Int J Hematol (2015) 102:689–696
DOI 10.1007/s12185-015-1883-0

ORIGINAL ARTICLE

Effects of conditioning intensity in allogeneic stem cell transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia

Shuichiro Takashima[1,2] · Toshihiro Miyamoto[1] · Tomohiko Kamimura[2] · Goichi Yoshimoto[1] · Shuro Yoshida[3] · Hideho Henzan[3] · Ken Takase[3] · Koji Kato[1] · Yoshikiyo Ito[2,4] · Yuju Ohno[5] · Koji Nagafuji[6] · Tetsuya Eto[3] · Takanori Teshima[7] · Koichi Akashi[1]

Received: 13 May 2015 / Revised: 4 September 2015 / Accepted: 5 October 2015 / Published online: 16 October 2015
© The Japanese Society of Hematology 2015

Abstract We retrospectively analyzed the outcomes of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph^+ALL) who underwent first allogeneic stem cell transplantation (allo-SCT) at complete remission (CR) with myeloablative conditioning (MAC, $n = 31$) or reduced-intensity conditioning (RIC, $n = 15$) between 2001 and 2012. All the patients had received tyrosine kinase inhibitor (TKI)-based chemotherapy prior to allo-SCT. Overall survival (OS) rates (57 vs 63 %, $p = 0.53$), leukemia-free survival rates (50 vs 65 %, $p = 0.29$), and non-relapse mortality rates (39 vs 35 %, $p = 0.62$) at 2 years were similar between the MAC and RIC groups. The minimal residual disease (MRD) status evaluated by sensitive polymerase chain reaction prior to allo-SCT did not influence the OS rate (77 vs 54 %, $p = 0.28$) and leukemia-free survival rate (69 vs 51 %, $p = 0.48$), irrespective of the conditioning intensity. Our data suggest that the RIC regimen may represent a sufficient intensity of therapeutic pre-transplant conditioning for patients with Ph^+ALL who have maintained a hematological CR with TKI-combined chemotherapy.

Keywords Ph^+ALL · Tyrosine kinase inhibitor · Pretransplant conditioning · Allo-SCT · Minimal residual disease

✉ Toshihiro Miyamoto
toshmiya@intmed1.med.kyushu-u.ac.jp

1 Department of Medicine and Biosystemic Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

2 Department of Hematology, Harasanshin Hospital, 1-8 Taihaku-machi, Hakata-ku, Fukuoka 812-0033, Japan

3 Department of Hematology, Hamanomachi Hospital, 3-1-1 Nagahama Chuo-ku, Fukuoka 810-8539, Japan

4 Department of Internal Medicine, Kyushu University Beppu Hospital, 4546 Tsurumibaru, Tsurumi, Beppu 874-0838, Japan

5 Department of Internal Medicine, Kitakyushu Municipal Medical Center, 2-1-1 Bashaku, Kokurakita-ku, Kitakyushu 802-0077, Japan

6 Department of Medicine, Division of Hematology and Oncology, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan

7 Department of Hematology, Hokkaido University Graduate School of Medicine, N15 W7, Kita-Ku, Sapporo 060-8638, Japan

Introduction

Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph^+ALL) is a biologically and clinically distinct variant of ALL, and the prognosis of patients with Ph^+ALL is poor when treated with chemotherapy alone [1, 2]. Prior to the era of tyrosine kinase inhibitors (TKIs), the probability of disease-free survival was around 10 % [3–5] and approximately only a quarter of the patients could manage to receive allogeneic stem cell transplantation (allo-SCT) [3]. Recently, the introduction of TKIs including imatinib and dasatinib has dramatically improved the prognosis of Ph^+ALL patients [6–13]. However, the vast majority of these patients treated with a combination of imatinib and chemotherapy will ultimately relapse without allo-SCT [3, 14]. In the UKALLXII/ECOG2993 study, 4-year relapse-free survival was significantly superior in the 76 patients who underwent allo-SCT with myeloablative conditioning compared with the 38 patients who did not receive allo-SCT (69 vs 18 %) [3]. Thus, allo-SCT is still recommended for patients with Ph^+ALL in first remission even in the era of TKIs.

