leukemia (n = 12), plasma cell leukemia (n = 1), multiple myeloma (n = 1), and AA (n = 2). Three patients had previous autologous hematopoietic cell transplantation. For disease status, those with hematologic malignancies in first or second complete remission at the time of transplant, those in the chronic phase or accelerated phase of CML, those with refractory anemia of MDS, and those with nonmalignant diseases were defined as being at standard risk (n = 15), whereas those in other situations were defined as being at high risk (n = 55). Patients were assessed for their comorbidity by the previously reported scoring system [20].

Conditioning Regimens and Postgrafting Immunosuppression

Pretransplant conditioning varied, and was determined by each attending physician according to the patient's disease, disease status, and history of prior therapy. Sixty-five patients underwent conditioning regimens with 125-180 mg/m^2 of fludarabine (Flu; 25 mg/m^2 for 5 days or 30 mg/m^2 for 6 days), along with 80 mg/m^2 of melphalan (Mel; 40 mg/m^2 for 2 days) and total-body irradiation (TBI) at a total dose of 4 Gy for 63 and 2 Gy for 2. Four patients in relatively poor performance status were conditioned with busulfan to avoid severe gastrointestinal tract toxicity induced by the use of Mel. One patient underwent a conditioning regimen with thiotepa (5 mg/kg for 2 days) in addition to 125 mg/m^2 of Flu and 80 mg/m^2 of Mel, because of the urgent transplant schedule that did not allow access to TBI. Valproate sodium (300 mg/day) was administered to all patients who received Bu. Immunosuppressive therapy with cyclosporine A (CsA, 3 mg/kg continuous infusion, aiming for a serum concentration of 250-400 ng/mL) or tacrolimus (Tac, 0.03 mg/kg continuous infusion, aiming for 12-17 ng/mL) was started on day −1. CsA was used for patients in the early phase of this study, and, based on our early experience of high early mortality related to PIR in the patients with CsA prophylaxis, Tac was subsequently used to substitute for CsA.

Supportive Care

Prophylactic antibiotics, including fluorquinolone, fluconazole, and acyclovir, were used routinely. Patients received ganciclovir or foscarnet for any sign of a cytomegalovirus reactivation, such as isolation of CMV or detection of viral proteins (pp65) or nucleic acid in any body fluid or tissue specimen. *Pneumocystis jiroveci* prophylaxis included trimethoprim-sulfamethoxazole as first-line therapy.

Definition of Engraftment, Preengraftment Immune Reaction, and End Points

OS ands PFS were computed from the date of transplantation. Engraftment was defined as absolute neutrophil count >0.5 × 10^9/L for 3 consecutive days. Chimerism was assessed using fluorescent in situ hybridization in sex-mismatched donor-recipient pairs. In sex-mismatched pairs, PCR for variable number of tandem repeats was used with donor cells detected at a sensitivity of 10%. Whole blood or BM cells were assessed at the time of granulocyte engraftment. PIR was characterized by the presence of at least 2 of the following symptoms with no direct consequences of infection or adverse effects of medication 6 or more days before engraftment, as described previously [12,18]; a high fever (>38.5°C), skin eruptions, diarrhea, jaundice (serum levels of total bilirubin >2.0 mg/dL), or body weight gain >10% of baseline. NRM was defined as death in the absence of disease progression. Deaths occurring after disease progression were categorized as relapse regardless of the cause of death. Infection was considered the cause of death when bacterial, viral, or fungal infection was determined to be the proximate cause of death in patients who had not relapsed. Patients underwent BM aspiration at the time of engraftment or if clinically indicated. Relapse for AML, ALL, CML, or MDS was determined by flow cytometric, morphologic, or cytogenetic evidence of malignant or dysplastic cells with clonal markers similar to those observed before transplantation. Relapse for NHL was defined as progressive adenopathy or BM involvement. Acute and chronic GVHD (aGVHD, cGVHD) were defined and graded by standard criteria [21]. The following factors were considered potential predictors of outcomes: recipient's age, disease risk (standard versus high), ECOG performance status, HCT-specific comorbidity index score, history of prior chemotherapy (all cytoreductive chemotherapy excluding hydroxyurea and imatinib mesylate), history of prior documented infections (infectious episode with positive culture results for bacterial or yeast infections, and at least probable diagnosis of mold infection by EORTC/NIH-MSG criteria [22]), number of total nucleated cord blood cells, number of CD34$^+$ cells, HLA disparity, conditioning regimen, GVHD prophylaxis, grade of aGVHD, and the presence or absence of PIR.

