Biology of Blood and Marrow Transplantation 14:568-575 (2008)

1083-8791/08/1405-0001$32.00/0
doi:10.1016/j.bbmt.2008.02.018

Excellent Outcome of Allogeneic Hematopoietic Stem Cell Transplantation Using a Conditioning Regimen with Medium-Dose VP-16, Cyclophosphamide and Total-Body Irradiation for Adult Patients with Acute Lymphoblastic Leukemia

Akio Shigematsu,[1] *Takeshi Kondo*,[2] *Satoshi Yamamoto*,[3] *Junichi Sugita*,[1] *Masahiro Onozawa*,[2] *Kaoru Kahata*,[2] *Tomoyuki Endo*,[3] *Soichi Shiratori*,[1] *Shuichi Ota*,[2] *Masato Obara*,[3] *Kentaro Wakasa*,[1] *Mutsumi Takahata*,[2] *Yukari Takeda*,[3] *Junji Tanaka*,[1] *Satoshi Hashino*,[2] *Mitsufumi Nishio*,[3] *Takao Koike*,[3] *Masahiro Asaka*,[2] *Masahiro Imamura*[1]

[1] Department of Hematology and Oncology, [2] Department of Gastroenterology and Hematology, and [3] Department of Medicine II, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Correspondence and reprint requests: Akio Shigematsu, MD, Hematology and Oncology, Hokkaido University Graduate School of Medicine, Kita-15 Nishi-7, Kita-ku, Sapporo, Hokkaido, 060-8638, Japan (e-mail: shigemap@r9.dion.ne.jp).

Received January 8, 2008; accepted February 26, 2008

ABSTRACT

We retrospectively evaluated the outcomes of 37 adult patients with acute lymphoblastic leukemia (ALL) undergoing allogeneic hematopoietic stem cell transplantation (allo-SCT) conditioned with medium-dose VP-16 (VP, 30 mg/kg), cyclophosphamide (CY, 120 mg/kg), and fractionated total-body irradiation (TBI, 12 Gy) (medium-dose VP/CY/TBI). The median age of the patients was 26 years. Thirteen patients underwent transplantation from HLA-matched related donors (MRD), 18 patients underwent transplantation from HLA-matched unrelated donors (MUD), and 6 patients underwent transplantation from HLA-mismatched donors (MMD). Thirty-two patients received bone marrow and 4 patients received peripheral blood stem cells. Ten patients were Philadelphia chromosome-positive (Ph^+) and 35 patients were in complete remission (CR) at transplantation. All of the patients achieved engraftment, and grade 3 organ toxicity before engraftment occurred in 27 patients. Grade II-III acute graft-versus-host disease (GVHD) and chronic GVHD (cGVHD) occurred in 15 and 18 patients, respectively. No patient developed grade IV acute GVHD (aGVHD) or died of GVHD. At median follow-up of 35.1 months, 32 patients were alive and all Ph^+ patients were alive. Three patients died of relapse and 2 died of transplant-related mortality (TRM). The actuarial 3-year overall survival (OS) rate, relapse rate, and TRM rate were 89.2%, 8.1%, and 5.4%, respectively. Non-CR at transplantation, MRD, and no aGVHD were significant adverse prognostic factors for survival. Medium-dose VP/CY/TBI for adult ALL patients was associated with lower relapse rate and no increase in toxicity, resulting in better survival.

KEY WORDS

VP-16 • Acute lymphoblastic leukemia • Adult • Hematopoietic stem cell transplantation • Conditioning regimen

INTRODUCTION

Although complete remission (CR) has been induced by multiagent chemotherapies in the majority of patients with acute lymphoblastic leukemia (ALL), prognosis for adult ALL has not been satisfactory due to a high rate of relapse [1-5]. Allogeneic hematopoietic stem cell transplantation (allo-SCT) has been widely used as postremission therapy, especially for patients with high-risk ALL [6-8]. Even in patients treated with allo-SCT using a standard regimen of cyclophosphamide with total-body irradiation (CY/TBI), relapse has been a significant cause of death [7-12]. Various

intense conditioning regimens, including some regimens using VP-16 (VP) combined with CY/TBI (VP/CY/TBI), have therefore been developed [13-21]. The use of some intense regimens resulted in better disease control, but higher rates of toxicity and transplant-related mortality (TRM) have also been reported. We speculated that the high rates of TRM in these studies were mainly due to the doses of VP (45-60 mg/kg). Recently, we reported successful outcomes of patients with various kinds of hematologic malignancies treated with a medium-dose VP (30 mg/kg) /CY/TBI regimen at Hokkaido University Hospital in Japan: all of the 11 patients with adult ALL were alive after a median follow-up period of 77.0 months, and the actuarial 5-year disease-free survival (DFS) rate was 100% [22].

In this retrospective study, we confirmed the safety and efficacy of the medium-dose VP/CY/TBI regimen for 37 patients with adult and adolescent ALL or related disorders and revealed suitable patients for this regimen.

