-56.67)		12.6 (2.22-22.98)		27.82 (14.9-42.2)	
Donor	MRD	21	69.4 (48.82-89.98)	0.3	47.6 (26.24-68.96)	0.05	7.1 (0-20.62)	0.01	48.4 (26.65-70.15)	0.3
	MUD/ MMUD	58	64.2 (50.48-77.92)		52.1 (27.99-76.21)		15.4 (5.41-25.39)		38.3 (23.41-53.19)	
	Haploidentical	10	60.0 (29.62-90.38)		26.7 (0-56.1)		40 (9.62-70.38)		55.6 (12.09-99.1)	
Busulfan dosage	8 mg/kg	30	64.8 (47.16-82.44)	0.5	48.7 (30.48-66.92)	0.5	6.7 (4.35-9.05)	0.2	47.2 (28.39-66.01)	0.9
	10 mg/kg	14	64.3 (43.06-85.54)		50.0 (23.74-76.26)		17.5 (6.14-28.86)		39.01 (12.06-66.14)	
	≥12 mg/kg	44	56 (47.84-64.16)		43.3 (27.23-59.3)		23.2 (8.5-37.9)		43.3 (25.27-61.33)	
GvHD prophylaxis	PtCy-based	56	71.6 (57.3-85.9)	0.03	59.1 (44.8-73.4)	0.002	9.7 (1.47-17.93)	0.03	34.5 (19.8-49.2)	0.02
	Other	33	50 (31.58-68.42)		29.5 (13.63-45.37)		29.5 (11.67-47.33)		57.3 (37.51-77.09)	
Chronic GvHD	Yes	37	68.6 (52.14-68.6)	0.2	60 (43.54-76.46)	0.03	12.5 (0.94-24.06)	0.3	31.4 (14.94-47.86)	0.04
	No	51	62.9 (48.4-77.4)		38.4 (22.92-53.88)		16.5 (5.96-27.04)		53.7 (35.87-71.53)	

Table 3. TKIs after allo-HSCT according to the aim of administration

TKI	Prophylaxis group, n(%)	Preemptive group, n(%)	Relapse group, n(%)
Imatinib	29 (48)	4 (38)	1 (1)
Dasatinib	24 (40)	7 (62)	7 (8)
Nilotinib	1 (1.7)	0 (0)	1 (1)
Bosutinib	2 (3.3)	0 (0)	0 (0)
Combinations	4 (7)	0 (0)	0 (0)

Note: combinations, switch from imatinib to dasatinib (n=2), dasatinib to bosutinib (n=1), imatinib to nilotinib (n=1).

In a multivariate analysis of RFS performed to assess the impact of MRD and relapsed/refractory (r/r) disease before allo-HSCT in the context of posttransplant TKIs, the following factors were associated with reduced risk of relapse or death: allo-HSCT after 2012 (HR=0.46, 95%CI 0.26-0.83, p=0.009), any MRD status of the disease before allo-HSCT except active disease with relatively the same HR in the context of the posttransplant TKIs prophylaxis. With another distribution of statuses and TKIs (CR and MRD statuses), we confirmed the data of favorable impact of later year of transplant (HR=0.49, 95%CI 0.27-0.89, p=0.019), and the ability of posttransplant TKIs to reduce negative effect of measurable disease. In addition, allo-HSCT from haploidentical donor increased the risks in both models (HR=2.71, 95% CI 1.20-6.13, p=0,016, and HR=2.49, 95% CI 1.08-5.75, p=0.032, respectively), as seen from Fig. 3. When analyzing RFS with another classification of donor (matched *vs* others) we confirmed the data about favorable impact of prophylaxis with TKIs, despite the status of the disease prior to allo-HSCT (p<0.001).

To assess the effect of chronic GvHD on RFS in the context of TKI therapy after allo-HSCT, a landmark analysis was performed for day+180, +270, +360. By day+ 360, almost all patients with active disease and haploidentical donor have died, and this factor was excluded from the model. The following reasons were identified as the cause of death during first year after allo-HSCT in this group of patients: relapse, 9 patients (50%); acute GvHD grade IV, 3 patients (17%); infectious complications, 5 (28%); toxicity, 1 (5%). There was no impact of chronic GvHD on RFS when performing landmark analysis on day+180 and day+270 as based on available data (HR=0.43, 95% CI 0.13-1.45, p=0.17 and HR=0.5, 95% CI 0.19-1.32, p=0.161, respectively). Moreover, all remaining factors lose their significance on RFS for those patients who survived by day +360 (Fig. 4).

Toxicity of TKIs after allo-HSCT

While being very effective, the TKIs applied after allo-HSCT also have a toxicity profile that is relatively favorable. Among the entire group of patients who received any TKIs after allo-HSCT aimed for prophylaxis, preemptive, or relapse treatment, the TKIs' dosage was reduced in 24 patients (30%), treatment was discontinued in 4 patients (5%), changed to another TKI type, in 5 patients (6%), temporarily stopped and then re-prescribed in 10 patients (13%), due to intolerance or severe toxicity. In prophylaxis group, the most common side effects were hematological (26%) and gastrointestinal (9%) toxicity. Rare adverse events included fluid retention (5%), fever (5%), skin rash (3%), muscle pain (2%), autoimmune thyroiditis (2%). Four patients had multiple manifestations of toxicity. Toxicity profile in prophylaxis TKIs group according to the TKI type is presented in Table 4.

The presented toxicity profile in the prophylaxis TKIs group is described for the non-standard TKI dosage. In most cases of TKIs dose modifications, the drug dosage was reduced, in order to manage the TKI-related side effects. After allo-HSCT, only about 32% of patients received prophylaxis with imatinib at a full dose of 400-600 mg, whereas 29% of patients were treated at a dose of 200 mg, and 39% of patients received a significantly reduced dose of 100 mg *per* day. The same situation was with dasatinib: full dose was prescribed to 33% of patients; 70 mg, to 50% of patients, and 35-50 mg, to 17% of patients (Fig. 5).

