BLOOD RESEARCH
VOLUME 50 · NUMBER 3
September 2015
ORIGINAL ARTICLE

Favorable outcome of allogeneic hematopoietic stem cell transplantation followed by post-transplant treatment with imatinib in children with Philadelphia chromosome-positive acute lymphoblastic leukemia

Ye Jee Byun, Jin Kyung Suh, Seong Wook Lee, Darae Lee, Hyunjin Kim, Eun Seok Choi, Kyung-Nam Koh, Ho Joon Im, Jong Jin Seo

Division of Pediatric Hematology/Oncology, Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, Korea

p-ISSN 2287-979X / e-ISSN 2288-0011
http://dx.doi.org/10.5045/br.2015.50.3.147
Blood Res 2015;50:147-53.

Received on May 4, 2015
Revised on July 23, 2015
Accepted on July 27, 2015

*This study was supported by a grant from the Korea Healthcare Technology R&D Project, Ministry of Health and Welfare, Korea (HI10C2020).

Correspondence to
Ho Joon Im, M.D., Ph.D.
Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: +82-2-3010-3371
Fax: +82-2-473-3725
E-mail: hojim@amc.seoul.kr

Background
Allogeneic hematopoietic stem cell transplantation (HSCT) is the preferred curative therapy for children with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL). We evaluated the treatment outcomes of children with Ph+ ALL who underwent allogeneic HSCT.

Methods
Fifteen children diagnosed with Ph+ ALL in Asan Medical Center Children's Hospital between 1998 and 2012 were retrospectively analyzed.

Results
Of 521 children diagnosed with ALL during the study period, 15 had a Philadelphia chromosome. Among these 15 patients, 13 attained complete remission (CR) following induction chemotherapy, and two died of intracerebral hemorrhage during leukapheresis and induction chemotherapy, respectively. Of the 13 patients who attained CR, 12 received allogeneic HSCT, mainly from unrelated donors. Of the 12 patients who received HSCT, one died of a transplant-related cause, one died of relapse after HSCT, and 10 remain in continuous CR. Of the 10 patients who remained in CR longer than six months after HSCT, seven received post-HSCT imatinib. For all 15 patients, the 5-year overall survival, event-free survival, and cumulative incidence of relapse were 60.0%, 48.6%, and 38.8%, respectively, with a median follow-up of 70 months. For the HSCT group, the 5-year overall survival, event-free survival, and cumulative incidence of relapse were 80.2%, 72.9%, and 29.3%, respectively, with a median follow-up of 100 months.

Conclusion
Allogeneic HSCT cures a significant proportion of Ph+ ALL patients. Because the use of imatinib appears to be a promising approach, strategies that include tyrosine kinase inhibitors before and after HSCT require further evaluation.

Key Words Philadelphia chromosome-positive acute lymphoblastic leukemia, Children, Allogeneic hematopoietic stem cell transplantation, Imatinib, Outcome

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is the preferred curative therapy for children with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL). The Philadelphia chromosome t(9;22)(q34;q11), from which the *BCR-ABL* fusion gene is formed, is detectable in 3% to 5% of children and approximately 25% to 30% of adults with ALL [1-4]. Children with Ph+ ALL typically have poor outcomes compared to children with conventional ALL, whose current cure rate is 85% or greater with precise

risk assessment and appropriate treatment [5]. In the Italian Association of Pediatric Hematology and Oncology (AIEOP) trials, patients with Ph+ ALL who underwent conventional chemotherapy had a 5-year overall survival (OS) of 51% and 5-year disease-free survival (DFS) of 47% [6]. Even in Ph+ ALL patients with a rapid early response, the relapse rate was high in those treated with chemotherapy alone [7, 8]. Accordingly, with the development of HSCT strategies and fewer HSCT-related complications, allogeneic HSCT has become the best treatment option for chemotherapy-resistant Ph+ ALL [9]. In an earlier study of Ph+ ALL patients treated with allogeneic HSCT, the reported 5-year OS and DFS were 29–54% and 26–48%, respectively [10].