PATIENTS AND METHODS

Patients

We studied outcomes in a consecutive series of 37 adult or adolescent patients diagnosed with ALL, acute biphenotypic leukemia (ABL), or T cell lymphoblastic lymphoma (T-LBL) who underwent allo-SCT using a conditioning regimen of medium-dose VP/CY/TBI during the period from 1993 to June 2007 at Hokkaido University Hospital. We have been using this regimen for all adult ALL patients without any intentional selection, and all of the patients in whom this regimen was used were included in this study. Data for patients with Burkitt leukemia (FAB classification: L3) were excluded from analysis because Burkitt leukemia is defined as a different category from ALL in the World Health Organization (WHO) classification. Almost all of the patients received mutiagent chemotherapies (CY, vincristine, doxorubicin, L-asparaginase, and glucocorticoid) as an induction therapy, and 7 of the 10 Philadelphia chromosome-positive (Ph^+) patients were treated with chemotherapies that included imatinib prior to allo-SCT. No patient was exposed to VP as an induction therapy, but 15 patients received 1 course of consolidation therapy that included VP at a dose of 100 mg/m^2 daily for 4 or 5 days (total dose: 400 mg/m^2 or 500 mg/m^2).

Conditioning Regimen

All patients received medium-dose VP/CY/TBI. This regimen consisted of VP at a dose of 15 mg/kg once daily administered intravenously (i.v.) on days -7 and -6 (total dose: 30 mg/kg) and CY at 60 mg/kg once daily i.v. on days -5 and -4 (total dose: 120 mg/kg) combined with fractionated TBI at 2 Gy twice daily on days -3 to -1 (total dose: 12 Gy). Until 2000, graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine A and a short course of methotrexate (MTX, 15 mg/m^2 on day 1 and 10 mg/m^2 on days 3 and 6) for all of the patients. Since 2001, cyclosporine A plus MTX has been given for HLA-matched related donor (MRD) recipients and tacrolimus plus a short course of MTX has been given for HLA-matched unrelated donor (MUD) or HLA-mismatched donor (MMD) recipients. GVHD prophylaxis was administered for 3 months and then tapered in patients with no active GVHD, and the dose of cyclosporine A or tacrolimus was adjusted by plasma level.

Supportive Care

Granulocyte colony-stimulating factor was administered from day 1 until engraftment. A standard regimen of antibiotic prophylaxis was used to prevent bacterial, viral, fungal, and *Pneumocysitis jiroveci* infections. Treatment of mucosal injury and neutropenic fever was performed in accordance with standard practice guidelines. Surveillance blood antigenemia for cytomegalovirus was monitored twice weekly between engraftment and day 100 post-SCT, and patients received preemptive ganciclovir at onset of cytomegalovirus antigenemia.

Evaluation of Response

In this study, high-risk ALL patients were defined as those with at least 1 of the following risk factors: Ph^+, ABL, age $\geq$35 years old, white blood count (WBC) $>3.0 \times 10^{10}$/L for B lineage and $>10 \times 10^{10}$/L for T lineage at diagnosis, and time to CR of $>$6 weeks. Patients with T-LBL were excluded from this risk stratification. Neutrophil engraftment and platelet engraftment were defined as the first of 2 days with absolute neutrophil count $>0.5 \times 10^9$/L and the first of 7 days with an untransfused platelet count $>50 \times 10^9$/L, respectively. Toxicity after SCT was graded by the National Cancer Institute (NCI) common toxicity criteria (NCI, Bethesda, MD). Acute GVHD (aGVHD) and chronic GVHD (cGVHD) were graded by standard criteria. Serial samples of peripheral blood or bone marrow were monitored for hematopoietic chimerism by using polymerase chain reaction (PCR)-based analyses of short tandem repeats. In some patients, minimal residual disease was assessed by using the PCR method for detecting *BCR-ABL* fusion gene or case-specific immunoglobulin heavy chain or T cell receptor rearrangement, as described previously [23]. In brief, bone marrow samples were collected at the time of initial diagnosis and DNA was extracted. DNA samples were amplified by the seminested PCR procedure using amplimers for clonal VH-JH for IgH, Vγ-Jγ for TCR γ, and nested PCR detecting each VDJδ1-TCR recombination and Vδ2-Dδ3 recombination for TCR δ gene rearrangements.

For the detection of residual leukemic cells in specimens from patients, genomic DNA from leukemic cells at the time of initial diagnosis was compared with that from leukemic cells obtained before and after SCT.

Statistical Analysis

Overall survival (OS) was calculated from the day of SCT until death or last follow-up. The probability of OS was estimated using the Kaplan-Meier method. Relapse and TRM rates were estimated using cumulative incidence analysis and considered as competing risks. The effects of various patient and disease categoric variables on survival probabilities were studied using the log-rank test. All *P*-values were 2-sided and a *P*-value of .05 was used as the cutoff for statistical significance.

