Received: 19 July 2019 | Revised: 6 August 2019 | Accepted: 8 August 2019

DOI: 10.1111/cas.14167

ORIGINAL ARTICLE

Cancer Science WILEY

Tyrosine kinase inhibitor prophylaxis after transplant for Philadelphia chromosome-positive acute lymphoblastic leukemia

Yu Akahoshi[1] | Satoshi Nishiwaki[2] | Shuichi Mizuta[3] | Kazuteru Ohashi[4] | Naoyuki Uchida[5] | Masatsugu Tanaka[6] | Takahiro Fukuda[7] | Yukiyasu Ozawa[8] | Satoshi Takahashi[9] | Makoto Onizuka[10] | Souichi Shiratori[11] | Hirohisa Nakamae[12] | Yoshinobu Kanda[1,13] | Tatsuo Ichinohe[14] | Yoshiko Atsuta[15] | Shinichi Kako[1] | On behalf of the Adult Acute Lymphoblastic Leukemia Working Group of the Japan Society for Hematopoietic Cell Transplantation

[1]Division of Hematology, Jichi Medical University Saitama Medical Center, Saitama, Japan

[2]Department of Advanced Medicine, Nagoya University Hospital, Nagoya, Japan

[3]Department of Hematology & Immunology, Kanazawa Medical University, Ishikawa, Japan

[4]Hematology Division, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan

[5]Department of Hematology, Federation of National Public Service Personnel Mutual Aid Associations Toranomon Hospital, Tokyo, Japan

[6]Department of Hematology, Kanagawa Cancer Center, Yokohama, Japan

[7]Division of Hematopoietic Stem Cell Transplantation, National Cancer Center Hospital, Tokyo, Japan

[8]Department of Hematology, Japanese Red Cross Nagoya First Hospital, Nagoya, Japan

[9]Division of Molecular Therapy, The Advanced Clinical Research Centre, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan

[10]Department of Hematology and Oncology, Tokai University School of Medicine, Kanagawa, Japan

[11]Department of Hematology, Hokkaido University Faculty of Medicine, Sapporo, Japan

[12]Department of Hematology, Osaka City University Graduate School of Medicine, Osaka, Japan

[13]Division of Hematology, Department of Medicine, Jichi Medical University, Tochigi, Japan

[14]Department of Hematology and Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan

[15]Japanese Data Center for Hematopoietic Cell Transplantation, Nagoya, Japan

Correspondence
Shinichi Kako, Division of Hematology, Saitama Medical Center, Jichi Medical University, Saitama, Japan.
Email: shinichikako@asahi-net.email.ne.jp

Abstract

Tyrosine kinase inhibitor (TKI) administration after allogeneic hematopoietic stem cell transplantation (HSCT) may carry a survival benefit in Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). Therefore, we investigated whether TKI prophylaxis for negative-minimal residual disease (MRD) after HSCT would improve patient outcomes in this nationwide retrospective cohort study. We included patients with Ph+ ALL who underwent their first allogeneic HSCT between 2001 and 2016, received TKI before HSCT, and achieved negative-MRD status within 180 days after HSCT. Of 850 patients for inclusion, 50 patients received TKI prophylaxis, mostly imatinib or dasatinib (median dose: 400 mg with imatinib and

40 mg with dasatinib). In a multivariate analysis, disease status at HSCT was the sole risk factor for relapse (hazard ratio, 3.58; $P < .001$ for positive-MRD with complete remission [CR] and hazard ratio, 6.13; $P < .001$ for active disease). TKI prophylaxis was not associated with a decreased risk of relapse or superior overall survival in either the whole cohort or in the analysis limited to negative-MRD or positive-MRD with CR1 at HSCT. Meanwhile, TKI prophylaxis limited to dasatinib might be associated with a decreased risk of relapse (hazard ratio, 0.34; $P = .140$), unlike imatinib. Alternative strategies using new-generation TKI for high-risk patients are warranted to improve the outcomes after allogeneic HSCT.

KEYWORDS
dasatinib, imatinib, minimal residual disease, Philadelphia chromosome-positive acute lymphoblastic leukemia, post-transplant tyrosine kinase inhibitor

1 | INTRODUCTION

Philadelphia chromosome (Ph) is the most common cytogenetic abnormality and is associated with dismal outcomes in adult acute lymphoblastic leukemia (ALL).[1,2] Introduction of tyrosine kinase inhibitor (TKI) has dramatically improved the survival outcomes in patients with Ph+ ALL.[3-6] However, relapse is the major problem in patients without allogeneic hematopoietic stem cell transplantation (HSCT) as a result of a high frequency of BCR-ABL1 kinase domain mutations.[7-9] Although allogenic HSCT might not be needed in patients with an early molecular response, which is achieved more frequently with second- or third-generation TKI, the long-term outcome is uncertain.[10-12] Therefore, allogeneic HSCT is the preferred curative approach for Ph+ ALL in current clinical practice.[13,14]

Development of the ability to detect minimal residual disease (MRD) far below the level of 5% blast cells has changed the landscape of risk stratification over the last decade.[11,15-17] Several studies have shown that chemotherapy combined with TKI, which gives a higher complete remission (CR) rate and further MRD reduction, enables allogenic HSCT in a larger proportion of patients.[18] Despite the evident benefit of giving TKI before allogenic HSCT, available data regarding the post-transplant use of TKI are limited.[19]

The largest study, which included 473 patients from the European Society for Blood and Marrow Transplantation (EBMT) Acute Leukemia Working Party, showed that post-transplant TKI was associated with a lower relapse rate and better overall survival.[6] However, this retrospective study included patients who did not receive TKI before HSCT and did not provide information on MRD status or the dose and timing of TKI. Consequently, it is unclear which patients derived this clinically relevant benefit. As a result of the particularly high relapse rate in patients with persistent positive-MRD or recurrent MRD detection after HSCT,[20,21] giving immediate TKI is recommended in these patients.[19] Meanwhile, the clinical benefit of giving prophylactic TKI before MRD detection is unclear. Suppression of tumor burden, not eradication, by giving TKI might be sufficient to achieve cure under a potent graft-versus-leukemia effect. In addition, because adverse events as a result of TKI after HSCT are common, the balance of risk and benefit of giving TKI after HSCT should be considered. Therefore, we conducted a nationwide retrospective study to evaluate whether TKI prophylaxis after allogenic HSCT in patients with negative-MRD would reduce relapse and improve overall survival.