The tyrosine kinase inhibitor imatinib mesylate (STI571, Glivec) has been widely used for the treatment of chronic myelogenous leukemia and has recently been used to treat Ph+ ALL [11]. Several studies have shown decreased relapse rates and improved DFS in patients who received imatinib-based treatment prior to allogeneic HSCT compared with those who received conventional allogeneic HSCT [12-14]. In addition, some studies have shown overall responses with mesylate in 60% to 70% of patients with relapsed or refractory Ph+ ALL, including patients who have previously undergone transplantation, with limited toxicity [15-17]. Thus, imatinib with conventional chemotherapy before and after HSCT currently appears to be the most curative therapy.

This approach is in agreement with earlier suggestions that successful remission induction of Ph+ ALL requires imatinib to be used in combination with standard chemotherapy. Maintenance therapy with imatinib during the post-transplant period has been used for patients with Ph+ ALL. However, its efficacy compared with that of induction therapy with imatinib during the pre-transplant period remains to be shown. One study has reported reduced relapse rate and improved DFS in Ph+ ALL patients with imatinib maintenance therapy after HSCT [18].

In our current study, we evaluated the treatment outcomes of children with Ph+ ALL who underwent allogeneic HSCT and examined the feasibility and effect of pre- and post-HSCT imatinib treatment in a single center.

MATERIALS AND METHODS

Patient eligibility

This study analyzed patients diagnosed with Ph+ ALL at Asan Medical Center Children's Hospital (AMCCH) in Seoul, Korea between 1998 and 2012. For all surviving patients, the end point of the last follow-up was April 30, 2013. ALL was diagnosed according to conventional criteria. Ph+ ALL was diagnosed by the presence of the Philadelphia chromosome t(9;22)(q34;q11.2) through metaphase cytogenetics, fluorescence in situ hybridization (FISH) analysis, and by positivity for *BCR-ABL* fusion gene transcripts using real-time quantitative polymerase chain reaction (q-PCR). First-line induction chemotherapy after diagnosis was based on the Children's Cancer Study Group (CCG) protocol for four patients (27%), the Pediatric Oncology Group (POG) protocol for three patients (20%), and the Asan Medical Center-Childhood Acute Lymphoblastic Leukemia 0601 (AMC-CALL0601) for eight patients (53%) (Table 1). The AMC-CALL0601 protocol was composed of cyclophosphamide (CPM), 6-mercaptoprine (6-MP), cytosine-arabinoside (Ara-C), vincristine (VCR), L-asparaginase, and intrathecal methotrexate (MTX). Patients who achieved hematologic remission underwent HSCT. Bone marrow biopsy was typically performed every three months after HSCT to determine the post-transplant status of the bone marrow. Cytogenetic remission was defined as the absence of the Philadelphia chromosome in all metaphase samples obtained from the bone marrow specimen. Molecular remission was defined as the absence of detectable *BCR-ABL* mRNA in real-time q-PCR. Adverse effects of imatinib treatment were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. We performed retrospective analysis via an electronic medical record review. This study was approved by the Institutional Review Board of the Asan Medical Center (2014-1136).

Statistical analysis

Patient-, disease-, transplantation-, and imatinib treatment-related variables were expressed as median and range, number, or percentage, as appropriate. We assessed the effects of treatment using OS and event-free survival (EFS). OS and EFS were calculated using the Kaplan-Meier method. Statistical analyses were performed using SPSS for Windows,

Table 1. Patient characteristics (N=15).

Variables	N (%)
Age at diagnosis, median (years)	9.6 (3.1–15.8)
Gender	
Male	10 (67)
Female	5 (33)
Initial WBC count, median (/mm^3)	30,000 (6,200–701,400)
Molecular analysis (*BCR-ABL* gene)	
Major (b3a2)	2 (13)
Minor (e1a2)	11 (85)
NA	2 (13)
Induction chemotherapy	
CCG 1881	1 (7)
CCG 1882	2 (13)
POG 9406	3 (20)
CCG 1961	1 (7)
AMC-CALL0601	8 (53)
Outcome of induction chemotherapy	
CR	13 (87)
Induction failure	2 (13)
Fallow-up duration, median (months)	70 (13–186)

Abbreviations: WBC, white blood cell; *BCR-ABL*, breakpoint cluster region-Abelson; CCG, Children's Cancer Study Group; POG, Pediatric Oncology Group; AMC-CALL, Asan Medical Center-Childhood Acute Lymphoblastic Leukemia; CR, complete remission; NA, not applicable.

version 21.0 (IBM Corp., Armonk, NY).