Furthermore, the majority of patients treated with chemotherapy in combination with TKIs gain hematological complete remission (CR) and proceed to allo-SCT in a favorable condition wherein molecular remission has been maintained. In patients whose leukemia burdens can be decreased as much as possible prior to allo-SCT, graft-versus-leukemia (GVL) effects function more effectively, resulting in markedly decreased leukemia relapse rates after allo-SCT. In addition, since TKIs-combined chemotherapy provides a faster and deeper response, the patients can avoid further excessive cycles of chemotherapy and then successfully receive allo-SCT with fewer comorbid conditions including infectious complications, cardiac, hepatic, and renal dysfunctions. Collectively, these advantages including pre-transplant administration of TKIs and negative results of minimal residual disease (MRD) prior to allo-SCT have dramatically improved the prognosis of Ph^+ALL patients allografted [6, 7, 15, 16]. Furthermore, in such patients who have achieved minimal leukemia burdens before allo-SCT, it is possible to reduce the dose intensity of a pre-transplant conditioning regimen, which can lead to a decrease in transplant-related mortality (TRM), ultimately resulting in an improved overall survival (OS) [17].

In this study, we evaluated the effects of pre-transplant conditioning intensity, either myeloablative conditioning (MAC) or reduced intensified conditioning (RIC) on the outcomes of Ph^+ALL patients who underwent allo-SCT in CR after TKIs-containing chemotherapy, and we also examined the significance of MRD status before allo-SCT.

Materials and methods

Patients

We retrospectively analyzed outcomes of 46 Japanese patients with Ph^+ALL who underwent allo-SCT at CR with either MAC ($n = 31$) or RIC ($n = 15$) at four institutions of the Fukuoka Blood and Marrow Transplantation Group between 2001 and 2012 (Table 1). The median follow-up time from transplantation was 1555 days in the MAC group and 584 days in the RIC group, respectively. Patients in the MAC group were significantly younger than those in the RIC group (median 39 vs 60 years old, $p < 0.01$). All the patients received TKIs (imatinib or dasatinib) in combination with chemotherapy prior to allo-SCT. In Japan, imatinib had been precedently approved for the treatment of Ph^+ALL compared with dasatinib; therefore, in this study, majority of the enrolled patients were treated with imatinib: 25 out of 31 patients in the MAC group and 12 out of 15 patients in the RIC group received imatinib, respectively ($p = 1.00$). The patient characteristics are summarized in Table 1. All the patients provided informed consent, and this study was approved by the Institutional Review Board.

Conditioning regimen, stem cell source, and graft-versus-host disease prophylaxis

In this study, the MAC regimen included total body irradiation (TBI, 12 Gy) plus intravenous cyclophosphamide (CY, 120 mg/kg) or either TBI/CY plus intravenous etoposide or cytarabine (AraC) in 27 patients; intravenous busulfan (BU, 12.8 mg/kg) and cyclophosphamide (CY, 120 mg/kg) in 3 patients; and TBI and cytarabine (AraC; 120 mg/kg) in 1 patient. The RIC regimen included fludarabine (FLU 125–180 mg/m^2) and BU (6.4 mg/kg) in 6 patients and fludarabine (FLU 125 mg/m^2) and melphalan (MEL, 80 mg/m^2) with or without TBI 2-4 Gy in 9 patients.

In the MAC group, 5 patients received G-CSF-mobilized peripheral stem cells, 22 patients received bone marrow cells, and 4 patients received cord blood stem cells. In the RIC group, 1 patient received G-CSF-mobilized peripheral stem cells, 9 patients received bone marrow cells, and 5 patients received cord blood stem cells. In the MAC group, all the 5 peripheral blood stem cell transplantation (PBSCT) and 2 bone marrow transplantation (BMT) recipients were transplanted from related donors, and the other 20 BMT recipients were from unrelated donors. In the RIC group, 1 PBSCT recipient was transplanted from related donor and all the 9 BMT recipients were from unrelated donors. A combination of a calcineurin inhibitor (cyclosporine or tacrolimus) and methotrexate was used for graft-versus-host disease (GVHD) prophylaxis except in five cord blood stem cell transplantation (CBT) recipients with RIC who received tacrolimus and mycophenolate mofetil for GVHD prophylaxis.

Minimal residual disease analysis

The MRD status was evaluated by polymerase chain reaction (PCR) analysis of the *BCR-ABL* fusion transcript. MRD was considered positive with any value above the threshold of the test sensitivity. MRD was evaluated within a 30-day period before transplantation.