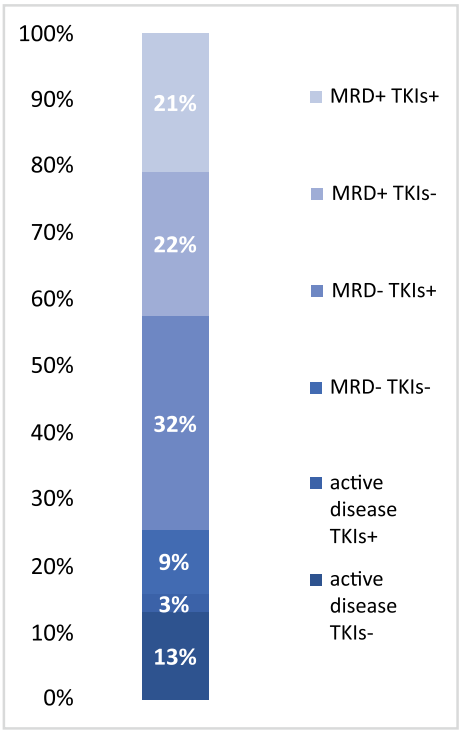

Figure 2. Distribution of MRD status and treatment with TKIs after allo-HSCT

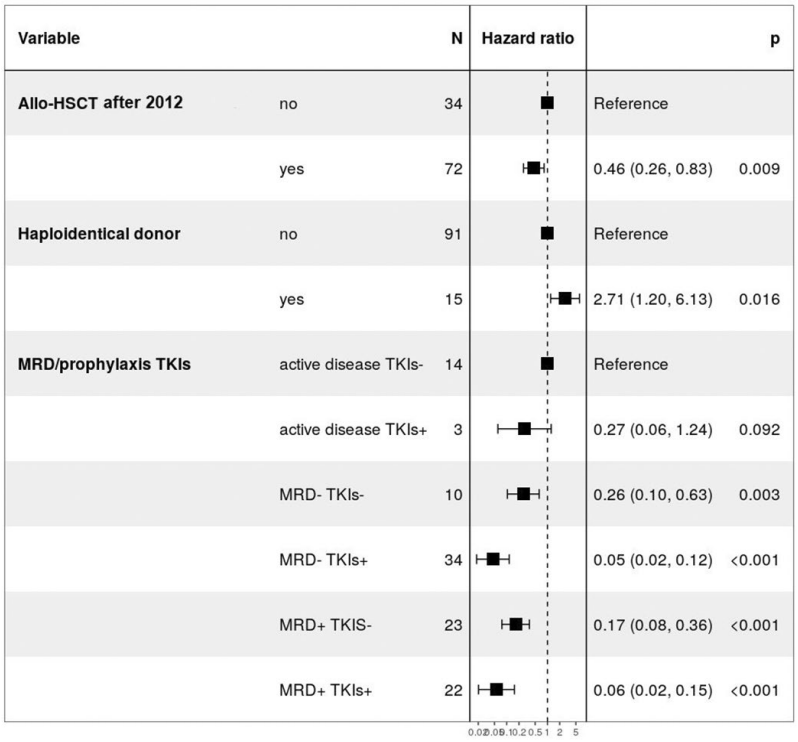

Figure 3. Multivariate analysis of the factors influencing RFS

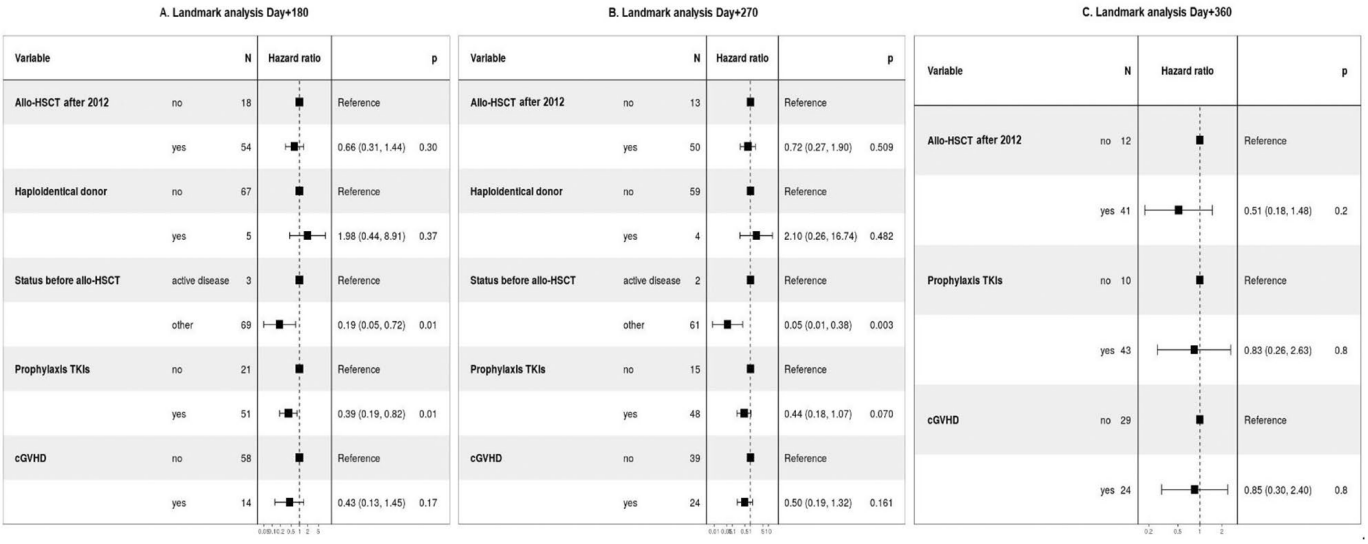

Figure 4. Multivariate analysis of the factors influencing RFS (landmark analysis)

Table 4. Adverse events in prophylaxis group according to the type of TKI

Side effect	Imatinib N (%)	Dasatinib N (%)	Bosutinib N (%)	Nilotinib N(%)
Anemia 2 grade	0 (0)	1 (2)	0 (0)	0 (0)
Neutropenia 3-4 grade	0 (0)	4 (9)	0 (0)	0 (0)
Trombocytopenia 2-3 grade	4 (9)	2 (5)	0 (0)	0 (0)
Cytopenia in 2 or 3 lineages	5 (12)	8 (18)	0 (0)	0 (0)
Fever	0 (0)	3 (7)	0 (0)	0 (0)
Skin rash	1 (2)	0 (0)	1 (33)	0 (0)
Hepatotoxicity 2-3 grade	1 (2)	0 (0)	0 (0)	0 (0)
Hydropericardium/hydrothorax	0 (0)	2 (5)	0 (0)	0 (0)
Diarrhea/colitis	2 (5)	3 (7)	1 (33)	0 (0)
Nausea/vomiting	1 (2)	2 (5)	2 (66)	0 (0)
Peripheral edema	1 (2)	1 (2)	0 (0)	0 (0)
Muscle pain	0 (0)	1 (2)	0 (0)	0 (0)
Autoimmune thyroiditis	0 (0)	1 (2)	0 (0)	0 (0)