2 | MATERIALS AND METHODS

2.1 | Data source and patient selection

Clinical data were obtained from the Transplant Registry Unified Management Program (TRUMP), which includes data from the Japan Society for Hematopoietic Cell Transplantation (JSHCT).[22,23]

This study included patients with Ph+ ALL aged more than 15 years who received TKI before HSCT and underwent their first allogenic HSCT between January 2001 and December 2016. Patients who did not achieve negative-MRD at first-time evaluation after HSCT were excluded. Cases of HSCT with peripheral blood from an unrelated donor were excluded as it is not allowed in Japan. This retrospective study was approved by the data management committee of TRUMP and by the Institutional Review Board of Saitama Medical Center, Jichi Medical University.

2.2 | Definitions of negative-MRD and treatment strategies

Minimal residual disease was determined by qualitative or real-time quantitative PCR. In most laboratories, qualitative PCR and real-time quantitative PCR were carried out based on previous reports,[24,25] and BCR-ABL mRNA copy numbers normalized relative to the number of transcripts of GAPDH were converted to copies per microgram of RNA. The threshold for quantification was 50 copies per microgram of RNA. Below this threshold by real-time quantitative PCR or an undetectable level by qualitative PCR was defined as negative-MRD. MRD status at HSCT was evaluated within 30 days prior to HSCT. Only data on MRD at HSCT and first-time evaluation after HSCT were available in this database.

Giving TKI within 180 days after HSCT in a patient who maintained negative-MRD was defined as prophylactic TKI. Upon the detection of MRD, the attending doctors at each institution made a clinical decision about whether to apply further observation or a treatment intervention. The end of TKI prophylaxis was defined until death, hematological relapse or discontinuation of TKI.

2.3 | Endpoints and statistical analysis

Primary endpoint was hematological relapse and secondary endpoints were overall survival and the incidence of chronic graft-versus-host disease (GVHD). Cumulative incidences of hematological relapse and GVHD were calculated by Gray's method. Probability of overall survival was estimated by the Kaplan-Meier method. Cox proportional hazards regression models were used to evaluate the impact of TKI prophylaxis and confounding variables. TKI prophylaxis, grade II-IV acute GVHD, and chronic GVHD were treated as time-dependent covariates. Impact of TKI prophylaxis was graphically illustrated using Simon-Makuch plots.[26] In subgroup analyses to determine the impact of TKI prophylaxis using imatinib or dasatinib, TKI prophylaxis using other than the target TKI were treated as censoring events.

The following variables were considered: the recipient's age at HSCT, recipient's gender (female vs male), performance status (0-1 vs 2-4), white blood cell count (WBC) at diagnosis (<30 000/μL vs ≥30 000/μL), breakpoint (minor vs major), time from diagnosis to HSCT (<180 days vs ≥180 days), donor source (human leukocyte antigen [HLA]-matched related donor vs HLA-mismatched related donor vs unrelated donor for bone marrow vs umbilical cord blood), conditioning intensity (myeloablative vs reduced-intensity), GVHD prophylaxis (cyclosporine-based vs tacrolimus-based), use of in vivo T-cell depletion, year of HSCT (2001-2011 vs 2012-2016), disease status at HSCT (negative-MRD with CR vs positive-MRD with CR vs active disease), grade II-IV acute GVHD, chronic GVHD and TKI prophylaxis. Additional cytogenetic abnormalities were not considered as confounding variables.[27] Acute and chronic GVHD were diagnosed by conventional criteria.[28,29] Intensity of the conditioning regimen was classified based on criteria from the Center for International Blood and Marrow Transplant Research.[30]

Factors with a two-sided *P* value of <.15 in univariate analyses and the use of TKI prophylaxis were included in multivariate analyses. All *P* values were two-sided and significance was set at .05. All statistical analyses were carried out with SAS (version 9.4) and EZR version 1.37,[31] which is a graphical user interface for R (version 3.2.2). The analyses including time-dependent covariates were completed with the use of PROC PHREG in SAS software.

3 | RESULTS

3.1 | Patient characteristics

During the study period, 1149 patients with Ph+ ALL received their first allogenic HSCT. One-hundred and sixty-five patients whose MRD information early after HSCT was not available and 134 patients who did not achieve negative-MRD after HSCT were excluded. Overall, we evaluated 850 patients who underwent their first allogenic HSCT and achieved negative-MRD within 180 days after HSCT (Table 1). Median observation period of the survivors was 1539 days (range, 91-5672 days) and the 4-year overall survival rate was 72.1% (95% confidence interval [CI], 68.7%-75.3%). Cumulative incidences of hematological relapse, grade II-IV acute GVHD and chronic GVHD were 12.6% (95% CI, 10.3%-15.0%), 43.2% (95% CI, 39.8%-46.5%) and 39.5% (95% CI, 36.2%-42.8%), respectively. In our cohort, 50 patients received TKI prophylaxis, and median time from HSCT to prophylaxis was 62.5 days (range, 21-180 days). Imatinib (44%) and dasatinib (54%) were commonly given as TKI prophylaxis. Median observation period of the survivors who received TKI prophylaxis with imatinib and dasatinib was 2561 days (range, 605-4796 days) and 1198 days (range, 309-1949 days), respectively. Median mode doses of imatinib and dasatinib were 400 mg per day (range, 60-600 mg per day) and 40 mg per day (range, 20-100 mg per day), respectively. Median duration of giving prophylactic TKI was 175.5 days (range, 3-3127 days). Of the 50 patients with TKI prophylaxis, six patients developed hematological relapse. Among these six patients, five patients continued TKI until hematological relapse, and one patient who received TKI prophylaxis between day + 56 and day + 146 ultimately developed hematological relapse at day + 462. Associations between patient characteristics and the cumulative incidence of TKI prophylaxis were evaluated using Cox proportional hazards regression models (Table 2). Multivariate analysis showed that prophylactic TKI was more frequently given during the late time periods of HSCT (hazard ratio [HR], 1.86; 95% CI, 1.02-3.38; *P* = .042) or with positive-MRD at HSCT (HR, 2.25; 95% CI, 1.21-4.16; *P* = .010). There was a trend toward less frequent administration of TKI prophylaxis in patients who developed grade II-IV acute GVHD (HR, 0.52; 95% CI, 0.27-1.01; *P* = .055).