Statistical analysis

We evaluated the probabilities of OS, leukemia-free survival (LFS), non-relapse mortality (NRM), and relapse incidence (RI) in this study. We analyzed OS and LFS using the log-rank test and RI and NRM using the Gray test. Chi-square testing was used for univariate comparison to examine categorical variables, and the Mann–Whitney U test was used to compare numerical variables. The p values

Table 1 Patient characteristics

Characteristics	MAC ($n = 31$)	RIC ($n = 15$)	p value
Sex, M/F	20/11	7–8	0.34
Median age (range)	39 (17–64)	60 (43–68)	<0.01
Disease status at time of allo-SCT			0.29
CR1	27	15	
≥CR2	4	0	
Year of allo-SCT	2008 (2001–2012)	2009 (2005–2012)	0.13
HLA compatibility			0.69
6/6	18	7	
5/6	8	5	
4/6 or less	5	3	
HCT-CI			0.57
0	13	7	
1	3	4	
2	1		
NE	14	4	
Pretransplant TKI			1.00
Imatinib	25	12	
Dasatinib	6	3	
Conditioning regimen			
	TBI/CY ± α 27	FLU/BU ± TBI 6	
	BU/CY 3	FLU/L-PAM ± TBI 9	
	TBI/AraC 1		
Stem cell source			0.31
G-CSF-mobilized peripheral stem cells	5	1	
Bone marrow	22	9	
Cord blood	4	5	
Pretransplant MRD (bcr-abl PCR)			0.45
+	10	3	
−	19	12	
Unknown	2	0	

MAC myeloablative conditioning, *RIC* reduced-intensity conditioning, *CR* complete remission, *allo-SCT* allogeneic stem cell transplantation, *HLA* human, leukocyte antigen, *HCT-CI* hematopoietic cell transplantation-comorbidity index, *NE* not examined, *TKI* tyrosine kinase inhibitor, *TBI* total body irradiation, *CY* cyclophosphamide, *FLU* fludarabine, *BU* busulfan, *L-PAM* melphalan, *AraC* cytarabine, *MRD* minimal residual disease, *PCR* polymerase chain reaction

<0.05 were considered to be statistically significant. All the statistical analyses were performed using EZR, a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [18].

Results

Engraftment and graft-versus-host disease

Engraftment was achieved in 26 of the 31 patients from the MAC group and 12 of 15 patients from the RIC group. The median time for neutrophil count recovery was 15.5 (range 11–23 days) and 16.5 (range 9–22 days) in the MAC and RIC group, respectively ($p = 0.86$). Engraftment was not evaluated in 4 patients (1 peripheral stem cell recipient, 2 bone marrow cell recipients, and 1 CBT recipient) in the MAC group because of severe infection ($n = 3$) and regimen-related toxicity ($n = 1$). Engraftment was also not evaluated in 1 CBT recipient in the RIC group because of regimen-related toxicity. Primary engraftment failure occurred in 1 CBT recipient in the MAC group and 2 CBT recipients in the RIC group. Grade II to IV acute GVHD was documented in 14 of the 31 patients (45 %) in the MAC group and 6 of the 15 patients (30 %) of the RIC group ($p = 0.82$, Table 2). Eight out of the 21 patients (38 %) in the MAC group and 3 out of 14 (21 %) in the RIC group developed chronic GVHD, which was comparable ($p = 0.44$, Table 2).

Table 2 GVHD and cause of death

Characteristics	MAC ($n = 31$)	RIC ($n = 15$)	p value
Acute GVHD			0.82
Grade 0–1	17	9	
Grade 2	9	5	
Grade 3–4	5	1	
Chronic GVHD (patients alive at day +90)	(21)	(14)	0.44
No	13	11	
Limited	1	1	
Extensive	7	2	
Causes of death			0.53
Relapse/disease progression	2	1	
Infection	7	2	
GVHD	1	0	
Idiopathic pneumonia syndrome	2	1	
Acute respiratory distress syndrome	1		
Liver dysfunction	1		
Pleural hemorrhage	1		
EBV-LPD	1		
Heart failure		1	
Multiple organ failure		1	

MAC myeloablative conditioning, *RIC* reduced-intensity conditioning, *GVHD* graft-versus-host disease, *EBV-LPD* Epstein–Barr virus-associated lymphoproliferative disease

OS, LFS, NRM and RI

Two-year OS rates were 56.5 ± 9.2 and 62.6 ± 13.5 % in the MAC and RIC groups, respectively ($p = 0.53$, Fig. 1a). Two-year LFS rates were similar between the MAC and RIC groups (50.0 ± 9.2 vs 64.6 ± 12.9 %, $p = 0.29$, Fig. 1b). Two-year NRM was also similar between the MAC and RIC groups (38.6 ± 6.5 vs 35.4 ± 7.0 %, $p = 0.62$, Fig. 1c). Five of the 31 patients relapsed in the MAC group, while 1 of the 15 patients in the RIC group relapsed at 2 years, giving an RI of 18.5 ± 1.7 % in the MAC group and 7.7 ± 0.6 % in the RIC group ($p = 0.28$, Fig. 1d). Two patients received TKIs (dasatinib) for the treatment of molecular relapse after allo-SCT [19].