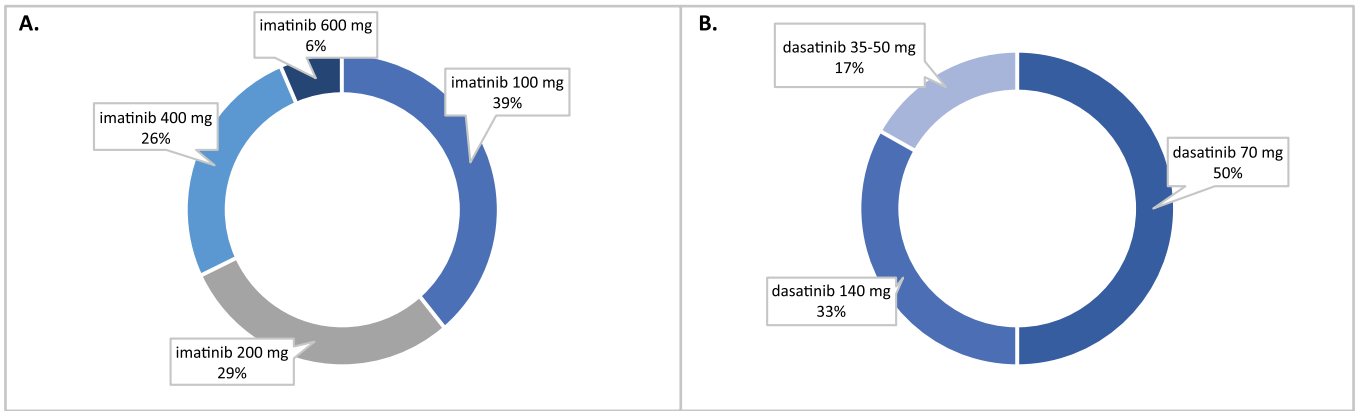

Figure 5. Doses of prophylactic imatinib (A) and dasatinib (B)

Discussion

MRD-positive status prior to allo-HSCT is a well-known unfavorable risk factor for allo-HSCT outcomes in Ph-positive ALL patients, who did not receive prophylactic TKIs post-transplant [47,48]. Lussana et al. showed that MRD negativity at the time of conditioning was associated with a significant benefit in terms of risk of relapse at 5 years, with a RI of 8% compared with 39% for patients with MRD positivity (p=0.007). However, in this study post-transplantation administration of TKIs alleviated the difference in DFS (58% *vs* 41%, p=0.17) and OS (58% *vs* 49%, p=0.55) in MRD-negative and MRD-positive patients, respectively. Nonetheless, TKIs were used not with prophylactic, but with treatment aim in this study [49]. In our retrospective single-center analysis, we also demonstrated that TKIs prophylaxis improves long-term RFS and alleviates the negative impact of MRD on the outcomes in an unfavorable group of Ph-positive ALL adult patients. Previously, the same conclusions were made in several non-randomized studies, however, in extremely small groups of patients. Chen et al. reported superior outcomes for patients who received imatinib as prophylactic or preemptive maintenance regimens after allo-HSCT (n=62) compared with those who did not receive post-transplant TKIs (n=20) (5-year OS, 86.7% *vs* 34.3%, p <0.001; EFS, 81.5% *vs* 33.5%, p <0.001) [50]. At the same time, the data of a single randomized trial from the German multicenter study group for adult ALL obtained in 55 patients with Ph-positive ALL who underwent allo-HSCT, were randomly assigned to receive imatinib as prophylaxis or based on MRD positivity. Although prophylactic imatinib prevented molecular recurrence, EFS and OS did not differ significantly between the 2 treatment arms: 5-year OS was 80% in the prophylactic group *vs* 75% in the preemptive group [38]. Burke et al. compared outcomes for patients who received prophylactic imatinib (for 1 year) with patients who did not receive post-transplant TKIs: OS at 2 years for patients with imatinib (n=2) and without (n=17) were 100% and 41%, respectively, with a corresponding relapse-free survival of 100% and 35% [51]. The data about 2nd generation of TKIs after allo-HSCT are very scarce: dasatinib or nilotinib were studied as maintenance regimen after allo-HSCT in few studies (n=62) [35]: in the study by Czyz et al., 19 patients received dasatinib (treatment duration of 11 months), either prophylactically or preemptively. After a median follow-up of 3 years after allo-HSCT, the OS and LFS were 87% and 88%, respectively. Fourteen of 15 patients (93%) who were MRD positive after transplant converted to MRD negativity and continued to be MRD negative at last follow up. At the same time, there is an important limitation of nilotinib trials: they presented common results for CML and Ph-positive ALL patients, but not separate results for the Ph-positive ALL group, mainly due to small number of enrolled patients.

In our group, most of the patients (57%) received prophylactic TKIs after allo-HSCT. The majority of patients not assigned to prophylaxis and preemptive treatment with TKIs (n=35) was transplanted (n=21) before 2014. The patient group allografted since 2014 (n=11) who reached day+80 after allo-HSCT without TKIs, included patients with severe infectious complications, severe poor graft function, or uncontrolled GvHD. Six of them died from relapse, one patient was lost from infectious complications, two patients are alive without relapse. In two cases, the patients developed relapse and are alive at the last follow up. Thus, we presume that the results might be significantly affected by the time of transplant and status of patients. It is well known that the patients with severe poor graft function tend to have increased risk of NRM, but not relapse [52]. In early studies, TKIs demonstrated superior outcomes, but both prophylactic TKIs group, as well as patients without TKI prophylaxis included only limited number of patients. Authors did not explain the choice of strategy concerning prophylactic TKIs administration in non-randomized trials, but the reasons seem to be comparable across studies. A study by Ribera et al. concerned OS and DFS for 13 of 21 patients who received prophylaxis with imatinib that was only 30% (9-mo follow-up). Transplant- and treatment-related complications and patient selection may have contributed to poor outcomes in this small cohort. Ten of twelve patients had interruptions in treatment for various reasons, including relapse, severe chronic graft-versus-host disease (GVHD), grades 3 to 4 toxicity, non-relapse death, and patient preference [53]. Nishiwaki et al. showed superior outcomes for patients who received imatinib (pre-emptive, n=4; prophylactic, n=3) after allo-HSCT when compared with cases without TKI treatment (n=27). The OS at 1 year with TKIs *versus* without TKIs was 100% *vs* 33.3%, and the 2-year OS was 66.7% *vs* 29.6%, respectively (p=0.03). EFS was not significantly different between the 2 groups at 1 and 2 years (55.6% *versus* 55.6% and 33.3% *versus* 29.6%, p = 0.29).