RESULTS

Patient characteristics

A total of 15 children (2.9%) were diagnosed with Ph+ ALL and 521 children were diagnosed with ALL at AMCCH during the study period. Patient characteristics are listed in Table 1. Ten patients were male (67%) and 5 were female (33%). The median patient age at diagnosis was 9.6 years (range, 3.1–15.8 years) and the median white blood cell count was 30,000/mm^3 (range, 6,200–701,400/mm^3). No patients had central nervous system involvement, although the central nervous system involvement of one patient was not evaluated due to death from multifocal intracranial hemorrhage during induction chemotherapy on leukapheresis. Immunophenotypic analysis showed that all patients had B-cell precursor ALL. Eleven patients had minor *BCR-ABL* transcripts, two had major *BCR-ABL* transcripts, and no information was available on two cases. Nine patients (60%) also had other chromosomal abnormalities in addition to the t(9;22)(q34;q11) translocation.

Of the 15 Ph+ ALL patients in our current series, two died during induction chemotherapy. One of these patients had an initial peripheral white blood cell count at diagnosis of 701,400/mm^3 and developed intracranial hemorrhage on leukapheresis. The other had tumor lysis syndrome and also developed intracranial hemorrhage on hemodialysis. Thirteen patients, excluding the above-mentioned cases, achieved hematologic complete remission (CR) after induction chemotherapy. One subsequently died of relapse and disease progression despite achieving a second CR following imatinib treatment. Consequently, 12 patients received allogeneic HSCT. Among these 12 cases, the median age at HSCT was 9.3 years (range, 3.1–15.8 years) and the median time to HSCT after diagnosis was 5.8 months (range, 3.2–6.9 months). All 12 patients achieved hematologic remission before HSCT, although one relapsed before HSCT and achieved a second hematologic remission following a second induction chemotherapy regimen. Ten patients achieved cytogenetic remission, one still had the t(9:22) chromosome, and there were no chromosomal data before HSCT for one case. Seven patients achieved molecular remission, three patients did not, and there were no *BCR-ABL* molecular analysis data before HSCT for two patients. The type of HSCT donor varied: there was one matched sibling, one HLA-DR mismatched sibling, and one haploidentical donor; the other nine donors were unrelated. Four of the nine unrelated donors were mismatched unrelated donors: two were 7/8 HLA matched donors, one was 6/8 HLA matched donor and the other one was 5/8 HLA matched donor. The graft sources were bone marrow in four patients, mobilized peripheral blood stem cell in five, and umbilical cord blood in three patients. All patients received fractionated total body irradiation of 6.0–14.0 Gy followed by cyclophosphamide at a dose of 50–60 mg/kg/day over two days and/or fludarabine 25–40 mg/m^2/day over three days. Three of the 12 patients received a conditioning regimen including fludarabine; two received cord blood transplants and the other a haploidentical donor transplant. Most patients (8 of 12) received cyclosporine and methotrexate for graft versus host disease (GVHD) prophylaxis (Table 2).

HSCT outcomes

Of the 12 patients in our cohort who underwent HSCT, two relapsed after treatment. One subsequently died of disease progression; the other had an extramedullary relapsed lesion and was alive without disease after additional chemotherapy. There was one case of transplant-related mortality (TRM) involving a patient who died of pulmonary hemorrhage at post-transplantation day 8. The other 10 cases remained in continuous CR. Of 11 evaluable patients, six had acute GVHD: three grade I–II, two grade III, and one grade IV; three had chronic GVHD: two of limited disease

Table 2. Characteristics of patients treated with HSCT (N=12).