RESULTS

Patients and Transplant Characteristics

Patients and transplant characteristics are summarized in Table 1. The median age of the patients was 26 years (range: 15-58 years). Twenty-eight (75.7%) of the patients had ALL (B cell: 64.9%, T cell: 10.8%), 4 (10.8%) had ABL and 5 (13.5%) had T-LBL. Cytogenetic study was performed in 31 patients (83.8%) at diagnosis and Ph was positve in 10 (32.3%) of those patients. Twenty-one (68.8%) of the 32 evaluable patients were at high risk: age >35 years (13 patients, 35.1%), Ph^+ (mentioned above), ABL (4 patients, 12.5%), WBC $>3.0 \times 10^{10}$/L for B lineage at diagnosis (6 patients, 18.8%) and time to CR >6 weeks (7 patients, 21.9%). Central nervous system involvement of leukemia during the course of disease was seen in 3 patients (8.1%). Thirty-five (94.6%) of the patients were in CR at the time of SCT, 75.7% in first CR (CR1), and 18.9% in second CR (CR2). Only 2 patients were not in CR (non-CR). The *BCR-ABL* fusion gene was undetectable in 4 Ph^+ patients at the time of transplant. Patients received allo SCT from an MRD (13 patients, 35.1%), MUD (18 patients, 48.6%), or MMD (6 patients, 16.2%), and 32 patients (86.5%) received bone marrow.

Table 1. *Patient and Transplant Characteristics*

	n (%)
Total	**37**
Median age (range)	**26 (15.58)**
Age ≥ 35	**13 (35.1%)**
Age ≥ 40	**7 (18.9%)**
Sex	
Male	**20 (54.1%)**
Female	**17 (45.9%)**
Diagnosis	
B-ALL	**24 (64.9%)**
T-ALL	**4 (10.8%)**
ABL	**4 (10.8%)**
T-LBL	**5 (13.5%)**
Philadelphia chromosome*	**10 (32.3%)**
WBC $>3\times10^{10}$ for B-ALL†	**6 (18.8%)**
WBC $>10\times10^{10}$ for T-ALL†	**0 (0.0%)**
Time to CR >6 weeks†	**7 (21.9%)**
Disease risk†	
Standard	**10 (31.3%)**
High	**22 (68.8%)**
CNS involvement during course	**3 (8.1%)**
Disease status at transplantation	
CR	**35 (94.6%)**
CR1	**28 (75.7%)**
CR2	**7 (18.9%)**
non-CR	**2 (5.4%)**
Minimal residual disease at transplantation in CR patients	
PCR^+	**11 (31.4%)**
PCR^-	**9 (25.7%)**
N.D.	**15 (42.9%)**
Donor	
MRD	**13 (35.1%)**
MUD	**18 (48.6%)**
MMRD	**2 (5.4%)**
MMUD	**4 (10.8%)**
Stem cell source	
Bone marrow	**32 (86.5%)**
Peripheral blood stem cell	**4 (10.8%)**
Cord blood	**1 (2.7%)**
GVHD prophylaxis	
CSP+MTX	**28 (75.7%)**
TK+MTX	**9 (24.3%)**

All indicates acute lymphoblastic leukemia; ABL, acute bi phenotypic leukemia; T-LBL, T cell lympho plastic lymphoma; MRD, matched related donor; MUD, matched unrelated donor; MMD, mismatched donor; CR, complete remission; WBC, white blood cell; MMRD, mismatched related donor; MMUD, mismatched unrelated donor.

*Cytogenetic study was performed in 31 patients.

†Five patients with T-LBL were excluded from risk stratification.

Engraftment

All patients engrafted with median neutrophil recovery at day 16 (range: 8-25 days) and 34 patients engrafted with median platelet recovery at day 27 (range: 18-74 days). Results of engraftment analysis using short tandem repeats were available for 20 patients, showing 100% donor chimerism in all of them with median time of 100% chimerism being day 28 (range: 12-49 days). No recipient developed secondary graft failure.

Disease Control

Posttransplant bone marrow studies were not performed in 2 patients because of early deaths. None of the remaining 35 patients showed evidence of residual disease by morphology or cytogenetics. In 11 patients with morphologic CR but with minimal residual disease (PCR^+ CR) at the time of transplant, 10 patients (90.9%) became PCR-negative (PCR^- CR) after transplant and the remaining patient had persistent PCR positivity with no relapse. All Ph^+ patients were