Newer TKIs' generation, such as dasatinib and nilotinib, were shown to be more potent (respectively, 325-fold and 50-100-fold) when compared with imatinib [54]. Whether or not this higher potency plays any role in the context of post-transplant administration remains to be proven. Dasatinib demonstrated similar or better EFS and OS rates compared with imatinib in several trials [30, 33]. Nonetheless, the studies were retrospective and long-term outcomes were not available. Nilotinib also had similar clinical outcomes when compared with imatinib, but the studies on post-transplant nilotinib therapy included mixed group of CML and Ph-positive ALL patients [55, 56]. The numbers of patients in studies using 2nd TKIs generations are small and non-randomized. E.g., Saini et al. aimed to compare the efficacy of new-generation TKIs *versus* imatinib treatment: 28 patients received imatinib in the TKIs prophylactic group and 33 patients received newer generation TKIs. The relapse rate was similar, with three patients relapsing in each arm. However, in the MRD-triggered group, 6 (75%) out of 8 patients who received imatinib relapsed compared to 6 (45%) out of 11 patients who received new-generation TKI [36]. The newer generation TKIs appear to improve prognosis for these high-risk patients, but these results should be proven in further prospective trials. First and 2nd-generation TKIs were used with the prophylaxis aim in our group of patients. Imatinib was the most commonly used (48%) in the entire group, due to wider availability of the TKI in real clinical practice. At the same time, dasatinib was more frequently used (40%) over recent years, due to its broader activity and ability to penetrate the blood-brain barrier and prevent CNS relapses [54]. Isolated CNS relapse occurs in up to 20% of patients

with Ph-positive ALL during imatinib monotherapy [57]. We did not find any difference in relapse risk dependent on the type of prophylactic TKIs (imatinib vs. dasatinib), p=0.1. First of all, we did not compare relapse rates for imatinib and dasatinib subgroups according to the disease status before allo-HSCT. In addition, the lack of difference between imatinib and dasatinib groups of patients may be due to pronounced graft-versus-leukemia (GvL) effect and shift of Ph-positive ALL subclones to less aggressive ones, thus lacking a need for a more active TKI in this case after allo-HSCT. Several studies have shown that BCR-ABL1 kinase mutation is the major cause of relapse in Ph-positive ALL, even after allo-HSCT [58], and newer TKIs generations can potentially overcome some of these mutations and lead to lower relapse rates in patients with resistant disease. However, lack of the data about the mutational status and insufficient patients' numbers in study does not allow to make definitive conclusions.

There are also studies which did not show positive impact of post-transplant TKIs. E.g., Nishiwaki et al. confirmed that MRD status at allo-HSCT is one of the most important predictive factors for Ph-positive ALL patients transplanted in CR1. Post-transplant TKIs were administered to 103 patients. Surprisingly, post-transplant administration of TKIs was suggested to be a significant adverse prognostic factor for relapse, i.e., OS was significantly better in patients with post-transplant TKI therapy, but there was no significant difference in RFS. As for NRM, it might be underestimated in patients with post-transplant TKI administration because of technical issues for the competing risk analyses: of 103 patients with post-transplant administration, NRM occurred in only 3 patients (3%), whereas relapse was observed in 71 patients (69%). Since a decision to administer TKIs after allo-HSCT was made by each institution in this study, the TKIs might have been prescribed to the patients who were potentially at high risk for relapse [48]. The main difference between the studies is the patients' enrollment, i.e., we described the patients in various disease status, while Nishiwaki and colleagues included only CR1 patients prior to allo-HSCT, and observed surprisingly high relapse rate without TKIs. In the retrospective study of Kebriaei et al., 102 adults and 11 children were included. TKIs' use for maintenance (n=32) did not improve the outcomes. Only subgroups of younger patients who achieved CR1 at the time of allo-HSCT, and underwent transplants after 2000, demonstrated better outcomes and improved prognosis. In this study, on the contrary to Nishiwaki et al., the presence of MRD prior to allo-HSCT was not a significant predictor for progression-free survival [31]. Patients observed by Zheng et al. did not show favorable survival outcomes despite maintenance imatinib therapy after allo-HSCT. This result may be, in part, explained by the high proportion (36%) of patients who were not in CR at the time of allo-HSCT in this small cohort (n=11) [59].