Variables	N (%)
Age at HSCT, median (years)	9.3 (3.1–15.8)
Time to HSCT after diagnosis, median (months)	5.8 (3.2–6.9)
Disease status at HSCT	
Hematologic remission	
CR1	11 (92)
CR2	1 (8)
Cytogenetic remission	
Yes	10 (83)
No	1 (8)
NA	1 (8)
Molecular remission	
Yes	7 (58)
No	3 (25)
NA	2 (17)
Donor	
Matched sibling	1 (8)
Mismatched sibling	1 (8)
Haploidentical	1 (8)
Matched unrelated	5 (42)
Mismatched unrelated	4 (33)
Stem cell source	
BM	4 (33)
PBSC	5 (42)
UCB	3 (25)
Conditioning regimen	
TBI/Cy	9 (75)
TBI/Flu/Cy	3[a] (25)
GVHD prophylaxis	
CSA/MTX	8 (67)
Others	4 (33)

[a]UCB and haploidentical donors in two patients one patient, respectively.
Abbreviations: NA, not applicable; BM, bone marrow; PBSC, peripheral blood stem cell; UCB, umbilical cord blood; TBI, total body irradiation; Cy, cyclophosphamide; Flu, fludarabine; CSA, cyclosporine; MTX, methotrexate.

and one of extensive disease. Table 3 lists the HSCT outcomes of the 12 patients analyzed in this study.

Imatinib treatment and outcomes

Table 4 lists diagnostic information for each patient as well as the HSCT and imatinib treatment outcomes in the 12 study patients who underwent HSCT. Ten of these cases received pre-HSCT imatinib treatment: two underwent imatinib during induction and consolidation chemotherapy and eight received imatinib only during consolidation chemotherapy. The median duration of imatinib treatment until HSCT was 2.5 months (range, 1.3–4.2 months) and the median imatinib dosage was 332 mg/m^2 (range, 243–400 mg/m^2). Among our 12 patients, seven received post-transplant imatinib treatment and two did not due to early TRM and relapse. Of the 10 patients who remained in CR for longer than six months after HSCT, seven were started on imatinib at a median of 6.3 months after HSCT (range, 2.9–9.6 months) and continued this treatment for a median of 4.8 months (range, 4.2–8.4 months), with a median imatinib dose of 213 mg/m^2 (range, 105–353 mg/m^2). Four of the 10 patients who received pre- or post-HSCT imatinib treatment underwent imatinib dose reduction because of grade 1 neutropenia, grade 3 febrile neutropenia, grade 1 impaired liver function, and grade 1 skin eruption (one case each). All patients who received post-HSCT imatinib treatment were alive at the time of writing.

Table 3 Outcomes of patients who underwent HSCT (N=12).

Variables	N (%)
Acute GVHD (evaluable)	11
None	5 (45)
Grade I–II	3 (27)
Grade III	2 (18)
Grade IV	1 (9)
Chronic GVHD (evaluable)	11
None	8 (72)
Limited	2 (18)
Extensive	1 (9)
Relapse	2 (17)
Death	
TRM	1 (8)
Disease progression	1 (8)

Abbreviations: GVHD, graft versus host disease; TRM, transplant-related mortality.

OS and EFS

For the 15 study patients, the 5-year OS was 60.0% (Standard error [SE], 14.2%) and the EFS was 48.6% (SE, 14.1%), with a median follow-up of 70 months (Fig. 1). For the specific HSCT group (N=12), the 5-year OS and EFS were 80.2% (SE, 12.8%) and 72.9% (SE, 13.6%), respectively, with a median follow-up of 100 months (Fig. 2). Seven patients who received pre- and post-HSCT imatinib treatment were alive without relapse.

Table 4. Diagnostic information for each patient and HSCT and imatinib treatment outcomes.

Patient	At diagnosis			At HSCT				Imatinib treatment		Outcome after HSCT (months)
	Age (years)	WBC counts (/mm^3)	CNS involvement	Disease state	Age (years)	Donor type	Conditioning regimen	Pre-HSCT	Post-HSCT	
1	6.6	48,700	no	NA	NA	NA	NA	NA	NA	NA
2	3.7	10,300	no	CR2	4.3	MRD (6/6)	TBI/Cy	no	no	NED@179.2
3	5.1	55,400	no	CR1	5.6	MUD (6/6)	TBI/Cy	no	no	NED@158.2
4	14.2	701,400	NA	NA	NA	NA	NA	NA	NA	NA
5	14.3	6,200	no	CR1	14.8	MUD (8/8)	TBI/Cy	yes	no	NED@102.2
6	14.0	8,800	no	CR1	14.3	MUD (8/8)	TBI/Cy	yes	no	TRM@0.3
7	9.6	6,200	no	CR1	10.1	mmUD (5/8)	TBI/Flu/Cy	yes	yes	NED@73.5
8	15.8	30,000	no	CR2	16.3	MUD (8/8)	TBI/Cy	yes	no	DOD@37.6
9	5.8	25,200	no	CR1	6.1	mmUD (7/8)	TBI/Cy	yes	yes	NED@56.2
10	3.1	94,400	no	CR1	3.3	mmUD (7/8)	TBI/Cy	yes	yes	NED@46.2
11	6.8	147,400	no	CR1	7.3	mmRD (7/8)	TBI/Cy	yes	yes	NED@8.3
12	10.4	49,300	no	CR1	10.8	MUD (8/8)	TBI/Cy	yes	yes	NED@33.3
13	12.8	65,100	no	NA	NA	NA	NA	NA	NA	NA
14	7.2	12,500	no	CR1	7.4	mmUD (6/8)	TBI/Flu/Cy	yes	yes	NED@13.1
15	15.0	11,200	no	CR1	15.3	Haploidentical (5/8)	TBI/Flu/Cy	yes	yes	NED@8.6

