Transplantation of allogeneic hematopoietic stem cells for adult T-cell leukemia: a nationwide retrospective study

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Allogeneic hematopoietic stem cell transplantation (HSCT) is increasingly used as a curative option for adult T-cell leukemia (ATL), an intractable mature T-cell neoplasm causally linked with human T-cell leukemia virus type I (HTLV-I). We compared outcomes of 386 patients with ATL who underwent allogeneic HSCT using different graft sources: 154 received human leukocyte antigen (HLA)–matched related marrow or peripheral blood; 43 received HLA-mismatched related marrow or peripheral blood; 99 received unrelated marrow; 90 received single unit unrelated cord blood. After a median follow-up of 41 months (range, 1.5-102), 3-year overall survival for entire cohort was 33% (95% confidence interval, 28%-38%). Multivariable analysis revealed 4 recipient factors significantly associated with lower survival rates: older age (> 50 years), male sex, status other than complete remission, and use of unrelated cord blood compared with use of HLA-matched related grafts. Treatment-related mortality rate was higher among patients given cord blood transplants; disease-associated mortality was higher among male recipients or those given transplants not in remission. Among patients who received related transplants, donor HTLV-I seropositivity adversely affected disease-associated mortality. In conclusion, allogeneic HSCT using currently available graft source is an effective treatment in selected patients with ATL, although greater effort is warranted to reduce treatment-related mortality. (*Blood.* 2010;116(8):1369-1376)

Introduction

Adult T-cell leukemia (ATL) is a mature T-cell neoplasm developing in a minority of persons infected with human T-cell leukemia virus type I (HTLV-I), the first retrovirus isolated from a human malignant disease.[1-4] HTLV-I is estimated to infect 10 to 20 million people worldwide and is endemic in some areas of Japan, sub-Saharan Africa, the Caribbean Basin, and South America.[5,6] The area with the highest HTLV-I prevalence is the Kyushu district in southwestern Japan, where more than 10% of the general population is infected and the cumulative incidence of developing ATL among adult virus carriers is estimated at approximately 6.6% for males and 2.1% for females.[7] The onset of ATL after HTLV-I infection appears to require a long latency period because the median age at diagnosis ranges from 40 to 60 years in most endemic regions where mother-to-child viral transmission had been previously common.[4-6]

Clinical manifestation of ATL is heterogeneous and characterized by various degrees of lymphadenopathy, abnormal lymphocytosis, hepatosplenomegaly, skin lesions, and hypercalcemia, dividing the disease into 4 subtypes: acute, lymphomatous, chronic, and smoldering.[8] Patients with acute or lymphomatous type had extremely poor prognosis, mainly because of resistance to a variety of cytotoxic agents and susceptibility to opportunistic infections. Chronic and smoldering forms have relatively indolent clinical courses but can transform into more aggressive subtypes. During the past 3 decades since the clinical discovery of ATL,[1] the results of conventional cytotoxic chemotherapy remain dismal because of low response rates and lack of long-term efficacy. The

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median survival time that followed the best clinical results to date is approximately 13 months[9,10]; complete response can only be achieved in 25%-40% of treated cases and most of them eventually relapsed with the median progression-free survival time of 5 to 7 months, whereas available treatment options are extremely limited in those who failed initial chemotherapy.[11-14]

Although the early experience of ablative chemoradiotherapy with autologous hematopoietic stem cell rescue for ATL resulted in a high incidence of relapse and fatal toxicities,[15] allogeneic hematopoietic stem cell transplantation (HSCT) has been explored as a promising alternative that can provide long-term remission in a proportion of patients with ATL.[16-19] Although the mechanisms by which allografting can eradicate HTLV-I–infected neoplastic T cells are not fully elucidated, several reports have suggested the role of graft-versus-HTLV-I or graft-versus-ATL effects.[20-23] Over the past decade, improved access to alternative stem cell sources and the development of less toxic conditioning regimens have led to a rapid increase in the number of cases of ATL treated with allogeneic HSCT, albeit without consistent efficacy.[24-30] Therefore, we conducted a nationwide retrospective cohort study to identify pretransplantation factors that affect survival after allografting for ATL, with special emphasis on the effect of graft source: we compared the outcomes of human leukocyte antigen (HLA)–mismatched related bone marrow or peripheral blood transplantation, unrelated bone marrow transplantation, and unrelated cord blood transplantation with those of HLA-matched related bone marrow or peripheral blood transplantation as treatment for ATL. We also evaluated the effect of donor HTLV-I serostatus on outcomes among patients who received transplants from related donors.