Another valuable topic of interest is an influence of chronic GvHD upon RFS and RI. In CIBMTR-led study which recruited a large cohort of adult ALL patients (n=2593), the impact of acute GvHD and chronic GvHD of varying severity on transplant outcomes was explored. The patients with advanced ALL had better OS (reduction in mortality; HR, 0.69-0.73) when they developed chronic GvHD with or without grades I and II acute GvHD, which is explained by an increased GVL effect in ALL [59]. Simultaneously, the results refer to the common group of ALL patients, without any clarification regarding Ph-negative and Ph-positive ALL patients. There are also no conclusions about the GvHD incidence in case of TKIs maintenance after allo-HSCT. In another study (Akahoshi et al.), the association between TKIs prophylaxis and incidence of chronic GvHD was not described: WBC at diagnosis (HR, 1.36; 95% CI 1.10-1.68; p=0.004), unrelated cord blood transplantation (HR, 0.70; 95% CI 0.52-0.95; p=0.022), reduced conditioning intensity (HR, 0.77; 95% CI 0.60-0.99; p=0.042), and grade II-IV acute GvHD (HR, 1.36; 95% CI 1.10-1.68; p=0.004) were significantly associated with the incidence of chronic GVHD, while the incidence of chronic GvHD did not show significant association with TKIs prophylaxis (HR, 0.82; 95% CI 0.49-1.35; p=0.428) in the multivariate analysis [34].In our study, chronic GvHD was significantly associated with reduced risk of relapse in our group: 31.4% (95% CI 14.94-47.86%) *vs* 53.7% (95% CI 35.87-71.53%), p=0.04 and increased RFS: 60% (95% CI 43.54-76.46) *vs* 38.4% (95% CI 22.92-53.88), p=0.003 in univariate analysis. At the same time, we were unable to prove a positive impact of chronic GvHD upon the landmark analysis. We realize the fact, that, due to the small groups of patients in our study, we can't confidentially claim that, in the context of TKIs maintenance, chronic GvHD associated with GvL effect has no influence on clinical outcomes. We understand that a larger group of patients is needed to assess the effect of chronic GvHD upon RFS in the time-dependent manner. It is worth to mention, that TKIs, especially imatinib, being a multikinase inhibitor of several signaling pathways implicated in skin fibrosis, is known as potential option to treat sclerotic steroid refractory GvHD, in view of fibroblast growth inhibition, and decreased collagen production in dermal fibroblasts [60, 61]. However, the incidence of chronic GVHD in our group was even higher in the TKIs prophylaxis group. Among 31 patients who experienced chronic GvHD in the prophylaxis group, 23 (74.2%) of the patients exhibited skin involvement, and 12 of them (52.2%) received prophylaxis with post-transplant imatinib. Only 1 patient died from severe chronic GvHD in each group (imatinib vs other TKIs). In our opinion, not only imatinib, but also improvement of GvHD prophylaxis and treatment over recent years contributes to this low incidence of GvHD-associated mortality [62, 63]. In our study, several patients received other TKIs as a prophylactic component (nilotinib, n=2; bosutinib, n=3). Four of these patients developed chronic GvHD, 3 of them displayed skin involvement. However, clinical data concerning the potential use of 2nd-generation TKIs, which are active against a broader spectrum of kinases, are lacking in patients with chronic GVHD. Nonetheless, *in vitro* addition of nilotinib to chronic GVHD fibroblast cultures induced a decrease in the expression of both COL1α1 and COL1α2 mRNAs, indicating the antifibrotic potential of this drug [64]. On the other hand, ponatinib, 3rd-generation TKI, is described as a drug, which induces GvHD, suggesting that the efficacy of ponatinib could be related not only to the direct antileukemic effect but also to its ability to promote an indirect GvL effect. Petrungaro et al. have shown an increased number of circulating CD8+ and natural killer T cells, along with reduced numbers of CD4+

T cells observed during ponatinib treatment after allo-HSCT in patient without T315I mutation, which might be correlated with the onset of GVHD and GVL [65].

Conclusion

The study demonstrated positive impact of prophylactic TKIs in adult patients with Ph-positive ALL after allo-HSCT. Prophylactic TKIs can overcome the negative effects of MRD on clinical outcomes. However, in some cases, post-transplant TKIs administration is not possible, mainly because of transplantation-derived complications, rather than drug-specific toxicity. Final safe dose in the majority of patients was lower than recommended, thus dose de-escalation strategy is more justifiable after allo-HSCT. The issue of using first- or second-generation TKIs, as well as optimal duration of therapy should be clarified by the working group consensus.

Conflicts of interest

No conflicts of interest are reported by the authors.

References

1. Kang Z-J, Liu Y-F, Xu L-Z, Long Z-J, Huang D, Yang Y, et al. The Philadelphia chromosome in leukemogenesis. Chin J Cancer. 2016;35:48. doi: 10.1186/s40880-016-0108-0

2. Burmeister T, Schwartz S, Bartram CR, Gökbuget N, Hoelzer D, Thiel E. Patients' age and BCR-ABL frequency in adult B-precursor ALL: a retrospective analysis from the GMALL study group. Blood. 2008;112:918-919. doi: 10.1182/BLOOD-2008-04-149286

3. Chiaretti S, Vitale A, Cazzaniga G, Orlando SM, Silvestri D, Fazi P, et al. Clinico-biological features of 5202 patients with acute lymphoblastic leukemia enrolled in the Italian AIEOP and GIMEMA protocols and stratified in age cohorts. Haematologica. 2013;98:1702-1710. doi: 10.3324/HAEMATOL.2012.080432

4. Kantarjian HM, O'Brien S, Smith TL, Cortes J, Giles FJ, Beran M, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. J Clin Oncol. 2000;18:547-561. doi: 10.1200/JCO.2000.18.3.547

5. Radich JP. Philadelphia Chromosome–positive acute lymphocytic leukemia. Hematol Oncol Clin North Am. 2001;15:21-36. doi: 10.1016/S0889-8588(05)70198-2

6. Ravandi F. Managing Philadelphia chromosome-positive acute lymphoblastic leukemia: role of tyrosine kinase inhibitors. Clin Lymphoma Myeloma Leuk. 2011;11:198. doi: 10.1016/J.CLML.2011.03.002

7. Bassan R, Rossi G, Pogliani EM, Di Bona E, Angelucci E, Cavattoni I, et al. Chemotherapy-phased imatinib pulses improve long-term outcome of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: Northern Italy Leukemia Group protocol 09/00. J Clin Oncol. 2010;28:3644-3652. doi: 10.1200/JCO.2010.28.1287

8. Fielding AK, Rowe JM, Buck G, Foroni L, Gerrard G, Litzow MR, et al. UKALLXII/ECOG2993: addition of imatinib to a standard treatment regimen enhances long-term outcomes in Philadelphia positive acute lymphoblastic leukemia. Blood 2014;123:843-50. https://doi.org/10.1182/BLOOD-2013-09-529008

9. Daver N, Thomas D, Ravandi F, Cortes J, Garris R, Jabbour E, et al. Final report of a phase II study of imatinib mesylate with hyper-CVAD for the front-line treatment of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Haematologica. 2015;100:653-661. doi: 10.3324/HAEMATOL.2014.118588

10. Mizuta S, Matsuo K, Yagasaki F, Yujiri T, Hatta Y, Kimura Y, et al. Pre-transplant imatinib-based therapy improves the outcome of allogeneic hematopoietic stem cell transplantation for BCR-ABL-positive acute lymphoblastic leukemia. Leukemia. 2011;25:41-47. doi: 10.1038/LEU.2010.228

11. Chalandon Y, (GRAALL) for the G for R on AALL, Thomas X, (GRAALL) for the G for R on AALL, Hayette S, (GRAALL) for the G for R on AALL, et al. Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. Blood. 2015;125:3711-3719. doi: 10.1182/BLOOD-2015-02-627935

12. Jabbour E, Short NJ, Ravandi F, Huang X, Daver N, DiNardo CD, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: long-term follow-up of a single-centre, phase 2 study. Lancet Haematol. 2018;5:e618-627. doi: 10.1016/S2352-3026(18)30176-5