In total, 16 of the 31 patients (52 %) died in the MAC group: 2 of disease progression, 7 of infectious complications, 1 of GVHD, 2 of idiopathic intestinal pneumonia, 1 of acute respiratory distress syndrome, 1 of liver dysfunction, 1 of pleural hemorrhage and 1 of EB virus-associated lympho-proliferative disease. Pathogen of infections included Enterococcus faecium, Klebsiella oxytoca, Pseudomonas aeruginosa, Staphylococcus haemolyticus, Aspergillus and RS virus. There is one case of sepsis lacking the information of microorganism in the MAC group. In contrast, 6 of the 15 patients (20 %) died in the RIC group: 1 of disease progression, 2 of infection, 1 of idiopathic intestinal pneumonia, 1 of heart failure and 1 of multiple organ failure (Table 2). Infection included sepsis of Enterobactor cloaca and multiple pathogen-induced bacterial pneumonia. There was no significant difference in rate and cause of NRM among the RIC and MAC groups ($p = 0.27$, $p = 0.53$).

MRD

We also evaluated the influence of pretransplant qualitative MRD status on OS and LFS rates in 44 patients (29 in the MAC group and 15 in the RIC group) (Fig. 2). 19 of the 29 patients (66 %) and 12 of the 15 patients (80 %) achieved molecular remission in the MAC and RIC groups, respectively ($p = 0.45$, Table 1). In total, 31 of the 44 patients were MRD negative before allo-SCT. There is no significant difference in relapse rates according to pretransplant MRD status ($p = 0.50$). 2-year OS and 2-year LFS rates were similar between the MRD-negative and MRD-positive patients ($p = 0.28$ and 0.48, respectively, Fig. 2a, b). The same trend was observed in the MAC group ($p = 0.16$ and 0.29, respectively, Fig. 2c, d) as well as in the RIC group ($p = 0.94$ and 0.99, respectively, Fig. 2e, f).

Discussion

Several groups retrospectively analyzed for factors affecting outcomes after allo-SCT in the patients with Ph$^+$ALL who received RIC or MAC pre-transplant regimen and the previous reports are summarized in Table 3 [7, 16, 20, 21]. Bachanova et al. have reported that in the RIC group ($n = 67$), pre-transplant TKIs were administered to 76 % of the patients, with 39 % MRD-negative prior to sllo-SCT. In contrast, 78 % received pre-transplant TKIs in the MAC group ($n = 130$) and 49 % were MRD negative, which were statistically equal to those of the RIC group ($p = 0.71$ and $p = 0.79$). In this study, the 1-year TRM was significantly superior in the RIC group compared with the MAC group (13 vs 36 %, $p < 0.001$), whereas the 3-year relapse rate was higher in the RIC group than in the MAC group (49 vs 28 %, $p = 0.058$), resulting in the counterbalanced similar outcomes in terms of 3-year OS among the two groups (39 vs 35 %, $p = 0.62$). Multivariate analyses also demonstrated that pre-transplant TKI had a significant impact on the relapse rate [HR = 1.88 (1.11–3.17), $p = 0.018$], while the MRD status was not statistically associated with the relapse rate [HR = 1.60 (0.96–2.67), $p = 0.13$] [20]. Brissot et al. have retrospectively analyzed the results from 473 Ph$^+$ALL patients allografted. The multivariate analyses revealed that pre-transplant TKIs had a significant