Abbreviations: WBC, white blood cell; CNS, central nervous system; NA, not applicable; HSCT, hematopoietic stem cell transplantation; CR1, achieved complete remission after induction chemotherapy before HSCT; CR2, relapsed before HSCT and achieved complete remission after reinduction chemotherapy; MRD, matched related donor; MUD, matched unrelated donor; mmUD, mismatched unrelated donor; mmRD, mismatched related donor; TBI/Cy, total body irradiation/cytoxan; TBI/Flu/Cy, total body irradiation/fludarabine/cytoxan; NED, no evidence of disease; TRM, transplant-related mortality; DOD, died of disease.

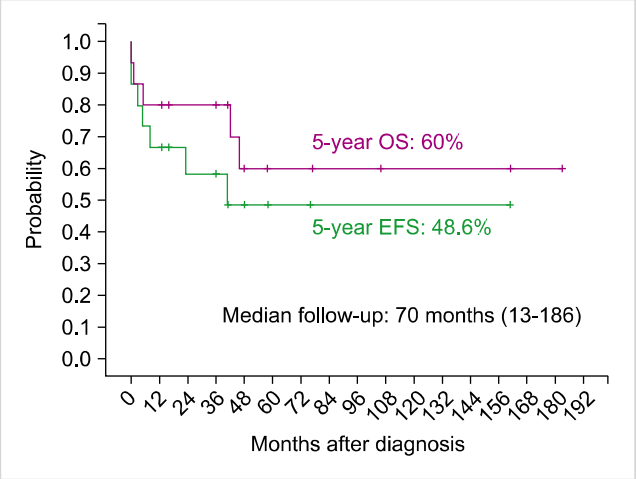

Fig. 1. Five-year OS and EFS outcomes for the entire Ph+ ALL patient cohort (N=15).

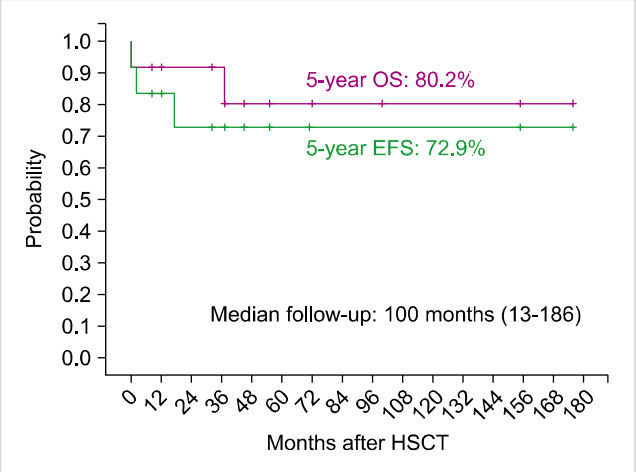

Fig. 2. Five-year OS and EFS outcomes for Ph+ ALL study patients who underwent HSCT (N=12).

DISCUSSION

Treatment outcomes for both Ph+ ALL and ALL patients have improved in recent years due to improvements in chemotherapy and HSCT methods. In our current study, the 5-year OS and EFS of Ph+ ALL patients were higher than previously reported [2, 6, 19-21]: of 12 patients who received HSCT, 10 were still living at the time of writing–one patient died of TRM and one died of the disease–resulting in 5-year OS and EFS rates of 80.2% and 72.9%, respectively, with a median follow-up of 100 months. These results suggest that allogeneic HSCT may be a curative option for a significant portion of patients with Ph+ ALL.