13. Foà R, Bassan R, Vitale A, Elia L, Piciocchi A, Puzzolo M-C, et al. Dasatinib-blinatumomab for Ph-positive acute lymphoblastic leukemia in adults. N Engl J Med 2020;383:1613-1623. doi: 10.1056/NEJMoa2016272

14. Guidelines Detail n.d. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1410 (accessed May 10, 2022).

15. Duarte RF, Labopin M, Bader P, Basak G, Bonini C, et al. Indications for haematopoietic stem cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2019. Bone Marrow Transplant. 2019;54:1525-1552. doi: 10.1038/s41409-019-0516-2

16. Snowden JA, Sánchez-Ortega I, Corbacioglu S, Basak GW, Chabannon C, de la Camara R, et al. Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe. Bone Marrow Transplant 2022:1-23. doi: 10.1038/s41409-022-01691-w

17. Fielding AK, Richards SM, Chopra R, Lazarus HM, Litzow MR, Buck G, et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. Blood. 2007;109: 944-950. doi: 10.1182/BLOOD-2006-05-018192

18. Tavernier E, Boiron JM, Huguet F, Bradstock K, Vey N, Kovacsovics T, et al. Outcome of treatment after first relapse in adults with acute lymphoblastic leukemia initially treated by the LALA-94 trial. Leukemia. 2007;21:1907-1914. doi: 10.1038/SJ.LEU.2404824

19. Gökbuget N, Leukemia on behalf of the GMSG for AAL, Stanze D, Leukemia on behalf of the GMSG for AAL, Beck J, Leukemia on behalf of the GMSG for AAL, et al. Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation. Blood 2012;120:2032-2041. doi: 10.1182/BLOOD-2011-12-399287

20. Bazarbachi A, Labopin M, Aljurf M, Niittyvuopio R, Balsat M, Blaise D, et al. 20-year steady increase in survival of adult patients with relapsed philadelphia-positive acute lymphoblastic leukemia post allogeneic hematopoietic cell transplantation. Clin Cancer Res. 2022;28:1004-1012. doi: 10.1158/1078-0432.CCR-21-2675

21. Farnsworth P, Ward D, Reddy V. Persistent complete molecular remission after nilotinib and graft-versus-leukemia effect in an acute lymphoblastic leukemia patient with cytogenetic relapse after allogeneic stem cell transplantation. Exp Hematol Oncol. 2012 11 2012;1:1-5. doi: 10.1186/2162-3619-1-29

22. Kantarjian HM, DeAngelo DJ, Stelljes M, Martinelli G, Liedtke M, Stock W, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. N Engl J Med. 2016; 375:740-753. doi: 10.1056/NEJMoa1509277

23. He JB, Zhang X, Guo ZW, Liu MM, Xu N, Huang F, et al. Ponatinib therapy in recurrent Philadelphia chromosome-positive central nervous system leukemia with T315I mutation after allo-HSCT. Int J Cancer. 2020;147:1071-1077. doi: 10.1002/IJC.32817

24. Botta C, Caruso N, Bossio S, Storino F, Console G, Martino M, et al. Long-Term remission achieved by ponatinib and donor lymphocytes infusion in a ph+ acute lymphoblastic leukemia patient in molecular relapse after allogenic stem cell transplant and dasatinib: a case report. Front Oncol. 2020;10:967. doi: 10.3389/fonc.2020.00967

25. Martinelli G, Boissel N, Chevallier P, Ottmann O, Gökbuget N, Rambaldi A, et al. Long-term follow-up of blinatumomab in patients with relapsed/refractory Philadelphia chromosome-positive B-cell precursor acute lymphoblastic leukaemia: Final analysis of ALCANTARA study. Eur J Cancer. 2021;146:107-114. doi: 10.1016/J.EJCA.2020.12.022

26. Short NJ, Konopleva M, Kadia T, Kebriaei P, Daver N, Huang X, et al. An effective chemotherapy-free regimen of ponatinib plus venetoclax for relapsed/refractory Philadelphia chromosome-positive acute lymphoblastic leukemia. Am J Hematol. 2021; 96:E229-232. doi: 10.1002/AJH.26175

27. Couturier MA, Thomas X, Raffoux E, Huguet F, Berthon C, Simand C, et al. Blinatumomab + ponatinib for relapsed/refractory Philadelphia chromosome-positive acute lymphoblastic leukemia in adults. Leuk Lymphoma. 2021; 62:620-629. doi: 10.1080/10428194.2020.1844198

28. Jain N, Maiti A, Ravandi F, Konopleva M, Daver N, Kadia T, et al. Inotuzumab ozogamicin with bosutinib for relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia or lymphoid blast phase of chronic myeloid leukemia. Am J Hematol. 2021;96:1000-1007. doi: 10.1002/AJH.26238

29. Ribera JM, Oriol A, González M, Vidriales B, Brunet S, Esteve J, et al. Concurrent intensive chemotherapy and imatinib before and after stem cell transplantation in newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. Final results of the CSTIBES02 trial. Haematologica. 2010;95:87-95. doi: 10.3324/HAEMATOL.2009.011221

30. Caocci G, Vacca A, Ledda A, Murgia F, Piras E, Greco M, et al. Prophylactic and preemptive therapy with dasatinib after hematopoietic stem cell transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia. Biol Blood Marrow Transplant. 2012; 18:652-654. doi: 10.1016/J.BBMT.2011.12.587

31. Kebriaei P, Saliba R, Rondon G, Chiattone A, Luthra R, Anderlini P, et al. Long-term follow-up of allogeneic hematopoietic stem cell transplantation for patients with Philadelphia chromosome positive acute lymphoblastic leukemia: Impact of tyrosine kinase inhibitors on treatment outcomes. Biol Blood Marrow Transpl. 2012; 18:584-592. doi: 10.1016/j.bbmt.2011.08.011

32. Brissot E, Labopin M, Beckers MM, Socié G, Rambaldi A, Volin L, et al. Tyrosine kinase inhibitors improve long-term outcome of allogeneic hematopoietic stem cell transplantation for adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia. Haematologica. 2015;100:392-399. doi: 10.3324/HAEMATOL.2014.116954

33. Maher KR, McBride A, Amaraneni A, Okolo O, Farooqui SR, Anwer F. Post-allogeneic stem cell transplantation maintenance dasatinib in Philadelphia chromosome positive acute leukemia. Biol Blood Marrow Transplant. 2017; 23:S289. doi: 10.1016/J.BBMT.2016.12.201