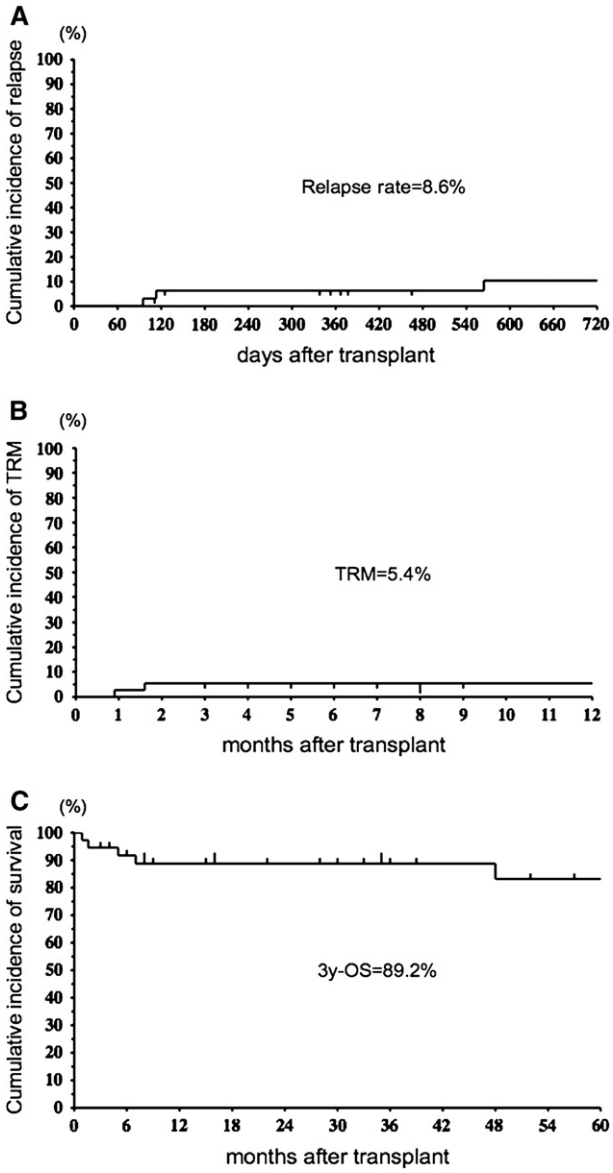

Figure 1. Cumulative incidence of relapse (a), TRM (b), and OS (c). TRM indicates transplant-related mortality; OS, overall survival.

alive without relapse during the follow-up period, and all of the 6 Ph^+ patients who were PCR-positive at transplantation became PCR-negative after allo-SCT. Therefore, no patients received imatinib after SCT. Only 3 patients (8.1%) relapsed after allo-SCT on days 95, 113, and 564, respectively, and all of them died (Figure 1a). Two of the 3 patients with earlier relapse had T-LBL and the other had B-ALL. These patients were in PCR^- CR1 at transplantation, and 2 (40%) of the 5 T-LBL patients relapsed.

Toxicity and GVHD

Table 2 shows a summary of organ toxicity and GVHD. Toxicity before engraftment could be assessed in 33 patients but not in 4 patients because of insufficient medical records. NCI grade ≥3 nonhematologic

Table 2. *Organ Toxicities and GVHD*

	No (%)
Organ toxicity*	
Any grade 3 toxicity	**27 (81.8%)**
Stomatitis	**19 (57.6%)**
Diarrhea	**11 (33.3%)**
Cardiovascular	**2 (6.1%)**
Pulmonary/DAH	**1 (3.0%)**
Hepatic	**3 (9.1%)**
VOD	**2 (6.1%)**
TMA	**2 (6.1%)**
Death due to organ toxicity	**2 (5.4%)**
Febrile episode before engraftment	**23 (69.7%)**
GVHD†	
Acute GVHD total	**29 (78.4%)**
Acute GVHD grade II-IV	**15 (40.5%)**
Chronic GVHD total	**18 (54.5%)**
Chronic GVHD extensive	**12 (36.4%)**
Death due to GVHD	**0 (0.0%)**

DAH indicates diffuse alveolar hemorrhage; VOD, veno-occlusive disease of the liver, TMA, thrombotic microangiopathy.

*Toxicity is graded by NCI common toxicity criteria. Only patients with grade 3 toxicity are presented. Some patients had toxicity in more than one organ system. Organ toxicity was evaluated in 33 patients.

†Acute GVHD and chronic GVHD were evaluted in 37 and 33 patients, respectively.

organ toxicity occurred in 27 patients (81.8%). NCI grade 3 stomatitis and diarrhea were common findings, occurring in 19 patients (57.6%) and 11 patients (33.3%), respectively. Febrile episodes were also common during the neutropenic period, occurring in 23 patients (69.7%). Although blood cultures and chest X-rays were frequently performed, pathogens of the fever could be detected in only 4 patients. Cardiovascular toxicity (congestive heart failure), pulmonary toxicity, hepatic toxicity including veno-occulusive disease (VOD) and transplant-related thrombotic microangiopathy occurred in 2 patients (6.1%), 1 patient (3%), 3 patients (9.1%), and 2 patients (6.1%), respectively. A clinical diagnosis of VOD could be made by the Jones criteria in only two patients (6.1%), and 1 of them, who had active disease at transplantation, died of hepatic failure on day 27. One patient of relatively advanced age (58 years old) died of respiratory failure due to interstitial pneumonitis of unknown etiology on day 48. Total and grade II–III aGVHD occurred in 29 and 15 patients with cumulative incidences of 78.4% and 40.5%, respectively. No patient developed grade IV aGVHD. Median onset day of aGVHD was day 19 (range: 7-59 days). Chronic GVHD occurred in 18 of the 33 evaluable patients, extensive in 12 patients, and limited in 6 patients (cumulative incidence: 54.5%), at median day 118 (range: 48-254 days). No patient died of complications related to aGVHD or cGVHD, and no secondary malignancy was observed during the follow-up period. TRM occurred in only 2 patients with a cumulative incidence of 5.4% at 3 years after SCT (Figure 1b).