3.2 | Impact of TKI prophylaxis on hematological relapse, overall survival and chronic GVHD

Four-year cumulative incidences of hematological relapse without TKI prophylaxis (n = 800) were 12.6% (95% CI, 10.2%-15.1%). According to the univariate analysis regarding hematological relapse, WBC at diagnosis, donor source, conditioning intensity, and disease status at HSCT were considered the confounding variables (*P* < .15). Multivariate analysis showed that disease status at HSCT was the sole independent risk factor for hematological relapse (HR, 3.58; 95% CI, 2.30-5.57; *P* < .001 for positive-MRD with CR, and HR, 6.13; 95% CI, 3.12-12.04; *P* < .001 for active disease) (Table 3). TKI prophylaxis as a time-dependent covariate did not significantly affect hematological relapse in a multivariate analysis (HR, 0.69; 95% CI, 0.30-1.59; *P* = .384). A Simon-Makuch plot was constructed to illustrate the effect of TKI prophylaxis on hematological relapse (Figure 1A).

We next evaluated the effect of TKI prophylaxis on overall survival. Univariate analysis showed that age at HSCT, performance status, WBC at diagnosis, time from diagnosis to HSCT,

TABLE 1 Characteristics of patients who underwent their first allogenic HSCT and achieved negative-MRD within 180 days after HSCT

	Disease status at HSCT			
	Whole cohort	Negative-MRD	Positive-MRD	Active disease
	n = 850	n = 585	n = 163	n = 38
Median age at HSCT, y (range)	46 (16-71)	46 (16-70)	46 (16-71)	45.5 (16-67)
Recipient gender				
Female	367 (43.2)	259 (44.3)	64 (39.3)	16 (42.1)
Male	483 (56.8)	326 (55.7)	99 (60.7)	22 (57.9)
Performance status				
0-1	792 (93.2)	549 (93.8)	149 (91.4)	30 (78.9)
2-4	52 (6.1)	34 (5.8)	10 (6.1)	8 (21.1)
Missing data	6 (0.7)	2 (0.3)	4 (2.5)	0 (0)
WBC at diagnosis				
<30 000/μL	473 (55.7)	339 (57.9)	75 (46.0)	17 (44.7)
≥30 000/μL	363 (42.7)	236 (40.3)	87 (53.4)	18 (47.4)
Missing data	14 (1.7)	10 (1.7)	1 (0.6)	3 (7.9)
Breakpoint				
Minor	639 (75.2)	438 (74.9)	118 (72.4)	30 (78.9)
Major	169 (19.9)	114 (19.5)	41 (25.2)	6 (15.8)
Both	24 (2.8)	19 (3.2)	2 (1.2)	2 (5.3)
Missing data	18 (2.1)	14 (2.4)	2 (1.2)	0 (0)
Time from diagnosis to HSCT				
<180 d	398 (46.8)	288 (49.2)	71 (43.6)	8 (21.1)
≥180 d	451 (53.1)	296 (50.6)	92 (56.4)	30 (78.9)
Missing data	1 (0.1)	1 (0.2)	0 (0)	0 (0)
Donor source				
HLA-matched related	192 (22.6)	128 (21.9)	36 (22.1)	8 (21.1)
HLA-mismatched related	38 (4.5)	16 (2.7)	13 (8.0)	6 (15.8)
Unrelated, bone marrow	400 (47.1)	291 (49.7)	66 (40.5)	16 (42.1)
Unrelated, cord blood	220 (25.9)	150 (25.6)	48 (29.4)	8 (21.1)
Conditioning intensity				
Myeloablative	610 (71.8)	425 (72.6)	118 (72.4)	23 (60.5)
Reduced intensity	239 (28.1)	159 (27.2)	45 (27.6)	15 (39.5)
Missing data	1 (0.1)	1 (0.2)	0 (0)	0 (0)
GVHD prophylaxis				
CSA-based	296 (34.8)	203 (34.7)	64 (39.3)	9 (23.7)
TAC-based	540 (63.5)	369 (63.1)	98 (60.1)	29 (76.3)
Missing data	14 (1.7)	13 (2.2)	1 (0.6)	0 (0)
Use of in vivo T-cell depletion				
No	811 (95.4)	562 (96.1)	155 (95.1)	34 (89.5)
Yes	39 (4.6)	23 (3.9)	8 (4.9)	4 (10.5)
Year of HSCT				
2001-2011	413 (48.6)	271 (46.3)	92 (56.4)	15 (39.5)
2012-2016	437 (51.4)	314 (53.7)	71 (43.6)	23 (60.5)
Disease status at HSCT				
Negative-MRD with CR	585 (68.8)			
CR1	552 (94.4)			

(Continues)

TABLE 1 (Continued)