Statistical Methods

OS was calculated from the day of transplantation until death from any cause or last follow-up. Disease-free survival (DFS) was calculated from the day of transplantation until relapse or death from any cause or last follow-up. The probabilities of survival and DFS were estimated and plotted using the Kaplan-Meier method [23]. Relapse and NRM rates were estimated using cumulative incidence analysis and were considered competing risks [24]. Similarly, in the analysis of GVHD rates, death because of other causes or relapse leading to early withdrawal of immune suppression were considered competing risks. The effect

of various patient and disease categoric variables on survival probabilities was studied with the log-rank test. A Cox proportional hazard model with limited variables because of small sample was used to determine the significance of multiple variables in determining these outcomes. Cumulative incidence curves were drawn using Gray's method [25].

RESULTS

Engraftment

Ten of the 70 patients were not evaluable for donor engraftment because of early death (before 28 days posttransplant) from disease progression (n = 1), infection (n = 7), and complications of central nervous system (n = 2). Of the 60 evaluable patients, the cumulative incidence of primary donor engraftment was 92% at a median of 18 days after transplantation (range: 11-53 days). Platelet recovery $>20 \times 10^9$/L was observed in 38 patients (63%), at a median of 35 days (range: 25-95 days). All patients required transfusions of platelets and red blood cells. Recovery of neutrophil counts $>0.5 \times 10^9$/L did not occur in 5 patients who survived beyond 28 days posttransplant; these patients were classified as primary graft failures. Two of these patients received secondary RI-UCBT and died of infection. The remaining 3 patients died of infection. All engrafting patients without BM relapse were complete donor chimeras beyond 1 month after transplantation (data not shown). Remarkably, all 3 evaluated patients of 10 who died before day 28 showed complete donor chimerism (94%, 100%, and 94.6% on days 12, 15, and 20 posttransplant, respectively).

PIR and GVHD

Forty-three patients experienced clinical symptoms defined as PIR, as described previously [12,18]. Patients who received Tac as GVHD prophylaxis tended to have a lower chance of experiencing PIR compared with those who received CsA, although differences were not statistically significant (53% versus 72%, respectively; $P = .1$).

Among 54 evaluable patients, 33 patients (61%) developed aGVHD of grade II or higher, including 23 patients (43%) who developed that of grade III or IV. Of the 30 patients who survived longer than 100 days posttransplant, 12 (40%) developed cGVHD, including 7 with limited and 5 with extensive form (Table 2).

Survival, Disease Progression, and NRM

At the time of analysis, 20 of 70 patients survived a median of 512 days (range: 103-1213 days) after transplantation. The Kaplan-Meier estimates of OS and PFS at 2 years were both 23% (Figure 1). The median OS time was 114 days (range: 7–1213 days), and the median PFS time was 92 days (range: 7–1213 days).

Table 2. *The Incidence and Severity of Graft-versus-Host Disease (GVHD)*

	Patients (n = 54)
	No. (%)
Acute GVHD	45 (83)
Grade II-IV	33 (61)
Grade III-IV	23 (43)
	Patients (n = 30)
	No. (%)
Chronic GVHD	12 (40)
Limited	7 (23)
Extensive	5 (17)

Eighteen patients (26%) showed progression of the underlying disease at a median of 134 days (range: 13–785 days) after transplantation, and 15 of these patients died of their disease.

Thirty-seven patients died of nonrelapse causes (Table 3). Nineteen of them were from infections, which was the leading cause of NRM. Among 33 deaths observed before day 100 posttransplant, 30 were from nonrelapse causes and 3 from disease progression. The cumulative incidences curves of NRM and disease progression are shown in Figure 2.