Survival

At the end of a median follow-up period of 35.1 months (range: 0.9-163.2 months), 32 patients were alive and 5 had died. Two patients died of treatment-related complications before day 100 and 3 patients died of disease relapse. The actuarial 3-year OS and 5-year OS rates were 89.2% and 86.5%, respectively (Figure 1c). The 3-year OS rates for allo-SCT at CR1, CR2, and non-CR were 92.6%, 85.7%, and 50%, respectively. OS rates were 92.9% for patients with ALL, 100% for those with ABL, and 60% for those with T-LBL. All Ph^+ patients were alive and OS rate was 83.3% for those without Ph. OS rates for patients with aGVHD and those without aGVHD were 93.1% and 75.1%, respectively, and OS rates for patients transplanted from MRDs and those from MUDs were 76.9% and 100%, respectively. Table 3 shows the results of univariate analysis of factors influencing OS. Univariate analysis revealed non-CR at transplantation ($P < .01$), MRD ($P = .01$) and no aGVHD ($P = .02$) to be significant adverse prognostic factors for OS. Although not statistically significant, diagnosis of T-LBL ($P = .06$) or no cGVHD ($P = .08$) tended to have an adverse impact on OS. Age, patient's sex, central nervous system involvement, disease risk, type of CR (CR1 or CR2, PCR^+ or PCR^-) and GVHD prophylaxis were not predictive factors for the outcome.

DISCUSSION

We have previously reported the safety and efficacy of medium-dose VP/CY/TBI as a conditioning regimen of allo-SCT for hematologic malignancies [22]. In the current study, focusing on adult patients with ALL, engraftment was achieved in all patients. Although grade 3 stomatitis and febrile episodes in the neutropenic period were common, severe GVHD and TRM were not increased compared with those in previous studies [7-12]. The 3-year OS of 89.2% in our case series compares favorably with the results of other studies using a standard conditioning regimen of CY/TBI [7-12], our good results being because of reduction in relapse. In the LALA-94 trial, patients in CR1 with MRD were allocated to allo-SCT using CY/TBI. In the patients treated with allo-SCT, 3-year TRM rate, 3-year relapse rate, and 3-year disease-free survival (DFS) rate were 18%, 34%, and 47% respectively [10], indicating that relapse was the main cause of death even after allo-SCT. There have been many reports on intensified conditioning regimens of allo-SCT including high-dose VP (60 mg/kg or 1.5-1.8 g/m^2) /CYTBI for the purpose of reduction in relapse rate [13-22]. Most of those studies using VP/CY/TBI included patients with various kinds of hematologic malignancy, but our study was limited to adult ALL. In our study, relapse occurred in only 3 patients (8.1%), indicating much better disease control than that of CY/TBI or other regimens. Although our patients with GVHD showed better outcome than those without GVHD, which may suggest a graft-versus-leukemia (GVL) effect, better disease control in this study was thought to be mainly due to eradication of residual disease by the conditioning regimen. The reasons are that GVL effect has been reported to have limited efficacy for ALL patients, occurrence of aGVHD or cGVHD in our study was the same as that in other studies, and PCR^+ CR patients at transplantation became PCR^- CR soon after allo-SCT, suggesting a direct antitumor effect of the conditioning regimen. Although Ph^+ patients have been reported to have a poorer outcome than that of Ph^- patients after allo-SCT [10,24,25], all Ph^+ patients in our study were alive without relapse. Furthermore, some studies have shown that the outcome for patients in CR2 at transplantation was worse than that for patients in CR1 [26-28], but the outcomes of patients in CR1 and CR2 in the present study were comparable. Marks et al. [29] reported that a VP/TBI regimen showed better disease control than that of standard-dose CY/TBI for patients with ALL in CR2, indicating that VP has better anti-ALL activity than that of CY.