	Disease status at HSCT			
	Whole cohort	Negative-MRD	Positive-MRD	Active disease
	n = 850	n = 585	n = 163	n = 38
CR2 or CR3	33 (5.6)			
Positive-MRD with CR	163 (19.2)			
CR1	148 (90.8)			
CR2 or CR3	15 (9.2)			
Active disease	38 (4.5)			
Missing data for MRD status at HSCT	64 (7.5)			
Final use of TKI before HSCT				
Imatinib	505 (59.4)	366 (62.6)	89 (54.6)	12 (31.6)
Dasatinib	340 (40.0)	216 (36.9)	73 (44.8)	25 (65.8)
Nilotinib	5 (0.6)	3 (0.5)	1 (0.6)	1 (2.6)
Median time from HSCT to prophylaxis, days (range)	62.5 (21-180)	92 (21-180)	49.5 (21-161)	55 (42-62)
TKI prophylaxis				
Imatinib	22 (44.0)	17 (56.7)	4 (25.0)	1 (33.3)
Dasatinib	27 (54.0)	12 (40.0)	12 (75.0)	2 (66.7)
Nilotinib	1 (2.0)	1 (3.3)	0 (0)	0 (0)
Median dose of TKI prophylaxis, mg per day (range)				
Imatinib	400 (60-600)	400 (60-600)	400 (100-600)	400 (400-400)
Dasatinib	40 (20-100)	40 (20-50)	50 (20-100)	35 (20-50)
Median duration of prophylactic TKI exposure, days (range)	175.5 (3-3127)	105 (3-2757)	288.5 (5-3127)	44 (35-220)
Imatinib	140 (3-3127)	90 (3-2757)	1978 (97-3127)	35 (35-35)
Dasatinib	187 (5-802)	136.5 (12-642)	227 (5-802)	132 (44-220)

Abbreviations: CR, complete remission; CSA, cyclosporine; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease; TAC, tacrolimus; TKI, tyrosine kinase inhibitor; WBC, white blood cell count.

donor source, conditioning intensity, disease status at HSCT, grade II-IV acute GVHD, and chronic GVHD were associated with poor overall survival with at least borderline significance ($P < .15$). In the multivariate analysis, age at HSCT (HR, 1.03; 95% CI 1.01-1.04; $P < .001$), disease status at HSCT (HR, 1.96; 95% CI, 1.45-2.64; $P < .001$ for positive-MRD with CR, and HR, 2.59; 95% CI, 1.52-4.41; $P = .001$ for active disease), and grade II-IV acute GVHD (HR, 1.92; 95% CI, 1.46-2.53; $P < .001$) were significantly associated with inferior overall survival. TKI prophylaxis was not significantly associated with superior overall survival in a multivariate analysis (HR, 0.76; 95% CI, 0.42-1.37; $P = .367$) (Table 3). Effect of TKI prophylaxis on overall survival was illustrated using the Simon-Makuch method (Figure 1B).

We also determined the association between the incidence of chronic GVHD and TKI prophylaxis. In the multivariate analysis, WBC at diagnosis (HR, 1.36; 95% CI, 1.10-1.68; $P = .004$), unrelated cord blood transplantation (HR, 0.70; 95% CI, 0.52-0.95; $P = .022$), reduced conditioning intensity (HR, 0.77; 95% CI, 0.60-0.99; $P = .042$) and grade II-IV acute GVHD (HR, 1.36; 95% CI, 1.10-1.68; $P = .004$) were significantly associated with the incidence of chronic GVHD (Table S1). The incidence of chronic GVHD was not significantly associated with TKI prophylaxis in the multivariate analysis (HR, 0.82; 95% CI, 0.49-1.35; $P = .428$).

3.3 | Impact of TKI prophylaxis in patients with negative-MRD or positive-MRD at HSCT

Disease status at HSCT was significantly associated with hematological relapse and overall mortality even if patients achieved negative-MRD early after HSCT ($P < .001$, respectively) (Figure 2). Cumulative incidence of hematological relapse at 4 years was 7.8% (95% CI, 5.7%-10.4%) for negative-MRD with CR at HSCT, 24.4% (95% CI, 17.8%-31.5%) for positive-MRD with CR at HSCT, and 36.3% (95% CI, 20.6%-52.2%) for active disease at HSCT. Probability of overall survival at 4 years was 76.5% (95% CI, 72.5%-80.0%) for negative-MRD with CR at HSCT, 62.2% (95% CI, 53.7%-69.7%) for positive-MRD with CR at HSCT, and 40.2% (95% CI, 20.7%-58.9%) for active disease at HSCT. These results

TABLE 2 Associations between patient characteristics and TKI prophylaxis

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age at HSCT	1.01 (0.99-1.03)	.503		
Recipient gender				
Female	1	Reference		
Male	0.97 (0.56-1.70)	.926		
Performance status				
0-1	1	Reference		
2-4	1.79 (0.71-4.50)	.218		
WBC at diagnosis				
<30 000/μL	1	Reference		
≥30 000/μL	1.32 (0.76-2.29)	.331		
Breakpoint				
Minor	1	Reference		
Major	0.75 (0.40-1.41)	.375		
Time from diagnosis to HSCT				
<180 d	1	Reference		
≥180 d	0.89 (0.51-1.55)	.677		
Donor source				
HLA-matched related	1	Reference		
HLA-mismatched related	1.20 (0.34-4.19)	.781		
Unrelated, bone marrow	0.67 (0.33-1.37)	.272		
Unrelated, cord blood	1.07 (0.52-2.23)	.854		
Conditioning intensity				
Myeloablative	1	Reference		
Reduced intensity	1.00 (0.54-1.85)	1.000		
GVHD prophylaxis				
CSA-based	1	Reference		
TAC-based	0.71 (0.40-1.25)	.233		
Use of in vivo T-cell depletion				
No	1	Reference		
Yes	0.84 (0.20-3.44)	.803		
Year of HSCT				
2001-2011	1	Reference	1	Reference
2012-2016	1.56 (0.88-2.77)	.125	1.86 (1.02-3.38)	.042
Disease status at HSCT				
Negative-MRD with CR	1	Reference	1	Reference
Positive-MRD with CR	2.10 (1.14-3.87)	.017	2.25 (1.21-4.16)	.010
Active disease	1.69 (0.51-5.54)	.389	1.69 (0.51-5.56)	.388
Grade II-IV acute GVHD[a]	0.55 (0.29-1.05)	.068	0.52 (0.27-1.01)	.055
Chronic GVHD[a]	0.95 (0.32-2.82)	.930		

Abbreviations: CI, confidence interval; CR, complete remission; CSA, cyclosporine; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease; TAC, tacrolimus; TKI, tyrosine kinase inhibitor; WBC, white blood cell count.