Although previous studies have reported that patients who underwent HSCT from a matched related donor had a significantly lower risk of treatment failure [19, 20], the 5-year OS and EFS results for alternative donors in our study were quite favorable. Among the donors for our 12 HSCT patients, nine (75%) were unrelated and the other three consisted of a haploidentical, an HLA-DR mismatched sibling, and a matched sibling donor. Thus, HSCT using alternative donors can be considered for patients without matched family donors.

The International Childhood Acute Lymphoblastic Leukemia Study Group [19] reported a 5-year OS and EFS of 40±3% and 28±3%, respectively, for 326 Ph+ ALL patients diagnosed between 1986 and 1996 and 5-year OS and EFS of 72±8% and 65±8%, respectively, for 38 patients treated with HSCT from HLA-matched related donors among 267 Ph+ ALL patients who achieved CR after induction chemotherapy. These previous studies also reported a 7-year OS and EFS of 32±2% and 44.9±2.2% for 610 Ph+ ALL patients treated between 1995 and 2005, respectively, and 5-year OS and EFS of 54±2.8% and 43.5±2.9% for 325 patients who underwent HSCT with different types of donors among 542 Ph+ ALL patients who achieved remission by the end of induction therapy [2]. The King Hussein Cancer Center has reported a 5-year OS and EFS of 91.6±7.9% and 75±12.5% for 12 Ph+ ALL childhood patients diagnosed from 2003 until 2011 who underwent HSCT, with a median follow-up of 42.2 months [22]. Although there is a controversy surrounding the best treatment for childhood Ph+ ALL patients, the results of our study and previous reports suggest that HSCT, especially with matched sibling donors, appears to be the best treatment option. The treatment results for childhood Ph+ ALL cases have improved over time with advances in chemotherapy and HSCT methods and decreased incidence of complications. Our current results indicate acceptable 5-year OS and EFS, despite our inclusion of patients who were diagnosed in the late 1990s and the predominant use of unrelated donors in this series.

Although the overall outcomes for children with ALL have continued to improve, the outcomes for the specific Ph+ ALL subgroup have not. *BCR-ABL* tyrosine kinase is a molecular abnormality that causes chronic myeloid leukemia and Ph+ ALL [15]. Imatinib, the first approved tyrosine kinase inhibitor, plays a major role in the outcomes of Ph+ ALL, as well as in chronic myeloid leukemia. Treatment outcomes, including the OS, EFS, CR, and relapse rate and minimal residual disease of newly diagnosed Ph+ ALL patients are reportedly improved following imatinib-based therapy. Furthermore, many previous studies have reported the favorable effect of imatinib on allogeneic HSCT outcomes. The patients analyzed in these studies usually received imatinib in induction or post-induction therapy before HSCT at 260–340 mg/m^2/day for 2 weeks or until HSCT [23, 24].

In contrast to the aforementioned findings, the overall effect of post-transplant imatinib administration on the outcomes of allogeneic HSCT remains undetermined. Several studies have reported the safety and efficacy of imatinib therapy after allogeneic HSCT. One study reported favorable 5-year OS and DFS (81.5±5% and 86.7±4.4%, respectively) in 62 Ph+ ALL patients receiving a post-HSCT imatinib treatment of 400 mg/day for adults (>17 years) and 260 mg/m^2/day for children (<17 years) [18]. Their median age was 29 years (range, 6–50 years), and they had received

imatinib for a median of 70 days post-HSCT (range, 20–270 days) with a median duration of 90 days (range, 13–540 days). Another related study reported a 3-year OS of 66.7% with post-HSCT imatinib administration, but there was no significant benefit found in terms of EFS compared with the post-HSCT non-imatinib group [25]. We administered a relatively small amount of imatinib over a longer period in our current study, and all patients who received post-HSCT imatinib are still living without relapse or disease-associated morbidity. Because of the small number of patients, we could not directly compare outcomes between the post-HSCT imatinib and no post-HSCT imatinib treatment groups in our study. However, post-HSCT imatinib treatment appeared to be a feasible option, with 100% OS in the post-HSCT imatinib group.