The rate of TRM in this study was also very low, occurring in only two patients (5.3%), and no patient died before engraftment despite the high rate of mucosal injury or febrile episodes. Furthermore, although there have been reports that aGVHD is related in part to cytokine release from damaged gastrointestinal tissues, incidence and severity of aGVHD in this study did not increase, and no patient died of GVHD. The dose used in VP/CY/TBI regimens in previous studies (60 mg/kg or 1.5-1.8 g/m^2) was higher than that used in our regimen, and the rate of TRM was higher in those studies (28%-47%), pulmonary toxicity (pulmonary hemorrhage and interstitial pneumonitis), and liver toxicity including VOD being the main causes of death [13-22]. Giralt et al. [14] and Yau et al. [16] reported that rates of TRM were 32.9% and 27.9%, respectively, and that incidences of diffuse alveolar hemorrhage causing death were 8% and 7%, respectively. In our study, only 1 patient (58 years old) died of interstitial pneumonitis, and no patient experienced diffuse pulmonary hemorrhage. Three patients developed grade 3 liver toxicity and 2 of them had VOD, and 1 of them with active disease died of hepatic failure due to VOD. Peterson et al. [15] and Spitzer et al. [20] reported that a lower dose of VP was associated with reduction in TRM, and we speculated that the difference between TRM in our study and that in other studies using VP/CY/TBI is mainly because of the dose of VP [22]. Although the dose of VP seemed to be important, TRM of 5.8% in this study was unexpectedly low. We have used a medium-dose VP/CY/TBI regimen for a total 92 patients with various kinds of hematologic

Table 3. *Univariate Analysis of Factors Predicting for Overall-Survival after allo-SCT*

	n	Alive (%)	HR	(95%CI)	*P*-value*
Age					
<40	30	27 (90.0%)	0.79	(0.07-8.25)	0.83
≥40	7	6 (85.7%)			
Sex					
Male	20	18 (90.0%)	0.59	(0.10-3.41)	0.55
Female	17	14 (82.4%)			
Diagnosis					
non T-LBL ALL	28	25 (89.3%)	0.21	(0.01-1.10)	0.06
ABL	4	4 (100%)			
T-LBL	5	3 (60.0%)			
Philadelphia chromosome					
Yes	10	10 (100%)	0.00	(0.04-1.68)	0.15
No	24	19 (79.2%)			
Disease risk					
Standard	10	9 (90.0%)	0.82	(0.07-8.95)	0.87
High	22	20 (90.9%)			
CNS involvement during course					
Yes	3	2 (66.7%)	1.17	(0.21-152.93)	0.30
No	34	30 (88.2%)			
Disease status at transplantation					
non-CR	2	1 (50.0%)	10.90	(9.78-1.5×10^6)	<0.01
CR	35	31 (88.6%)			
CR1	28	25 (89.3%)	0.79	(0.07-8.69)	0.83
CR2	7	6 (85.7%)			
PCR+CR	9	8 (88.9%)	1.17	(0.07-19.09)	0.91
PCR-CR	11	10 (90.9%)			
Donor					
MUD	13	13 (100%)	0.00	(0.01-0.61)	0.01
MRD	18	14 (77.8%)			
Acute GVHD prophylaxis					
CSP+MTX	28	24 (85.7%)	1.00	(0.11-9.03)	1.00
TK+MTX	9	8 (88.9%)			
Acute GVHD					
Yes	29	27 (93.1%)	0.15	(0.01-0.62)	0.02
No	8	5 (62.5%)			
Chronic GVHD					
Yes	18	18 (100%)	0.00	(0.00-1.37)	0.08
No	15	13 (86.7%)			

HR indicates hazard ratio; 95%CI, 95% confidence interval.
*Stastical analysis on OS was studied with the log-rank test.

malignancy and TRM rate was 15.2% (data not shown). Risk factors for TRM in this population were age ≥40 years (age <40 years: 8.7% versus age ≥40 years: 33.3%, $P = .001$) and non-CR at transplantation (CR: 10.8% versus non-CR: 25.9%, $P < .001$). Duerst et al. [21] reported that older age and advanced disease at transplantation were the main risk factors for TRM in their analysis of allo-SCT using medium-dose VP/CY/TBI for children with acute leukemia. In the current study, a smaller number of patients had these risk factors: 7 patients (19%) were older than 40 years and 2 patients (6%) were not in CR at transplantation, accounting for the unexpectedly low rate of TRM. The younger age of our patients may also explain our good results because of excellent disease control. Many clinical trials have shown higher remission rate and better prognosis among younger patients because of different biologic characteristics of leukemic cells and lower rate of complications despite intensified chemotherapy [30-33]. In our study, among 23 patients under the age of 30 years, 16 patients (69.6%) received SCT in CR1 and only 2 patients died due to disease progression. Two of the 3 patients with Ph were treated with imatinib before SCT, and 3 very young patients (<25 years of age) were treated using an intensified regimen like that used for childhood ALL. Nine patients received consolidation chemotherapies, which included high-dose cytarabine and high-dose MTX, and no patients developed central nervous system leukemia during the follow-up period. These developments in treatment strategy before SCT may also have contributed to the good results of our study.

A special consideration when using VP is secondary malignancies. Although VP is an active agent in ALL, many studies, mostly conducted in pediatric centers, have shown an increased risk of therapy-related leukemia and other malignancies by using VP [34-35], and VP has therefore been removed from most

induction regimens [35]. However, second malignancy should not be an issue with allo-SCT, and no patients in the present study developed second malignancy during a median follow-up period of 35.1 months. Therefore, this conditioning regimen for ALL would be an ideal venue to reintroduce this drug.