[a]Time-dependent covariate.

encouraged us to carry out post hoc analyses to identify each disease status at HSCT for which TKI prophylaxis may be beneficial. Cases of active disease at HSCT were not evaluated because of the limited number of patients.

TABLE 3 Risk factors for hematological relapse and overall survival in univariate and multivariate analyses

	Hematological relapse				Overall survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age at HSCT	1.01 (0.99-1.02)	.274			1.03 (1.02-1.04)	<.001	1.03 (1.01-1.04)	<.001
Recipient gender								
Female	1	Reference			1	Reference		
Male	1.05 (0.71-1.55)	.824			1.20 (0.92-1.55)	.175		
Performance status								
0-1	1	Reference			1	Reference	1	Reference
2-4	0.86 (0.35-2.11)	.740			1.48 (0.91-2.39)	.112	1.19 (0.72-1.97)	.492
WBC at diagnosis								
<30 000/μL	1	Reference	1	Reference	1	Reference	1	Reference
≥30 000/μL	1.46 (0.99-2.15)	.059	1.40 (0.92-2.12)	.114	1.22 (0.94-1.58)	.130	1.25 (0.95-1.63)	.112
Breakpoint								
Minor	1	Reference			1	Reference		
Major	1.12 (0.69-1.81)	.642			0.99 (0.73-1.35)	.959		
Time from diagnosis to HSCT								
<180 d	1	Reference			1	Reference	1	Reference
≥180 d	1.30 (0.88-1.93)	.184			1.53 (1.17-1.99)	.002	1.27 (0.94-1.70)	.115
Donor source								
HLA-matched related	1	Reference	1	Reference	1	Reference	1	Reference
HLA-mismatched related	1.99 (0.89-4.46)	.093	1.20 (0.49-2.95)	.694	1.60 (0.88-2.90)	.122	1.15 (0.60-2.23)	.672
Unrelated, bone marrow	0.94 (0.56-1.56)	.797	1.08 (0.63-1.86)	.779	1.28 (0.92-1.78)	.150	1.20 (0.83-1.75)	.329
Unrelated, cord blood	1.22 (0.71-2.10)	.476	1.24 (0.69-2.22)	.481	1.07 (0.72-1.57)	.749	0.96 (0.63-1.47)	.852
Conditioning intensity								
Myeloablative	1	Reference	1	Reference	1	Reference	1	Reference
Reduced intensity	1.57 (1.05-2.36)	.028	1.44 (0.92-2.26)	.108	1.37 (1.04-1.80)	.024	1.07 (0.75-1.52)	.709
GVHD prophylaxis								
CSA-based	1	Reference			1	Reference		
TAC-based	0.92 (0.62-1.38)	.699			1.17 (0.89-1.53)	.254		

(Continues)

TABLE 3 (Continued)

	Hematological relapse				Overall survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Use of in vivo T-cell depletion								
No	1	Reference			1	Reference		
Yes	1.40 (0.61-3.19)	.430			0.94 (0.48-1.83)	.850		
Year of HSCT								
2001-2011	1	Reference			1	Reference		
2012-2016	1.11 (0.75-1.66)	.606			1.05 (0.80-1.37)	.741		
Disease status at HSCT								
Negative-MRD with CR	1	Reference	1	Reference	1	Reference	1	Reference
Positive-MRD with CR	3.83 (2.49-5.89)	<.001	3.58 (2.30-5.57)	<.001	1.95 (1.46-2.60)	<.001	1.96 (1.45-2.64)	<.001
Active disease	7.00 (3.75-13.06)	<.001	6.13 (3.12-12.04)	<.001	3.03 (1.84-4.96)	<.001	2.59 (1.52-4.41)	.001
Grade II-IV acute GVHD[a]	0.93 (0.63-1.38)	.717			1.89 (1.46-2.44)	<.001	1.92 (1.46-2.53)	<.001
Chronic GVHD[a]	0.81 (0.52-1.25)	.337			1.22 (0.94-1.60)	.135	1.19 (0.90-1.58)	.232
TKI prophylaxis[a]								
No	1	Reference	1	Reference	1	Reference	1	Reference
Yes	0.99 (0.43-2.26)	.983	0.69 (0.30-1.59)	.384	0.90 (0.51-1.57)	.708	0.76 (0.42-1.37)	.367

Abbreviations: CI, confidence interval; CR, complete remission; CSA, cyclosporine; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease; TAC, tacrolimus; TKI, tyrosine kinase inhibitor; WBC, white blood cell count.

[a]Time-dependent covariate.

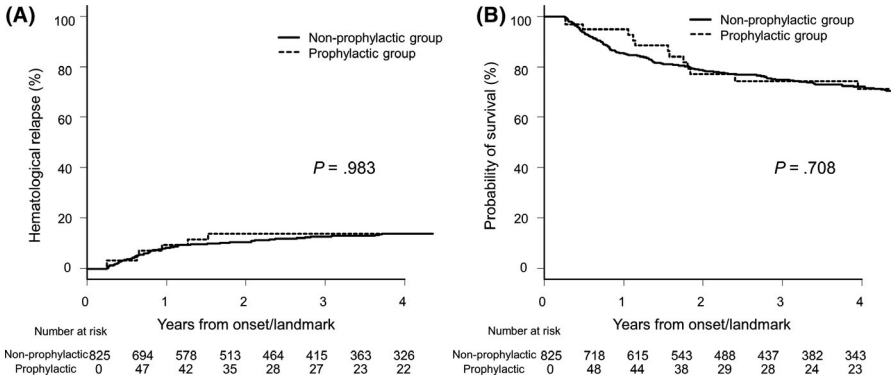

FIGURE 1 Simon-Makuch plot for the effect of tyrosine kinase inhibitor prophylaxis on the cumulative incidences of (A) hematological relapse and (B) overall survival, illustrated with a landmark at day 62.5, the median time from hematopoietic stem cell transplantation to prophylaxis