34. Akahoshi Y, Nishiwaki S, Mizuta S, Ohashi K, Uchida N, Tanaka M, et al. Tyrosine kinase inhibitor prophylaxis after transplant for Philadelphia chromosome-positive acute lymphoblastic leukemia. Cancer Sci. 2019;110:3255-3266. doi: 10.1111/CAS.14167

35. Warraich Z, Tenneti P, Thai T, Hubben A, Amin H, McBride A, et al. Relapse prevention with tyrosine kinase inhibitors after allogeneic transplantation for philadelphia chromosome-positive acute lymphoblast leukemia: a systematic review. Biol Blood Marrow Transplant 2020;26:e55-64. doi: 10.1016/J.BBMT.2019.09.022

36. Saini N, Marin D, Ledesma C, Delgado R, Rondon G, Popat UR, et al. Impact of TKIs post-allogeneic hematopoietic cell transplantation in Philadelphia chromosome–positive ALL. Blood. 2020;136:1786-17899. doi: 10.1182/BLOOD.2019004685

37. Liu H, Xuan L, Lin R, Deng L, Fan Z, Nie D, et al. A new pre-emptive TKIs strategy for preventing relapse based on BCR/ABL monitoring for Ph+ALL undergoing allo-HCT: a prospective clinical cohort study. Leuk. 2020; 35:2054-63. doi: 10.1038/s41375-020-01090-4

38. Pfeifer H, Wassmann B, Bethge W, Dengler J, Bornhäuser M, Stadler M, et al. Randomized comparison of prophylactic and minimal residual disease-triggered imatinib after allogeneic stem cell transplantation for BCR-ABL1-positive acute lymphoblastic leukemia. Leukemia. 2013; 27:1254-1262. doi: 10.1038/LEU.2012.352

39. Shimoni A, Volchek Y, Koren-Michowitz M, Varda-Bloom N, Somech R, Shem-Tov N, et al. Phase 1/2 study of nilotinib prophylaxis after allogeneic stem cell transplantation in patients with advanced chronic myeloid leukemia or Philadelphia chromosome-positive acute lymphoblastic leukemia. Cancer. 2015;121:863-871. doi: 10.1002/CNCR.29141

40. Giebel S, Czyz A, Ottmann O, Baron F, Brissot E, Ciceri F, et al. 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. Cancer. 2016;122:2941-2951. doi: 10.1002/CNCR.30130

41. Prabahran A, Koldej R, Chee L, Ritchie D. Clinical features, pathophysiology, and therapy of poor graft function post-allogeneic stem cell transplantation. Blood Adv. 2022; 6:1947-1959. doi: 10.1182/BLOODADVANCES.2021004537

42. Shah B, Abboud R, Advani A, Aoun P, Boyer MW, Burke PW, et al. NCCN Guidelines Version 1.2022 Acute Lymphoblastic Leukemia Continue NCCN.

43. Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, et al. National institutes of health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: i. the 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant. 2015;21:389-401.e1. doi: 10.1016/J.BBMT.2014.12.001

44. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant 1995;15:825-8.

45. McGowan-Jordan J, Simon A, Schmid M. An International System for Human Cytogenetic Nomenclature 2016:Karger: Basel, New York.

46. Soverini S, Hochhaus A, Nicolini FE, Gruber F, Lange T, Saglio G, et al. BCR-ABL kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: recommendations from an expert panel on behalf of European LeukemiaNet. Blood. 2011; 118:1208-1215. doi: 10.1182/BLOOD-2010-12-326405

47. Li SQ, Fan QZ, Xu LP, Wang Y, Zhang XH, Chen H, et al. Different effects of pre-transplantation measurable residual disease on outcomes according to transplant modality in patients with Philadelphia chromosome positive ALL. Front Oncol. 2020; 10:320. doi: 10.3389/fonc.2020.00320

48. Nishiwaki S, Imai K, Mizuta S, Kanamori H, Ohashi K, Fukuda T, et al. Impact of MRD and TKI on allogeneic hematopoietic cell transplantation for Ph+ALL: a study from the adult ALL WG of the JSHCT. Bone Marrow Transplant. 2016 ;51:43-50. doi: 10.1038/bmt.2015.217

49. Lussana F, Intermesoli T, Gianni F, Boschini C, Masciulli A, Spinelli O, et al. Allogeneic: adult achieving molecular remission before allogeneic stem cell transplantation in adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: impact on relapse and long-term outcome biology of blood and marrow transplantation. Biol Blood Marrow Transpl. 2016; 22:1983-1987. doi: 10.1016/j.bbmt.2016.07.021

50. Chen H, Liu KY, Xu LP, Liu DH, Chen YH, Zhao XY, et al. Administration of imatinib after allogeneic hematopoietic stem cell transplantation may improve disease-free survival for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. J Hematol Oncol. 2012;5. doi: 10.1186/1756-8722-5-29

51. Burke MJ, Trotz B, Luo X, Baker KS, Weisdorf DJ, Wagner JE, et al. Allo-hematopoietic cell transplantation for Ph chromosome-positive ALL: impact of imatinib on relapse and survival. Bone Marrow Transplant. 2008; 43:107-113. doi: 10.1038/bmt.2008.296

52. Rudakova TA, Kulagin AD, Klimova OU, Golubovskaya IK, Darskaya EI, Bykova TA, et al. Severe "poor graft function" after allogeneic hematopoietic stem cell transplantation in adult patients: Incidence, risk factors, and outcomes. Klin Onkogematologiya/Clinical Oncohematology. 2019;12:309-318. (In Russian). doi: 10.21320/2500-2139-2019-12-3-309-318

53. Ribera JM, Oriol A, González M, Vidriales B, Brunet S, Esteve J, et al. Concurrent intensive chemotherapy and imatinib before and after stem cell transplantation in newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. Final results of the CSTIBES02 trial. Haematologica. 2010; 95:87-95. doi: 10.3324/HAEMATOL.2009.011221

54. Porkka K, Koskenvesa P, Lundán T, Rimpiläinen J, Mustjoki S, Smykla R, et al. Dasatinib crosses the blood-brain barrier and is an efficient therapy for central nervous system Philadelphia chromosome-positive leukemia. Blood. 2008; 112:1005-1012. doi: 10.1182/BLOOD-2008-02-140665