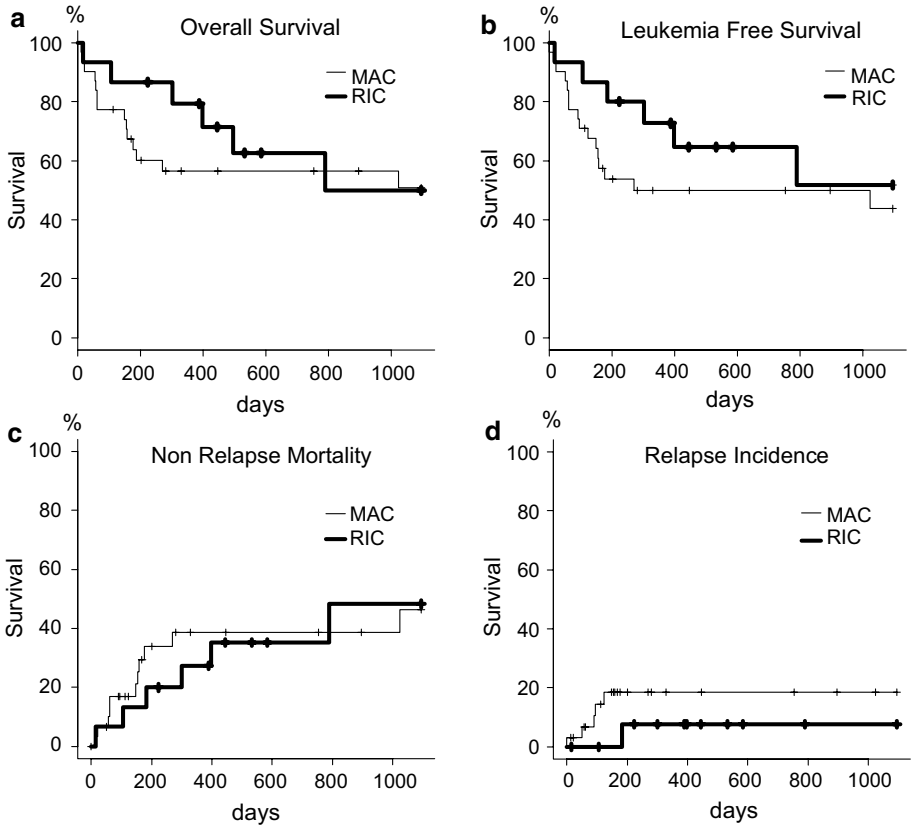

Fig. 1 Transplantation outcomes (2 years) according to the conditioning intensity: myloablative conditioning (MAC) vs reduced-intensity conditioning (RIC). **a** OS, 57 vs 63 % ($p = 0.53$), **b** LFS, 50 vs 65 % ($p = 0.29$), **c** NRM, 39 vs 35 % ($p = 0.62$), **d** RI, 19 vs 8 % ($p = 0.28$)

impact on relapse-free [HR = 0.56 (0.36–0.87), $p = 0.01$], and the RIC conditioning was closely associated with RI [HR = 1.69 (1.08–2.65), $p = 0.02$]. This study also found that there was no significant difference in OS, LFS and RI between MRD-positive and MRD-negative allo-SCT recipients [7].

In the present study, we retrospectively analyzed transplant outcomes of 46 patients with Ph^+ALL to clarify the impact of conditioning intensity on the outcome after allo-SCT. All patients had been treated with a TKIs-combined chemotherapy and then allografted during hematological CR with either RIC or MAC. In our study, there was no significant difference in 2-year OS (62 vs 56 %, $p = 0.53$), 2-year LFS (65 vs 50 %, $p = 0.29$), and NRM (35 vs 39 %, $p = 0.62$) between the RIC and MAC groups. We also found no significant impact of the MRD status prior to allo-SCT on 2-year OS (77 vs 54 %, $p = 0.28$), and 2-year LFS (69 vs 51 %, $p = 0.38$) among MRD-negative and MRD-positive groups. NRM in our study was relatively higher than that from the previous reports; however, there was no significant difference in rate and cause of NRM among the RIC and MAC groups. Despite the small number of cases retrospectively studied, our results suggest that if the patients have been treated by TKIs-combined chemotherapy and maintained hematological CR prior to allo-SCT, even though their MRD was detected by sensitive PCR, the RIC regimen could still provide a favorable outcome for such patients, equivalent to the MAC group.

In general, the MRD status prior to allo-SCT is regarded as one of the most important indicators to determine whether MAC or RIC conditioning would be recommended for each patient. A combination of TKIs and chemotherapy can induce both a marked and fast response, and currently, a 0.01 % threshold has been widely accepted to define an MRD-positive status [22, 23]. However, our results and previous reports revealed that the MRD status prior to allo-SCT was not predictive for the transplantation outcome in the era of TKIs, although other reports in the pre-TKIs era suggested that MRD was closely correlated with the treatment outcome [24, 25]. It is possible that this MRD threshold prior to allo-SCT might not be useful for completely discriminating between a warning sign of impending relapse and the process of MRD disappearance. Ph^+ALL cells possess aggressive proliferative potential, thus if few Ph^+ leukemia cells survive prior to allo-SCT, these cells can rapidly grow at a short interval before conditioning regimen. Therefore, it would be important to quantitatively evaluate MRD level not only at one point prior to allo-SCT but consecutive several points from induction therapy to allo-SCT. In addition, recent interests have focused on the post-transplant administration of TKIs for the prevention of relapse or eradicating persistent MRD [19, 26–31].