Although our analysis has limitations because of its retrospective fashion and small sample size, a medium-dose VP/CY/TBI regimen seems to be a promising treatment for adult patients with ALL, and a prospective study on this regimen for adult ALL is warranted. Although age was not a risk factor for survival in our analysis limited to ALL, age ≥40 years and non-CR at transplantation have been reported as risk factors for TRM, and we confirmed that patients with these risk factors were also at high risk for TRM after medium-dose VP/CY/TBI for hematologic malignancies (not limited to ALL). Therefore, we think that suitable patients for a prospective study are those aged <40 years and those in CR at transplantation.

In summary, the use of medium-dose VP/CY/TBI as a conditioning regimen for adult patients with ALL and related disorders enabled very good disease control without increase in TRM, resulting in better survival of patients.

REFERENCES

1. Hoelzer D, Thiel E, Löffler H, et al. Prognostic factors in a multicenter study for treatment of acute lymphoblastic leukemia in adults. *Blood*. 1988;71:123-131.
2. Larson RA, Dodge RK, Burns CP, 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;85:2025-2037.
3. Durrant IJ, Prentice HG, Richards SM. Intensification of treatment for adults with acute lymphoblastic leukaemia: results of U.K. Medical Research Council randomized trial UKALL XA. Medical Research Council Working Party on Leukaemia in Adults. *Br J Haematol*. 1997;99:84-92.
4. Kantarjian HM, O'Brien S, Smith TL, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. *J Clin Oncol*. 2000;18:547-561.
5. Annino L, Vegna ML, Camera A, et al. Treatment of adult acute lymphoblastic leukemia (ALL): long-term follow-up of the GIMEMA ALL 0288 randomized study. *Blood*. 2002;99: 863-871.
6. Yanada M, Matsuo K, Suzuki T, et al. Allogeneic hematopoietic stem cell transplantation as part of postremission therapy improves survival for adult patients with high-risk acute lymphoblastic leukemia: a metaanalysis. *Cancer*. 2006;106:2657-2663.
7. Sebban C, Lepage E, Vernant JP, et al. Allogeneic bone marrow transplantation in adult acute lymphoblastic leukemia in first complete remission: a comparative study. French Group of Therapy of Adult Acute Lymphoblastic Leukemia. *J Clin Oncol*. 1994;12:2580-2587.
8. Horowitz MM, Messerer D, Hoelzer D, et al. Chemotherapy compared with bone marrow transplantation for adults with acute lymphoblastic leukemia in first remission. *Ann Intern Med*. 1991;115:13-18.
9. Hahn T, Wall D, Camitta B, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute lymphoblastic leukemia in adults: an evidence-based review. *Biol Blood Marrow Transplant*. 2006;12:1-30.
10. Thomas X, Boiron JM, Huguet F, et al. Outcome of treatment in adults with acute lymphoblastic leukemia: analysis of the LALA-94 trial. *J Clin Oncol*. 2004;22:4075-4086.
11. Hunault M, Harousseau JL, Delain M, et al. Better outcome of adult acute lymphoblastic leukemia after early genoidentical allogeneic bone marrow tdransplantation (BMT) than after late high-dose therapy and autologous BMT: a GOELAMS trial. *Blood*. 2004;104:3028-3037.
12. Attal M, Blaise D, Marit G, et al. Consolidation treatment of adult acute lymphoblastic leukemia: a prospective, randomized trial comparing allogeneic versus autologous bone marrow transplantation and testing the impact of recombinant interleukin-2 after autologous bone marrow transplantation. BGMT Group. *Blood*. 1995;86:1619-1628.
13. Bostrom B, Weisdorf DJ, Kim T, et al. Bone marrow transplantation for advanced acute leukemia: a pilot study of high-energy total body irradiation, cyclophosphamide and continuous infusion etoposide. *Bone Marrow Transplant*. 1990;5:83-89.
14. Giralt SA, LeMaistre CF, Vriesendorp HM, et al. Etoposide, cyclophosphamide, total-body irradiation, and allogeneic bone marrow transplantation for hematologic malignancies. *J Clin Oncol*. 1994;12:1923-1930.
15. Petersen FB, Buckner CD, Appelbaum FR, et al. Etoposide, cyclophosphamide and fractionated total body irradiation as a preparative regimen for marrow trans-plantation in patients with advanced hematological malignancies: a phase 1 study. *Bone Marrow Transplant*. 1992;10:83-88.
16. Yau JC, LeMaistre CF, Andersson BS, et al. Allogeneic bone marrow transplantation for hematological malignancies following etoposide, cyclophosphamide, and fractionated total body irradiation. *Am J Hematol*. 1992;41:40-44.
17. Brown RA, Wolff SN, Fay JW, et al. High-dose etoposide, cyclophosphamide, and total body irradiation with allogeneic bone marrow transplantation for patients with acute myeloid leukemia in untreated first relapse: a study by the North American Marrow Transplant Group. *Blood*. 1995;85:1391-1395.
18. Brown RA, Wolff SN, Fay JW, et al. High-dose etoposide, cyclophosphamide and total body irradiation with allogeneic bone marrow transplantation for resistant acute myeloid leukemia: a study by the North American Marrow Transplant Group. *Leuk Lymphoma*. 1996;22:271-277.
19. Long GD, Amylon MD, Stockerl-Goldstein KE, et al. Fractionated total-body irradiation, etoposide, and cyclophosphamide followed by allogeneic bone marrow transplantation for patients with high-risk or advancedstage hematological malignancies. *Biol Blood Marrow Transplant*. 1997;3:324-330.
20. Spitzer TR, Peters C, Ortlieb M, et al. Etoposide in combination with cyclophosphamide and total body irradiation or busulfan as conditioning for marrow transplantation in adults and children. *Int J Radiat Oncol Biol Phys*. 1994;29:39-44.
21. Duerst RE, Horan JT, Liesveld JL, et al. Allogeneic bone marrow transplantation for children with acute leukemia: cytoreduction with fractionated total body irradiation, high-dose etoposide and cyclophosphamide. *Bone Marrow Transplant*. 2000;25:489-494.
22. Toubai T, Tanaka J, Mori A, et al. Efficacy of etoposide, cyclophosphamide, and total body irradiation in allogeneic bone marrow transplantation for adult patients with hematological malignancies. *Clin Transplant*. 2004;18:552-557.