Factors Contributing to OS and NRM

In univariate analyses, survival was associated with recipient's age ($P = .01$), disease risk ($P < .01$), aGVHD ($P < .01$), and PIR ($P < .01$), with favorable outcomes in younger recipients (<61 years), those with standard risk, those with lower grade aGVHD (grade 0-II), and those without PIR (Figure 3A-D). Potential risk factors such as ECOG performance status, HCT-specific comorbidity index score, history of prior documented infection, history of prior chemotherapy, HLA disparity,

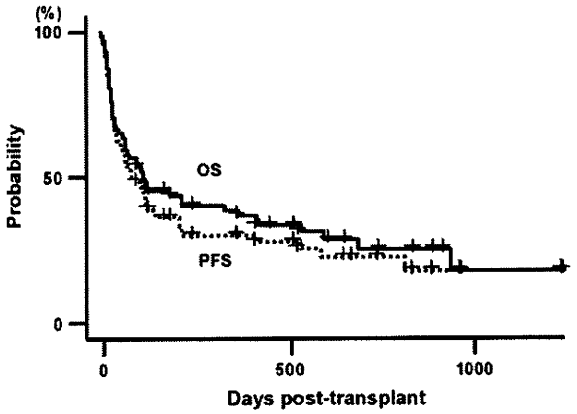

Figure 1. OS and PFS estimates for 70 patients with hematologic diseases treated with RI-UCBT.

Table 3. *Causes of Death*

	Patients (n = 70)
	No. (%)
NRM	37 (53)
Infection	19 (27)
GVHD	9 (12)
IP	4 (6)
TMA	3 (4)
Others	2 (3)
Relapse	13 (19)
Total	50 (71)

NRM indicates nonrelapse mortality; GVHD, graft-versus-host disease; IP, interstitial pneumonia; TMA, thrombotic microangiopathy.

sex mismatch, number of infused cells, number of infused $CD34^+$ cells, and cGVHD did not reach statistical significance.

In the Cox regression analyses, recipient's age equal to or older than 61 (hazard ratio [HR] = 3.33; 95% confidence interval [CI] = 1.39-7.14; $P = .006$), high risk disease (HR = 3.33; 95% CI = 1.01; 8.33 $P = .049$), grade III-IV aGVHD (HR = 2.5; 95% CI = 1.28; 5.88 $P = .0002$), and the presence of PIR (HR = 2.5; 95% CI = 1.14; 6.25 $P = .023$) were associated with statistically worse OS (Table 4). No other factors were significantly or suggestively associated with OS.

Regarding toxicity, multivariate analyses revealed that GVHD prophylaxis (HR = 3.9, 95% CI = 1.3-11.6 for CsA versus Tac; $P = .01$) and aGVHD (HR = 5.7, 95% CI = 2.1-15.7 for grade III–IV versus 0-II; $P = .001$) were associated with NRM.

DISCUSSION

This study was undertaken to evaluate engraftment and toxicities in elderly patients with advanced hematologic diseases who received UCBT matched for at least 4 loci of HLA-A, -B, and –DRB1 using a nonmyeloablative regimen.

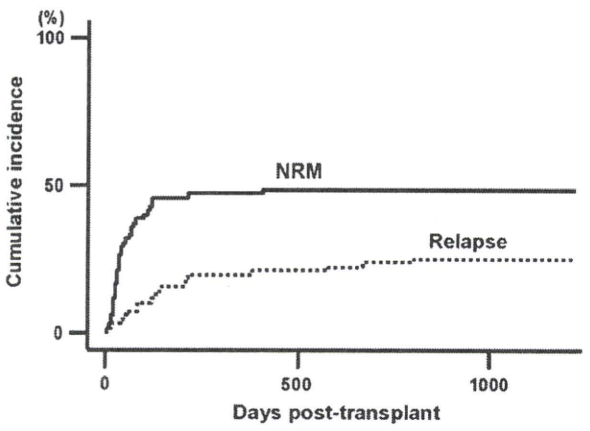

Figure 2. NRM and disease progression. Cumulative incidence estimates of NRM and disease progression for all 70 patients.