In 2009, the Children's Oncology Group (COG) reported that imatinib plus intensive chemotherapy improves the 3-year EFS in children and adolescents with Ph+ ALL with no appreciable increase in toxicity, but that HSCT plus imatinib offered no advantage over HSCT alone [26]. The related donor HSCT group in the COG study treated with 6 months of imatinib post-HSCT had a 3-year EFS of 56.6±21.5%, which was similar to that of a comparable historical HSCT group from the CCG-1921 study [26, 27]. Recently, the continuing COG study AALL0031, which is evaluating the 5-year outcome of imatinib plus intensive chemotherapy with and without allogeneic HSCT, reported a 5-year EFS for the imatinib plus intensive chemotherapy group of 70±12%, compared with 65±11% for related donor HSCT patients and 59±15% for unrelated donor HSCT patients [28]. This result suggests that imatinib plus intensive chemotherapy may be the best initial treatment of choice for Ph+ ALL children. However, there are insufficient long-term follow-up data at present to fully validate this possibility and it is still unclear when imatinib should be used. Longer-term outcomes and specific strategies for imatinib need to be studied to properly elucidate the effect of imatinib plus intensive chemotherapy and possible benefit of imatinib plus intensive chemotherapy over HSCT. In comparison, our results for imatinib plus HSCT are comparable with those of the COG study and showed a low TRM and GVHD rate, even though nearly all of our HSCT donors were unrelated. Thus, our findings suggest that allogeneic HSCT still plays an important role in the treatment of patients with Ph+ ALL.

Many previous studies have additionally investigated the effect of other tyrosine kinase inhibitors besides imatinib, including dasatinib and nilotinib. More studies are necessary to increase the efficacy and decrease the toxicity of these agents.

Despite our findings of favorable outcomes of allogeneic HSCT, this study had some limitations. These included the small number of patients analyzed and the long study period during which changes were made to the Ph+ ALL treatment regimen. Additionally, this study had a short follow-up duration, especially in the imatinib treatment group (median, 50 months).

In conclusion, the 5-year OS and EFS of patients with Ph+ ALL who received allogeneic HSCT are favorable with pre- and post-transplant administration of imatinib. Allogeneic HSCT with pre- and post-transplant maintenance using a tyrosine kinase inhibitor may thus be a curative option for Ph+ ALL. The outcomes of imatinib plus intensive chemotherapy without allogeneic HSCT should be compared with those of allogeneic HSCT in further studies. In addition, the dose and duration of pre- and post-transplant imatinib should be evaluated accurately to clarify the role of imatinib in childhood Ph+ ALL.

REFERENCES

1. Cytogenetic abnormalities in adult acute lymphoblastic leukemia: correlations with hematologic findings outcome. A Collaborative Study of the Group Français de Cytogénétique Hématologique. Blood 1996;87:3135-42.
2. Aricò M, Schrappe M, Hunger SP, et al. Clinical outcome of children with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia treated between 1995 and 2005. J Clin Oncol 2010;28:4755-61.
3. Ottmann OG, Pfeifer H. Management of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). Hematology Am Soc Hematol Educ Program 2009;1:371-81.
4. Ravandi F, Kebriaei P. Philadelphia chromosome-positive acute lymphoblastic leukemia. Hematol Oncol Clin North Am 2009;23:1043-63.
5. Schrappe M, Nachman J, Hunger S, et al. Educational symposium on long-term results of large prospective clinical trials for childhood acute lymphoblastic leukemia (1985-2000). Leukemia 2010;24:253-4.
6. Fagioli F, Zecca M, Rognoni C, et al. Allogeneic hematopoietic stem cell transplantation for Philadelphia-positive acute lymphoblastic leukemia in children and adolescents: a retrospective multicenter study of the Italian Association of Pediatric Hematology and Oncology (AIEOP). Biol Blood Marrow Transplant 2012;18:852-60.
7. Roy A, Bradburn M, Moorman AV, et al. Early response to induction is predictive of survival in childhood Philadelphia chromosome positive acute lymphoblastic leukaemia: results of the Medical Research Council ALL 97 trial. Br J Haematol 2005;129:35-44.
8. Schrappe M, Aricò M, Harbott J, et al. Philadelphia chromosome-positive (Ph+) childhood acute lymphoblastic leukemia: good initial steroid response allows early prediction of a favorable treatment outcome. Blood 1998;92:2730-41.
9. Mori T, Manabe A, Tsuchida M, et al. Allogeneic bone marrow transplantation in first remission rescues children with Philadelphia chromosome-positive acute lymphoblastic leukemia: Tokyo Children's Cancer Study Group (TCCSG) studies L89-12 and L92-13. Med Pediatr Oncol 2001;37:426-31.
10. Laport GG, Alvarnas JC, Palmer JM, et al. Long-term remission of Philadelphia chromosome-positive acute lymphoblastic leukemia after allogeneic hematopoietic cell transplantation from matched sibling donors: a 20-year experience with the fractionated total body irradiation-etoposide regimen. Blood 2008;112:903-9.
11. Wei G, Rafiyath S, Liu D. First-line treatment for chronic myeloid