23. Toubai T, Tanaka J, Ota S, et al. Minimal residual disease (MRD) monitoring using rearrangement of T-cell receptor and immunoglobulin H gene in the treatment of adult acute lymphoblastic leukemia patients. *Am J Hematol*. 2005;80:181-187.
24. Lee S, Kim DW, Kim YJ, et al. Influence of karyotype on outcome of allogeneic bone marrow transplantation for adults with precursor B-lineage acute lymphoblastic leukemia in first or second remission. *Br J Haematol*. 2002;117:109-118.
25. Dombret H, Gabert J, Boiron JM, et al. Groupe d'Etude et de Traitement de la Leucemie Aigue Lymphoblastique de l'Adulte (GET-LALA Group). Outcome of treatment in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia—results of the prospective multicenter LALA-94 trial. *Blood*. 2002;100:2357-2366.
26. Doney K, Hagglund H, Leisenring W, et al. Predictive factors for outcome of allogeneic hematopoietic cell transplantation for adult acute lymphoblastic leukemia. *Biol Blood Marrow Transplant*. 2003;9:472-481.
27. Doney K, Fisher LD, Appelbaum FR, et al. Treatment of adult acute lymphoblastic leukemia with allogeneic bone marrow transplantation. Multivariate analysis of factors affecting acute graft-versus-host disease, relapse, and relapse-free survival. *Bone Marrow Transplant*. 1991;7:453-459.
28. Woods WG, Nesbit ME, Ramsay NK, et al. Intensive therapy followed by bone marrow transplantation for patients with acute lymphocytic leukemia in second or subsequent remission: determination of prognostic factors (a report from the University of Minnesota Bone Marrow Transplantation Team). *Blood*. 1983; 61:1182-1189.
29. Marks DI, Forman SJ, Blume KG, et al. A comparison of cyclophosphamide and total body irradiation with etoposide and total body irradiation as conditioning regimens for patients undergoing sibling allografting for acute lymphoblastic leukemia in first or second complete remission. *Biol Blood Marrow Transplant*. 2006;12:438-453.
30. Larson RA, Dodge RK, Burns CP, 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;85:2025-2037.
31. Ueda T, Miyawaki S, Asou N, et al. Response-oriented individualized induction therapy with 6 drugs followed by 4 courses of intensive consolidation, 1 year maintenance and intensification therapy: the ALL90 study of the Japan Adult Leukemia Study Group. *Int J Hematol*. 1998;68:279-289.
32. Pui CH, Relling MV. Topoisomerase II inhibitor-related acute myeloid leukaemia. *Br J Haematol*. 2000;109:13-23.
33. Pui CH, Ribeiro RC, Hancock ML, et al. Acute myeloid leukemia in children treated with epipodophyllotoxins for acute lymphoblastic leukemia. *N Engl J Med*. 1991;325: 1682-1687.
34. Hijiya N, Hudson MM, Lensing S, et al. Cumulative incidence of secondary neoplasms as a first event after childhood acute lymphoblastic leukemia. *JAMA*. 2007;297:1207-1215.
35. Pui CH, Sandlund JT, Pei D, et al. Total Therapy Study XIIIB at St. Jude Children's Research Hospital. Improved outcome for children with acute lymphoblastic leukemia: results of Total Therapy Study XIIIB at St. Jude Children's Research Hospital. *Blood*. 2004;104:2690-2696.