Median time from HSCT to prophylaxis for negative-MRD and positive-MRD with first CR (CR1) was 90 days (range, 21-166 days) and 49 days (range, 21-161 days), respectively. Effect of TKI prophylaxis on hematological relapse for negative-MRD and positive-MRD with CR1 were illustrated using the Simon-Makuch method (Figure S1). Multivariate analysis showed that none of the covariates was associated with hematological relapse in patients with negative-MRD and positive-MRD with CR1 (Table S2). Overall survival was also analyzed in the same subgroups. Overall, TKI prophylaxis had no significant impact on hematological relapse or overall mortality among patients with negative-MRD and positive-MRD with CR1 (Table S3).

3.4 | Impact of TKI choices

We also assessed the impact of TKI prophylaxis limited to imatinib or dasatinib. In the multivariate analyses, TKI prophylaxis with imatinib did not affect hematological relapse (HR, 1.29; 95% CI, 0.47-3.56; $P = .626$) and overall mortality (HR, 0.96; 95% CI, 0.45-2.05; $P = .906$) (Table S4). In a multivariate analysis limited to dasatinib, disease status at HSCT was the only risk factor for hematological relapse (HR, 3.79; 95% CI, 2.41-5.96; $P < .001$ for positive-MRD with CR, and HR, 6.85; 95% CI, 3.41-13.77; $P < .001$ for active disease) (Table S5). TKI prophylaxis with dasatinib might be associated with a decreased risk of hematological relapse, but was not statistically significant (HR, 0.34; 95% CI, 0.08-1.42; $P = .140$). For overall mortality, HR was 0.59 in patients with TKI prophylaxis using dasatinib (95% CI, 0.24-1.45; $P = .253$).

4 | DISCUSSION

We showed that TKI prophylaxis was not associated with a lower relapse rate or overall mortality in the whole cohort of this study. Pfeifer et al[32] conducted a randomized trial that compared prophylactic and MRD-triggered imatinib groups who achieved negative-MRD early after HSCT. This trial, which included 54 patients, showed that the probabilities of relapse-free survival and overall survival did not significantly differ, which is consistent with our results. Interestingly, the 5-year overall survival rates in these groups (80% for prophylactic and 74.5% for MRD-triggered) were remarkably high, as in our study (72.1% 4-year overall survival rate). Another study also showed that the 2-year overall survival rates in patients who achieved negative-MRD and persistent MRD early after HSCT were 80% and 13%, respectively.[21] These results confirm that achieving negative-MRD after HSCT is associated with a favorable survival outcome due to a lower relapse rate. The lack of benefit with TKI prophylaxis might be attributed to the outstanding outcome in these populations.

Importantly, we identified that disease status at HSCT was a powerful risk factor for hematological relapse even if patients achieved negative-MRD after HSCT. However, TKI prophylaxis was not associated with a decreased incidence of hematological relapse even in the subgroup analysis limited to positive-MRD with CR1 at HSCT. In contrast, TKI prophylaxis using dasatinib might reduce hematological relapse in multivariate analysis. As this analysis limited to dasatinib might lack the power to detect a meaningful difference because of the small sample

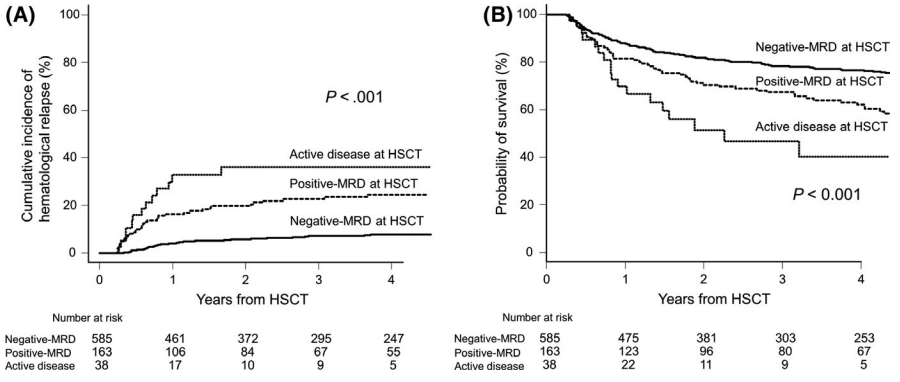

FIGURE 2 Cumulative incidences of (A) hematological relapse and (B) overall survival according to disease status at hematopoietic stem cell transplantation. HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease

size, this subgroup analysis needs to be interpreted with care. Several studies have shown that BCR-ABL1 kinase domain mutations are the major cause of relapse in Ph+ ALL.[7,8] Rousselot et al[9] reported that 10 of 43 patients (23%) at diagnosis had T315I mutations and eight of these 10 ultimately developed relapse despite undetectable MRD during CR. Another study suggested that tumor strains at post-transplant relapse had the same BCR-ABL1 kinase domain mutations before HSCT.[33] These findings suggest that disease status at HSCT may be associated with the presence of BCR-ABL1 kinase domain mutations. Therefore, patients with positive-MRD or active disease at HSCT require BCR-ABL1 kinase domain mutation analysis and close monitoring after HSCT, if possible. Considering the efficacy for BCR-ABL1 kinase domain mutation and the higher potency of second- or third-generation TKI, further investigation using new-generation TKI based on MRD status and BCR-ABL1 kinase domain mutation analysis is warranted.