55. Varda-Bloom N, Danylesko I, Shouval R, Eldror S, Lev A, Davidson J, et al. Immunological effects of nilotinib prophylaxis after allogeneic stem cell transplantation in patients with advanced chronic myeloid leukemia or philadelphia chromosome-positive acute lymphoblastic leukemia. Oncotarget. 2016; 8:418-429. doi: 10.18632/ONCOTARGET.13439

56. Shimoni A, Volchek Y, Koren-Michowitz M, Varda-Bloom N, Somech R, Shem-Tov N, et al. Phase 1/2 study of nilotinib prophylaxis after allogeneic stem cell transplantation in patients with advanced chronic myeloid leukemia or Philadelphia chromosome-positive acute lymphoblastic leukemia. Cancer. 2015; 121:863-871. doi: 10.1002/CNCR.29141

57. Leis JF, Stepan DE, Curtin PT, Ford JM, Peng B, Schubach S, et al. Central nervous system failure in patients with chronic myelogenous leukemia lymphoid blast crisis and Philadelphia chromosome positive acute lymphoblastic leukemia treated with imatinib (STI-571). Leuk Lymphoma. 2004;45:695-698. doi: 10.1080/10428190310001625728

58. Soverini S, De Benedittis C, Papayannidis C, Paolini S, Venturi C, Iacobucci I, et al. Drug resistance and BCR-ABL kinase domain mutations in Philadelphia chromosome-positive acute lymphoblastic leukemia from the imatinib to the second-generation tyrosine kinase inhibitor era: The main changes are in the type of mutations, but not in the frequency of mutation involvement. Cancer. 2014; 120:1002-1009. doi: 10.1002/CNCR.28522

59. Zhang FH, Ling YW, Zhai X, Zhang Y, Huang F, Fan ZP, et al. The effect of imatinib therapy on the outcome of allogeneic stem cell transplantation in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia. Hematology. 2013; 18:151-157. doi: 10.1179/1607845412Y.0000000052

60. Saidu NEB, Bonini C, Dickinson A, Grce M, Inngjerdingen M, Koehl U, et al. New approaches for the treatment of chronic graft-versus-host disease: current status and future directions. Front Immunol. 2020; 11:2625. doi: 10.3389/fimmu.2020.578314

61. Parra Salinas I, Bermudez A, López Corral L, Lopez Godino O, Móles-Poveda P, Martín G, et al. Treatment of steroid-refractory chronic graft-versus-host disease with imatinib: Real-life experience of the Spanish group of hematopoietic transplantation (GETH). Clin Transplant. 2021;35. doi: 10.1111/CTR.14255

62. Moiseev IS, Pirogova OV, Alyanski AL, Babenko EV, Gindina TL, Darskaya EI, et al. Graft-versus-host disease prophylaxis in unrelated peripheral blood stem cell transplantation with post-transplantation cyclophosphamide, tacrolimus, and mycophenolate mofetil. Biol Blood Marrow Transplant. 2016; 22:1037-1042. doi: 10.1016/J.BBMT.2016.03.004

63. Moiseev IS, Morozova EV, Bykova TA, Paina OV, Smirnova AG, Dotsenko AA, et al. Long-term outcomes of ruxolitinib therapy in steroid-refractory graft-versus-host disease in children and adults. Bone Marrow Transplant. 2020; 55:1379-1387. doi: 10.1038/s41409-020-0834-4

64. Marinelli Busilacchi E, Costantini A, Mancini G, Tossetta G, Olivieri J, Poloni A, et al. Nilotinib treatment of patients affected by chronic graft-versus-host disease reduces collagen production and skin fibrosis by downmodulating the TGF-β and p-SMAD pathway. Biol Blood Marrow Transplant. 2020; 26:823-834. doi: 10.1016/j.bbmt.2020.01.014

65. Petrungaro A, Gentile M, Mazzone C, Greco R, Uccello G, Recchia AG, et al. Ponatinib-induced graft-versus-host disease/graft-versus-leukemia effect in a patient with Philadelphia-positive acute lymphoblastic leukemia without the T315I mutation relapsing after allogeneic transplant. Chemotherapy. 2017; 62:353-356. doi: 10.1159/000477714

Ингибиторы тирозинкиназ: профилактика рецидива после аллогенной трансплантации гемопоэтических стволовых клеток у взрослых пациентов с Ph-позитивным острым лимфобластным лейкозом

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Резюме

Роль профилактического назначения ИТК (ингибиторов тирозинкиназ) после аллогенной трансплантации гемопоэтических стволовых клеток (алло-ТГСК) остается не вполне определенной. Мы провели ретроспективный анализ 106 случаев алло-ТГСК у взрослых пациентов, которым трансплантация была выполнена от полностью совместимого родственного донора (26%), полностью или частично совместимого неродственного донора (60%) и гаплоидентичного донора (14%) в первой полной ремиссии (59%), второй полной ремиссии (14%) или в продвинутых стадиях заболевания (27%). Из них 60 пациентам (57%) проводилась профилактика посттрансплантационного рецидива ингибиторами тирозинкиназ 1 или 2 поколения. В многофакторном анализе безрецидивной выживаемости следующие факторы были связаны со снижением риска рецидива или смерти: алло-ТГСК, выполненная после 2012 года (ОР=0,46, 95% ДИ 0,26-0,83, p=0,009), любой статус МОБ перед алло-ТГСК на фоне посттрансплантационной профилактики ИТК. Алло-ТГСК от гаплоидентичного донора повышала риск рецидива или смерти (ОР=2,71, 95% ДИ 1,20-6,13, p=0,016). Нам не удалось продемонстрировать значимость хронической РТПХ при проведении лэндмарк анализа на день+180 и день+270 на имеющихся данных (ОР=0,43, 95% ДИ 0,13–1,45, p=0,17 и ОР=0,5, 95% ДИ 0,19-1,32, p=0,161, соответственно) на фоне профилактической терапии ИТК. Настоящее исследование, проведенное на относительно большой группе взрослых пациентов с Ph-позитивным ОЛЛ, демонстрирует, что ИТК являются важным компонентом профилактики посттрансплантационного рецидива. Для того, чтобы сформулировать строгие клинические рекомендации для данной когорты, необходима большая группа пациентов.

Ключевые слова

Острый лимфобластный лейкоз, Ph-позитивный, BCR-ABL1, ингибиторы тирозинкиназ, аллогенная трансплантация гемопоэтических стволовых клеток, рецидив, минимальная остаточная болезнь, хроническая реакция «трансплантат-против-хозяина».