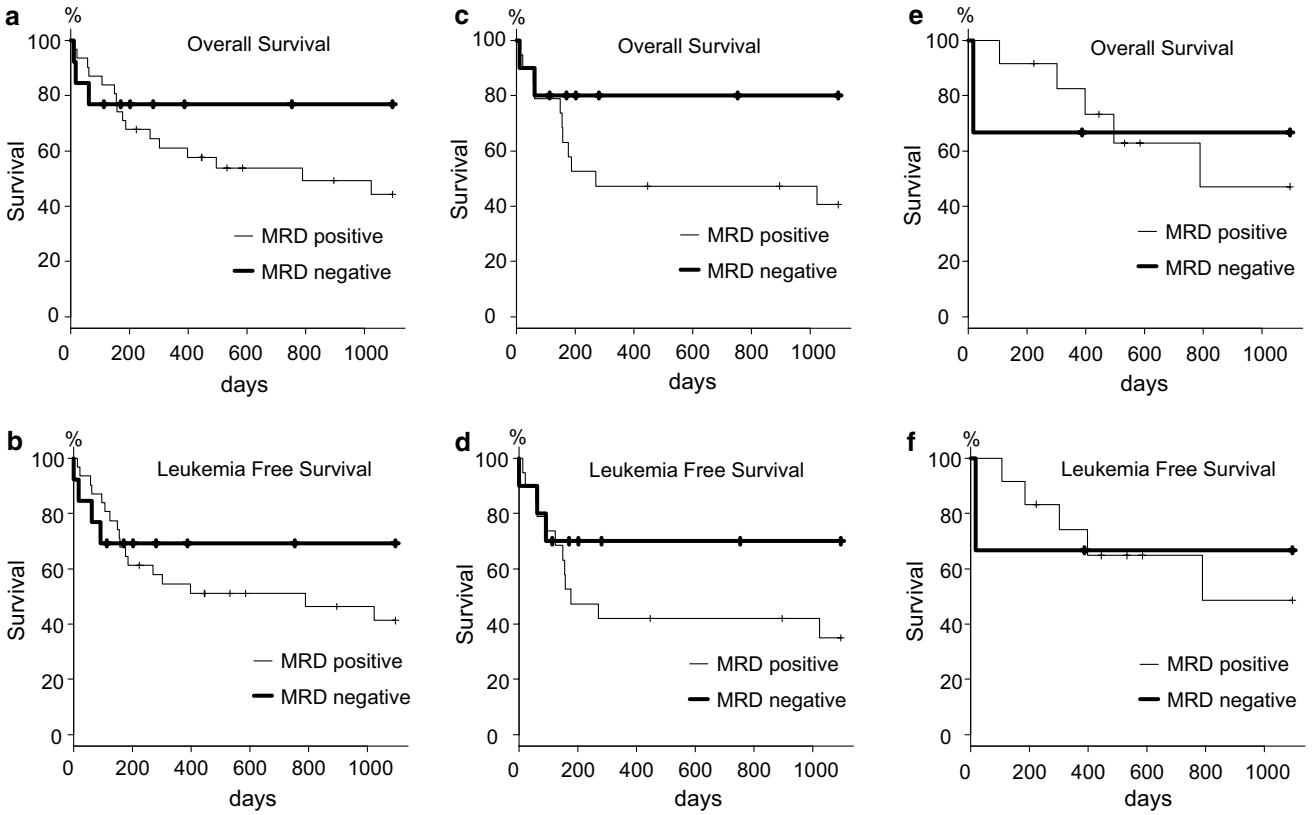

Fig. 2 Transplantation outcomes (2 years) according to the MRD status prior to allo-SCT: MRD positive vs MRD negative. **a** OS in all patients, 54 vs 77 % ($p = 0.28$), **b** LFS in all patients, 51 vs 69 % ($p = 0.48$), **c** OS in MAC group, 47 vs 80 % ($p = 0.16$), **d** LFS in MAC group, 42 vs 70 % ($p = 0.29$), **e** OS in RIC group, 63 vs 67 % ($p = 0.94$), **f** LFS in RIC group: 65 vs 67 % ($p = 0.99$)

Table 3 Comparison of pre-transplant conditioning intensity of allogeneic stem cell transplantation for Ph^+ALL