leukemia: dasatinib, nilotinib, or imatinib. J Hematol Oncol 2010;3:47.
12. de Labarthe A, Rousselot P, Huguet-Rigal F, et al. Imatinib combined with induction or consolidation chemotherapy in patients with de novo Philadelphia chromosome-positive acute lymphoblastic leukemia: results of the GRAAPH-2003 study. Blood 2007;109:1408-13.
13. Lee S, Kim YJ, Min CK, 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.
14. 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;24:460-6.
15. Druker BJ, Sawyers CL, Kantarjian H, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. N Engl J Med 2001;344: 1038-42.
16. Hoelzer D, Gökbuget N, Ottmann OG. Targeted therapies in the treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia. Semin Hematol 2002;39(4 Supple 3):32-7.
17. Ottmann OG, Druker BJ, Sawyers CL, et al. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. Blood 2002; 100:1965-71.
18. 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 lymphobla stic leukemia. J Hematol Oncol 2012; 5:29.
19. Aricò M, Valsecchi MG, Camitta B, et al. Outcome of treatment in children with Philadelphia chromosome-positive acute lymphoblastic leukemia. N Engl J Med 2000;342:998-1006.
20. Sharathkumar A, Saunders EF, Dror Y, et al. Allogeneic bone marrow transplantation vs chemotherapy for children with Philadelphia chromosome-positive acute lymphoblastic leukemia. Bone Marrow Transplant 2004;33:39-45.
21. Doki N, Ohashi K, Oshikawa G, Kobayashi T, Kakihana K, Sakamaki H. Clinical outcome of hematopoietic stem cell transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph + ALL): experience from a single institution. Pathol Oncol Res 2014;20:61-6.
22. Salami K, Alkayed K, Halalsheh H, Hussein AA, Riziq M, Madanat F. Hematopoietic stem cell transplant versus chemotherapy plus tyrosine kinase inhibitor in the treatment of pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL). Hematol Oncol Stem Cell Ther 2013;6:34-41.
23. Rives S, Estella J, Gómez P, et al. Intermediate dose of imatinib in combination with chemotherapy followed by allogeneic stem cell transplantation improves early outcome in paediatric Philadelphia chromosome-positive acute lymphoblastic leukaemia (ALL): results of the Spanish Cooperative Group SHOP studies ALL-94, ALL-99 and ALL-2005. Br J Haematol 2011;154:600-11.
24. Manabe A, Kawasaki H, Shimada H, et al. Imatinib use immediately before stem cell transplantation in children with Philadelphia chromosome-positive acute lymphoblastic leukemia: Results from Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG) Study Ph(+) ALL04. Cancer Med 2015;4:682-9.
25. Nishiwaki S, Miyamura K, Kato C, et al. Impact of post-transplant imatinib administration on Philadelphia chromosome-positive acute lymphoblastic leukaemia. Anticancer Res 2010;30:2415-8.
26. Schultz KR, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. J Clin Oncol 2009;27:5175-81.
27. Satwani P, Sather H, Ozkaynak F, et al. Allogeneic bone marrow transplantation in first remission for children with ultra-high-risk features of acute lymphoblastic leukemia: A children's oncology group study report. Biol Blood Marrow Transplant 2007;13:218-27.
28. Schultz KR, Carroll A, Heerema NA, et al. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. Leukemia 2014;28:1467-71.