Several observations were made. First and foremost, RI-UCBT was a feasible treatment strategy for elderly patients with a successful engraftment rate of 92% without secondary graft failure except disease progression. The average interval between transplant and neurtophil recovery to 500/μL was 18 days, which is comparable to previously reported in RIC [11,12]. The chimerism study confirmed rapid engraftment of donor cells in all engrafted patients. Together with the fact that all 3 evaluated patients who died before day 28 already achieved complete donor chimerism, these data indicate that our pretransplant conditioning regimens, mainly consisting of Flu, Mel, and TBI, along with single calcineurin inhibitors for GVHD prophylaxis, can exert sufficient immunosuppressive effects that allow engraftment of CB cells. Compared to the conditioning regimen containing cyclophosphamide reported from Minnesota group [11], which allow mixed chimeric state especially for myeloid lineages during the early period of posttransplant, our conditioning is more powerful in eradicating host myeloid cells as well, which may have beneficial effect for rapid control of myeloid malignancies. The OS and PFS were estimated as both 23% at 2 years posttransplant, almost comparable to or slightly less than the data reported previously [15,16,26], which can be reasonably explained by higher age range and poor disease status before transplant in this study cohort, which can be further supported by the result of subgroup analysis indicating those with standard disease status showed much better outcome (Figure 3B).

UCBT has been associated with lower incidence of aGVHD, possibly because of the immunologic naïvety of transplanted lymphocytes; however, this naïvety raises a concern about whether transplanted cells will have sufficient antimalignant activity. Several reports indicate the in vivo antimalignancy effect of cord blood cells [27-30]. Cumulative incidence of disease progression at 2 years posttransplant in our series was 24%, which is comparable to those previously reported [15,16,26]. It plateaued later than 795 days, indicating that our RI-UCBT treatment protocol offered fairly good disease control.

The incidence of GVHD was higher than previous reports in RIC [11,12], and was almost comparable to those of BM transplants, PB cell transplants, or UCBT with conventional conditioning [8-10,31-36]. Because of the poor disease status of the majority of patients included in this study, GVHD prophylaxis was initially planned to be less intensive with single calcineurin inhibitors. Older patients' age [37] or high incidence of infectious complications, which possibly induced excessive inflammatory cytokine secretions, could have been relevant to this result [38].

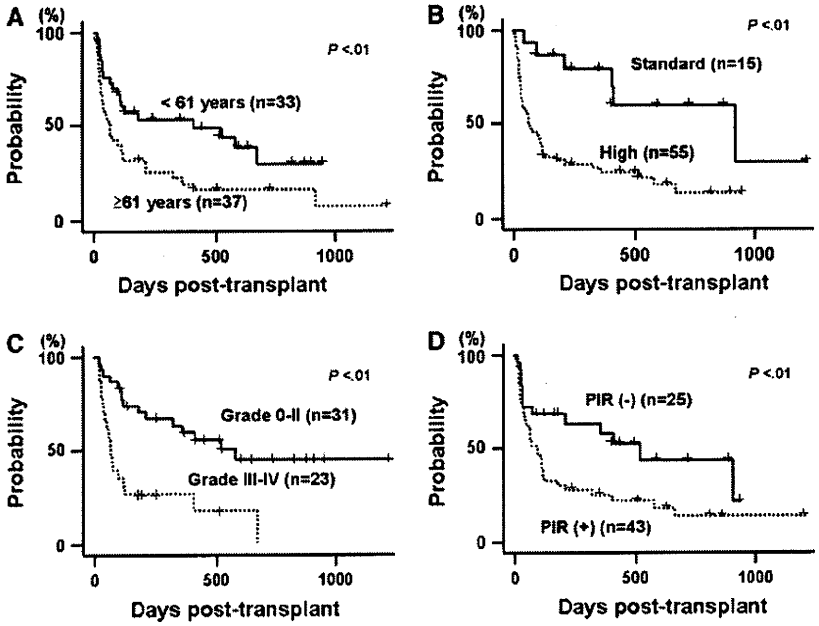

Figure 3. OS estimates after RI-UCBT (n = 70). (A) Effect of age. (B) Effect of disease status. (C) Effect of severity of aGVHD. (D) Effect of PIR.