Author	No. of Ph^+ (all)	Intensity of pretransplant conditioning	Overall survival	DFS	MRD status before allo-SCT	Overall survival	DFS
Brissot et al. [7]	473 (473)	MAC: 375	47 % at 5 year	38 % at 5 year	Negative: 255	48 % at 5 year	40 % at 5 year
		RIC: 98	39 % at 5 year	38 % at 5 year	Positive: 140	48 % at 5 year	40 % at 5 year
			$p = 0.54$	$p = 0.27$		$p = 0.82$	$p = 0.99$
Eom et al. [16]	81 (180)	MAC: 52	69.2 % at 5 year	63.5 % at 5 year	Negative: 12		
		RIC: 29	53.7 % at 5 year	49.8 % at 5 year	Positive: 69	*HR 7.19	*HR 6.12
			$p = 0.301$	$p = 0.286$		$p < 0.001$	$p = 0.001$
Bachanova et al. [20]	197 (197)	MAC: 130	35 % at 3 year	28 % at 3 year	Negative: 84		
		RIC: 67	39 % at 3 year	26 % at 3 year	Positive: 101	*HR 0.94	*HR 1.06
			$p = 0.62$	$p = 0.75$		$p = 0.71$	$p = 0.75$
Mohty et al. [21]	145 (576)	MAC: 104	47 % at 2 year	33 % at 2 year			
		RIC: 41	40 % at 2 year	34 % at 2 year			
Present study	46 (46)	MAC: 31	56.5 % at 2 year	50.0 % at 2 year	Negative: 31	76.9 % at 2 year	69.2 % at 2 year
		RIC: 15	62.6 % at 2 year	64.6 % at 2 year	Positive: 11	53.7 % at 2 year	51.1 % at 2 year
			$p = 0.53$	$p = 0.29$		$p = 0.28$	$p = 0.48$

Ph^+ Philadelphia chromosome positive, *DFS* disease-free survival, *MRD* minimal residual disease, *MAC* myeloablative conditioning, *RIC* reduced-intensity conditioning, *HR* hazard ratio, **HR* hazard ratio obtained by multivariate analysis

Therefore, a serial quantitative monitoring of MRD would be useful for predicting relapse or cure in the patients with Ph^+ALL.

We have shown that the intensity of pre-transplant conditioning did not affect the outcomes of Ph^+ALL patients who received allo-SCT during hematological CR after TKIs-combined chemotherapy. Prospective randomized trials comparing an MAC versus RIC regimen for allo-SCT might be useful for examining the effects of intensity of conditioning on the clinical outcomes of patients with Ph^+ALL in the era of TKIs.

Acknowledgments We appreciate the medical and nursing staff working on Kyushu University Hospital and participating hospitals. This work was supported by JSPS KAKENHI (23390254, 24659462 to T.M.).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Larson RA, Dodge RK, Burns CP, Lee EJ, Stone RM, Schulman P, et al. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811. Blood. 1995;85:2025–37.
2. Linker CA, Levitt LJ, O'Donnell M, Forman SJ, Ries CA. Treatment of adult acute lymphoblastic leukemia with intensive cyclical chemotherapy: a follow-up report. Blood. 1991;78:2814–22.
3. 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.
4. Takeuchi J, Kyo T, Naito K, Sao H, Takahashi M, Miyawaki S, et al. Induction therapy by frequent administration of doxorubicin with four other drugs, followed by intensive consolidation and maintenance therapy for adult acute lymphoblastic leukemia: the JALSG-ALL93 study. Leukemia. 2002;16:1259–66.
5. Ueda T, Miyawaki S, Asou N, Kuraishi Y, Hiraoka A, Kuriyama K, et al. Response-oriented individualized induction therapy with six drugs followed by four courses of intensive consolidation, 1 year maintenance and intensification therapy: the ALL90 study of the Japan Adult Leukemia Study Group. Int J Hematol. 1998;68:279–89.
6. Mizuta S, Matsuo K, Nishiwaki S, Imai K, Kanamori H, Ohashi K, et al. Pretransplant administration of imatinib for allo-HSCT in patients with BCR-ABL-positive acute lymphoblastic leukemia. Blood. 2014;123:2325–32.
7. Brissot E, Labopin M, Beckers MM, Socie 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;100:392–9.
8. Aoe M, Shimada A, Muraoka M, Washio K, Nakamura Y, Takahashi T, et al. ABL kinase mutation and relapse in 4 pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia cases. Int J Hematol. 2014;99:609–15.
9. Ravandi F, Jorgensen JL, Thomas DA, O'Brien S, Garris R, Faderl S, et al. Detection of MRD may predict the outcome of patients with Philadelphia chromosome-positive ALL treated with tyrosine kinase inhibitors plus chemotherapy. Blood. 2013;122:1214–21.
10. Yanada M, Takeuchi J, Sugiura I, Akiyama H, Usui N, Yagasaki F, 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;24:460–6.
11. Wassmann B, Pfeifer H, Goekbuget N, Beelen DW, Beck J, Stelljes M, et al. Alternating versus concurrent schedules of imatinib and chemotherapy as front-line therapy for Philadelphia-positive acute lymphoblastic leukemia (Ph^+ALL). Blood. 2006;108:1469–77.
12. Lee S, Kim YJ, Min CK, Kim HJ, Eom KS, Kim DW, et al. The effect of first-line imatinib interim therapy on the outcome of allogeneic stem cell transplantation in adults with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood. 2005;105:3449–57.
13. Thomas DA, Faderl S, Cortes J, O'Brien S, Giles FJ, Kornblau SM, et al. Treatment of Philadelphia chromosome-positive acute lymphocytic leukemia with hyper-CVAD and imatinib mesylate. Blood. 2004;103:4396–407.
14. 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;28:3644–52.
15. Tucunduva L, Ruggeri A, Sanz G, Furst S, Cornelissen J, Linkesch W, et al. Impact of minimal residual disease on outcomes after umbilical cord blood transplantation for adults with Philadelphia-positive acute lymphoblastic leukaemia: an analysis on behalf of Eurocord, Cord Blood Committee and the Acute Leukaemia working party of the European group for blood and marrow transplantation. Br J Haematol. 2014;166:749–57.
16. Eom KS, Shin SH, Yoon JH, Yahng SA, Lee SE, Cho BS, et al. Comparable long-term outcomes after reduced-intensity conditioning versus myeloablative conditioning allogeneic stem cell transplantation for adult high-risk acute lymphoblastic leukemia in complete remission. Am J Hematol. 2013;88:634–41.
17. Wahid SF. Indications and outcomes of reduced-toxicity hematopoietic stem cell transplantation in adult patients with hematological malignancies. Int J Hematol. 2013;97:581–98.
18. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Trans. 2013;48:452–8.
19. Ito Y, Miyamoto T, Kamimura T, Aoki K, Henzan H, Aoki T, et al. Characteristics of patients with development of large granular lymphocyte expansion among dasatinib-treated patients with relapsed Philadelphia chromosome-positive acute lymphoblastic leukemia after allogeneic stem cell transplantation. Clin Lymphoma Myeloma Leuk. 2015;15:e47–54.
20. Bachanova V, Marks DI, Zhang MJ, Wang H, de Lima M, Aljurf MD, 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;28:658–65.
21. Mohty M, Labopin M, Volin L, Gratwohl A, Socie G, Esteve J, et al. Reduced-intensity versus conventional myeloablative conditioning allogeneic stem cell transplantation for patients with acute lymphoblastic leukemia: a retrospective study from the European Group for Blood and Marrow Transplantation. Blood. 2010;116:4439–43.