Chronic GVHD is a well-recognized factor that influences relapse.[34] Several studies have reported TKI as a treatment option for steroid-refractory chronic GVHD[35,36] and TKI may reduce the incidence and severity of chronic GVHD.[37] Nevertheless, we did not observe a significant association between TKI prophylaxis and the incidence of chronic GVHD. Meanwhile, because parameters that reflect the severity of chronic GVHD such as National Institutes of Health severity scoring were not available in our database, the influence of TKI prophylaxis on the severity of chronic GVHD could not be evaluated. Further studies are required to confirm these results.

The dose, duration, and tolerability of TKI after HSCT are important topics. Side-effects of TKI such as gastrointestinal or hematological toxicities are common, especially after HSCT, and these adverse events often result in discontinuation or dose-reduction of TKI.[38,39] In the prospective trial by Pfeifer et al,[32] although criteria for starting imatinib included sufficient hematological recovery, adequate organ function, and absence of uncontrolled GVHD, approximately 70% of patients discontinued imatinib prematurely and required dose reduction. Other studies also showed that dasatinib and nilotinib required dose reduction because of intolerance.[14,40] In our cohort, the median dose (400 mg with imatinib and 40 mg with dasatinib), duration of TKI exposure (175.5 days), and time from HSCT to TKI prophylaxis (62.5 days) were comparable to those in previous prospective studies.[14,32] One of the strengths of our study was that information regarding dose, duration and onset of TKI administration were available, whereas the reasons for discontinuation or dose modification of TKI were uncertain. As the frequency of TKI prophylaxis tended to be lower in patients with acute GVHD in our analysis, we need to take into account a possible selection bias by the attending doctors regarding the administration of TKI even after adjusting for other confounding factors, such as GVHD and MRD status at HSCT.

The present study has other limitations. First, the second or subsequent MRD status after HSCT, and detailed information about treatment interventions after MRD detection were not available in our database. However, the impact of TKI given as prophylaxis before MRD detection could be evaluated despite the lack of this information. Second, the MRD detection method was not unified and centralized in this nationwide retrospective study. Therefore, a minimal sensitivity of MRD detection had variation to some extent. Third, the number of patients who were given TKI prophylaxis was not large, because the Japanese guidelines do not provide any recommendations about TKI prophylaxis after HSCT. It is presumed that TKI prophylaxis was carried out at the discretion of the attending physician. This was an exploratory retrospective study, and thus we did not calculate the sample size before collecting the samples. Based on 12.6% risk of hematological relapse without TKI prophylaxis in our cohort, which was lower than expected, large sample size with TKI prophylaxis might be needed to detect the impact of TKI prophylaxis with a statistically significant difference. This factor, along with the retrospective nature of the present study, requires that the current results be interpreted with caution. Because of the extraordinarily low risk of hematological relapse without TKI prophylaxis, TKI prophylaxis might be applied in selected patients who are more likely to relapse. Further studies using new-generation TKI for high-risk patients stratified by MRD status and BCR-ABL1 kinase domain mutation analysis will be needed.

In conclusion, disease status at HSCT was a significant risk factor for hematological relapse even in patients who achieved negative-MRD after HSCT. We failed to find a beneficial effect of TKI prophylaxis on hematological relapse or overall mortality despite MRD positivity at HSCT. In a subgroup analysis, TKI prophylaxis using dasatinib might be related to a lower frequency of hematological relapse. Given the lack of a large study that determined the effect of TKI prophylaxis, we believe this study provides an important insight for TKI use after HSCT in daily practice and for future studies.

ACKNOWLEDGMENTS

The authors greatly appreciate the contributions of many physicians and data managers throughout the JSHCT, the Japan Marrow Donor Program (JMDP), and the Japan Cord Blood Bank Network (JCBBN), who made this analysis possible. We would also like to thank the members of the Transplant Registry Unified Management committees at JSHCT, JMDP, and JCBBN for their dedicated management of data. This work was partly supported by the JMU Graduate Student Research Award. Thanks to the Adult Acute Lymphoblastic Leukemia Working Group of the Japan Society for Hematopoietic Cell Transplantation for its participation in this study.

DISCLOSURE

Authors declare no conflicts of interest for this article.