Although RI-UCBT has been a feasible approach in terms of engraftment, a significant number of patients died from treatment-related complications. NRM was close to 3 times higher than mortality from relapse or disease progression, and most NRM occurred within 100 days posttransplant. Of 37 deaths because of NRM, 19 were from infection. Delayed engraftment relative to other stem cell sources such as BM or PB cells has been suggested to account for the higher rate of infectious complications after UCBT [32,39,40], but the time to engraftment in our series of patients was not delayed. Higher grade of aGVHD and the presence of PIR were found to be significantly associated with poor OS in multivariate analysis, indicating that immune-mediated events have strong impact on patients' outcome (Table 4). PIR is the syndrome observed in our setting of RI-UCBT. Although the mechanism behind PIR has not been investigated extensively yet, it is assumed to be reflecting alloimmune event, given our experience that more intensive GVHD prophylaxis with Tac had tendency to decrease the incidence of PIR. Moreover, development of PIR may have been suppressed in reported cases from other institutes that utilized additional agents to calcineurin inhibitors, such as methotrexate [10,19], antithymocyte globulin [31], or mycophenolate mofetil [16]. There has been a similar early immune reaction-like syndrome reported as "hyperacute GVHD" observed following BM or PBSC transplant, and responded poorly to corticosteroids compared to traditional aGVHD [41,42]. The incidence of PIR was higher than that of hyperacute GVHD, and further investigation on biologic mechanisms may help us define PIR more precisely relative to other immune-mediated diagnosis and develop optimal treatment approach. The presence of PIR was shown to cause more NRM than the absence in univariate analysis (P = .02), although it did not reach statistical significance in multivariate analysis. Thus, better management of immune-mediated complications will be the key to reduce NRM and improve OS. Based on our early experience of high early mortality related to PIR in the patients with CsA prophylaxis, Tac was subsequently used to substitute for CsA, because Tac was shown to be more potent than CsA in BM transplant [43-45]. Patients who received Tac as GVHD prophylaxis had less chance of experiencing PIR compared with those who received CsA and had less NRM, indicating the potential benefit of using Tac as a standard agent for GVHD prophylaxis. Adding methotrexate, mycophenolate mofetile, or sirolimus to the calcineurin inhibitor may further improve the final outcome [10,11,46,47]. Older age was another factor that influenced OS with statistical significance, even within the age range studied (Figure 3A and Table 4). Patients aged 61 years and older experienced more NRM than patients younger than 61 years (65% versus 39%), whereas their death rate because of disease progression was comparable (19% versus 18%), suggesting the vulnerability of higher aged population to procedure toxicity. Although the possible impact of slight variation in conditioning regimen to the outcome cannot be excluded, it is unlikely, because the great majority (93%) were conditioned with Flu/Mel/TBI regimen fairly uniformly, and comparison between Flu/Mel/TBI and others did not reach statistical significance.

Table 4. *Cox Regression Analyses of Factors Potentially Associated with OS and NRM after RI-UCBT*

Variables	HR	95% CI	P
OS			
Age			
Less than 61 years (n = 33)	**0.3**	**0.14-0.72**	**.006**
At least 61 years (n = 37)	**1.0**		
Disease risk			
Standard (n = 15)	**0.3**	**0.12-0.995**	**.049**
High (n = 55)	**1.0**		
PIR			
No (n = 25)	**0.4**	**0.16-0.88**	**.023**
Yes (n = 43)	**1.0**		
Acute GVHD			
Grade 0-II (n = 31)	**0.4**	**0.17-0.78**	**.0002**
Grade III-IV (n = 23)	**1.0**		
NRM			
GVHD prophylaxis			
CsA (n = 37)	**3.9**	**1.3-11.6**	**.01**
Tac (n = 33)	**1.0**		
Acute GVHD			
Grade 0-II (n = 31)	**1.0**		
Grade III-IV (n = 43)	**5.7**	**2.1-15.7**	**.001**

GVHD indicates graft-versus-host disease; CsA, cyclosporine A; Tac, tacrolimus; NRM, nonrelapse mortality; CI, confidence interval; HR, hazard ratio; OS, overall survival.

In conclusion, this is the first study specifically focusing on elderly patients aged 55 years and older with advanced hematologic diseases to show the feasibility of RI-UCBT. Older age per se cannot be considered to be contraindication to RI-UCBT, although a high NRM has been observed. Further optimization of the treatment protocol, such as immunosuppressive therapy for GVHD prophylaxis, is warranted to establish the safety of this promising treatment strategy for elderly patients with advanced hematologic diseases.

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