22. Raff T, Gokbuget N, Luschen S, Reutzel R, Ritgen M, Irmer S, et al. Molecular relapse in adult standard-risk ALL patients detected by prospective MRD monitoring during and after maintenance treatment: data from the GMALL 06/99 and 07/03 trials. Blood. 2007;109:910–5.
23. Mortuza FY, Papaioannou M, Moreira IM, Coyle LA, Gameiro P, Gandini D, et al. Minimal residual disease tests provide an independent predictor of clinical outcome in adult acute lymphoblastic leukemia. J Clin Oncol. 2002;20:1094–104.
24. Pane F, Cimino G, Izzo B, Camera A, Vitale A, Quintarelli C, et al. Significant reduction of the hybrid BCR/ABL transcripts after induction and consolidation therapy is a powerful predictor of treatment response in adult Philadelphia-positive acute lymphoblastic leukemia. Leukemia. 2005;19:628–35.
25. Preudhomme C, Henic N, Cazin B, Lai JL, Bertheas MF, Vanrumbeke M, et al. Good correlation between RT-PCR analysis and relapse in Philadelphia (Ph1)-positive acute lymphoblastic leukemia (ALL). Leukemia. 1997;11:294–8.
26. Watanabe A, Chansu S, Ogawa A, Asami K, Imamura M. Prophylactic post-transplant dasatinib administration in a pediatric patient with Philadelphia chromosome-positive acute lymphoblastic leukemia. Pediatr Int. 2013;55:e56–8.
27. Teng CL, Yu JT, Chen HC, Hwang WL. Maintenance therapy with dasatinib after allogeneic hematopoietic stem cell transplantation in Philadelphia chromosome-positive acute lymphoblastic leukemia. Ann Hematol. 2013;92:1137–9.
28. Pfeifer H, Wassmann B, Bethge W, Dengler J, Bornhauser 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;27:1254–62.
29. 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;18:652–4.
30. Ribera JM, Oriol A, Gonzalez 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.
31. Wassmann B, Pfeifer H, Stadler M, Bornhauser M, Bug G, Scheuring UJ, et al. Early molecular response to posttransplantation imatinib determines outcome in MRD+ Philadelphia-positive acute lymphoblastic leukemia (Ph^+ALL). Blood. 2005;106:458–63.