ORCID

Yu Akahoshi https://orcid.org/0000-0001-6825-9340

REFERENCES

1. Moorman AV, Harrison CJ, Buck GA, et al. Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical

Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. *Blood*. 2007;109:3189-3197.
2. Wetzler M, Dodge RK, Mrozek K, et al. Prospective karyotype analysis in adult acute lymphoblastic leukemia: the cancer and leukemia Group B experience. *Blood*. 1999;93:3983-3993.
3. Yanada M, Takeuchi J, Sugiura I, et al. High complete remission rate and promising outcome by combination of imatinib and chemotherapy for newly diagnosed BCR-ABL-positive acute lymphoblastic leukemia: a phase II study by the Japan Adult Leukemia Study Group. *J Clin Oncol*. 2006;24:460-466.
4. Mizuta S, Matsuo K, Nishiwaki S, et al. Pretransplant administration of imatinib for allo-HSCT in patients with BCR-ABL-positive acute lymphoblastic leukemia. *Blood*. 2014;123:2325-2332.
5. Thomas DA, Faderl S, Cortes J, et al. Treatment of Philadelphia chromosome-positive acute lymphocytic leukemia with hyper-CVAD and imatinib mesylate. *Blood*. 2004;103:4396-4407.
6. Brissot E, Labopin M, Beckers MM, 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.
7. Soverini S, Vitale A, Poerio A, et al. Philadelphia-positive acute lymphoblastic leukemia patients already harbor BCR-ABL kinase domain mutations at low levels at the time of diagnosis. *Haematologica*. 2011;96:552-557.
8. Soverini S, De Benedittis C, Papayannidis C, 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.
9. Rousselot P, Coude MM, Gokbuget N, et al. Dasatinib and low-intensity chemotherapy in elderly patients with Philadelphia chromosome-positive ALL. *Blood*. 2016;128:774-782.
10. Jabbour E, Kantarjian H, Ravandi F, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: a single-centre, phase 2 study. *Lancet Oncol*. 2015;16:1547-1555.
11. Short NJ, Jabbour E, Sasaki K, et al. Impact of complete molecular response on survival in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood*. 2016;128:504-507.
12. Wang J, Jiang Q, Xu LP, et al. Allogeneic stem cell transplantation versus tyrosine kinase inhibitors combined with chemotherapy in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Biol Blood Marrow Transplant*. 2018;24:741-750.
13. Chalandon Y, Thomas X, Hayette S, et al. Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. *Blood*. 2015;125:3711-3719.
14. Ravandi F, Othus M, O'Brien SM, et al. US intergroup study of chemotherapy plus dasatinib and allogeneic stem cell transplant in Philadelphia chromosome positive all. *Blood Adv*. 2016;1:250-259.
15. Bachanova V, Marks DI, Zhang MJ, et al. Ph+ ALL patients in first complete remission have similar survival after reduced intensity and myeloablative allogeneic transplantation: impact of tyrosine kinase inhibitor and minimal residual disease. *Leukemia*. 2014;28:658-665.
16. Lussana F, Intermesoli T, Gianni F, et al. 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. *Biol Blood Marrow Transplant*. 2016;22:1983-1987.
17. Nishiwaki S, Imai K, Mizuta S, 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.
18. Fielding AK. Philadelphia-positive acute lymphoblastic leukemia–is bone marrow transplant still necessary? *Biol Blood Marrow Transplant*. 2011;17:S84-S88.
19. Giebel S, Czyz A, Ottmann O, 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.
20. Radich J, Gehly G, Lee A, et al. Detection of bcr-abl transcripts in Philadelphia chromosome-positive acute lymphoblastic leukemia after marrow transplantation. *Blood*. 1997;89:2602-2609.
21. Wassmann B, Pfeifer H, Stadler M, et al. Early molecular response to posttransplantation imatinib determines outcome in MRD+ Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL). *Blood*. 2005;106:458-463.
22. Atsuta Y. Introduction of Transplant Registry Unified Management Program 2 (TRUMP2): scripts for TRUMP data analyses, part I (variables other than HLA-related data). *Int J Hematol*. 2016;103:3-10.
23. Kanda J. Scripts for TRUMP data analyses. Part II (HLA-related data): statistical analyses specific for hematopoietic stem cell transplantation. *Int J Hematol*. 2016;103:11-19.
24. Kawasaki ES, Clark SS, Coyne MY, et al. Diagnosis of chronic myeloid and acute lymphocytic leukemias by detection of leukemia-specific mRNA sequences amplified in vitro. *Proc Natl Acad Sci USA*. 1988;85:5698-5702.
25. Towatari M, Yanada M, Usui N, et al. Combination of intensive chemotherapy and imatinib can rapidly induce high-quality complete remission for a majority of patients with newly diagnosed BCR-ABL-positive acute lymphoblastic leukemia. *Blood*. 2004;104:3507-3512.
26. Simon R, Makuch RW. A non-parametric graphical representation of the relationship between survival and the occurrence of an event: application to responder versus non-responder bias. *Stat Med*. 1984;3:35-44.
27. Akahoshi Y, Mizuta S, Shimizu H, et al. Additional cytogenetic abnormalities with Philadelphia chromosome-positive acute lymphoblastic leukemia on allogeneic stem cell transplantation in the tyrosine kinase inhibitor era. *Biol Blood Marrow Transplant*. 2018;24:2009-2016.
28. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant*. 1995;15:825-828.
29. Sullivan KM, Agura E, Anasetti C, et al. Chronic graft-versus-host disease and other late complications of bone marrow transplantation. *Semin Hematol*. 1991;28:250-259.
30. Giralt S, Ballen K, Rizzo D, et al. Reduced-intensity conditioning regimen workshop: defining the dose spectrum. Report of a workshop convened by the center for international blood and marrow transplant research. *Biol Blood Marrow Transplant*. 2009;15:367-369.
31. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant*. 2013;48:452-458.
32. Pfeifer H, Wassmann B, Bethge W, 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.
33. Egan DN, Beppu L, Radich JP. Patients with Philadelphia-positive leukemia with BCR-ABL kinase mutations before allogeneic transplantation predominantly relapse with the same mutation. *Biol Blood Marrow Transplant*. 2015;21:184-189.
34. Negrin RS. Graft-versus-host disease versus graft-versus-leukemia. *Hematology Am Soc Hematol Educ Program*. 2015;2015:225-230.
35. Magro L, Mohty M, Catteau B, et al. Imatinib mesylate as salvage therapy for refractory sclerotic chronic graft-versus-host disease. *Blood*. 2009;114:719-722.
36. Olivieri A, Cimminiello M, Corradini P, et al. Long-term outcome and prospective validation of NIH response criteria in 39 patients

receiving imatinib for steroid-refractory chronic GVHD. *Blood*. 2013;122:4111-4118.
37. Nakasone H, Kanda Y, Takasaki H, et al. Prophylactic impact of imatinib administration after allogeneic stem cell transplantation on the incidence and severity of chronic graft versus host disease in patients with Philadelphia chromosome-positive leukemia. *Leukemia*. 2010;24:1236-1239.
38. Carpenter PA, Snyder DS, Flowers ME, et al. Prophylactic administration of imatinib after hematopoietic cell transplantation for high-risk Philadelphia chromosome-positive leukemia. *Blood*. 2007;109:2791-2793.
39. Chen H, Liu KY, Xu LP, 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;5:29.
40. Shimoni A, Volchek Y, Koren-Michowitz M, 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.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Akahoshi Y, Nishiwaki S, Mizuta S, et al. Tyrosine kinase inhibitor prophylaxis after transplant for Philadelphia chromosome-positive acute lymphoblastic leukemia. *Cancer Sci*. 2019;110:3255–3266. https://doi.org/10.1111/cas.14167