Methods

Collection of data

Data on 417 patients with acute or lymphomatous type ATL who had received T-cell–replete allogeneic bone marrow, peripheral blood, or cord blood transplantation between January 1, 1996, and December 31, 2005, were collected through the 3 largest hematopoietic cell transplant registries in our country: the Japan Society for Hematopoietic Cell Transplantation (JSHCT), the Japan Marrow Donor Program (JMDP), and the Japan Cord Blood Bank Network (JCBBN). The patients were included from 102 transplant centers; the data were updated as of December 2008. To evaluate the effect of HTLV-I infection in donors on transplantation outcomes, additional questionnaires were sent to 77 centers in January 2010 to retrieve data on donor HTLV-I serostatus in 217 related transplants registered with the JSHCT. Our analysis included patients for whom there was data on age at transplantation, sex, donor type, stem cell source, and agents used in the conditioning regimen and graft-versus-host disease (GVHD) prophylaxis. Twenty-two patients who missed any of these data, and 8 patients who had a history of prior autologous or allogeneic stem cell transplantation were excluded from the analysis. One patient who had received an ex vivo T-cell–depleted graft was also excluded. Two independent physicians reviewed the quality of collected data, and a total of 386 patients (209 males and 177 females), with a median age of 51 years (range, 18-79 years), were found to fulfill the inclusion criteria: 197 patients from JSHCT, 99 from JMDP, and 90 from JCBBN. No overlapping cases were identified. Data on engraftment or graft failure were missing in 23 patients. Data on acute GVHD were not available in 53 patients because of early death or missing data.

The JSHCT registry currently includes more than 390 transplant centers variously located in Japan and collects data on transplantation by use of autologous or related stem cell grafts. The JMDP includes more than 190 centers and collects data on unrelated bone marrow transplantation. The JCBBN, a national network of 11 cord blood banks, collects data on unrelated cord blood transplantations reported individually from more than 220 transplant centers to each bank. Participating centers to these registries are requested to report each type of transplantation consecutively and longitudinally. Until 2005, the 3 registries were operated separately from one another: however, a project attempting to unify them has been launched via development of the Transplant Registry Unified Management Program, which enables participating centers to use a shared format for data submission to each registry.[31] All unrelated donor transplants in Japan were facilitated through the JMDP and JCBBN, although peripheral blood donation from unrelated volunteers has not yet been instituted as of March 2010. The study was approved by the data management committees of the JSHCT, JMDP, and JCBBN, as well as by the institutional review boards of Kyoto University, Graduate School of Medicine, where this study was organized.

End points

The primary end point of the study was overall survival, defined as the time from the date of transplantation until date of death from any cause. Patients who remained alive at the time of last follow-up were censored. Reported causes of death were reviewed and categorized into disease-associated or treatment-associated deaths. Disease-associated deaths were defined as deaths from relapse or progression of ATL among patients who survived for at least 30 days after transplantation. Treatment-related deaths were defined as any death other than disease-associated deaths. Neutrophil recovery was considered to have occurred when an absolute neutrophil count exceeded 0.5×10^9/L for 3 consecutive days after transplantation. Primary graft failure was evaluated in patients who survived at least 30 days and was defined as no evidence of neutrophil recovery after transplantation. Acute and chronic GVHD were diagnosed and graded using traditional criteria by the physicians who performed transplantations at each center.[32,33] The incidence of acute GVHD was evaluated in patients who survived for at least 7 days, and that of chronic GVHD was evaluated in patients who survived for at least 100 days.

Statistical analysis

Descriptive statistics were used for summarizing variables related to patient demographics and transplant characteristics. Comparisons among the groups were performed by use of the χ^2 statistic or extended Fisher exact test as appropriate for categorical variables, and the Kruskal-Wallis test for continuous variables. The probability of overall survival was estimated according to the Kaplan-Meier method, and univariable comparisons among the groups were made using the log-rank test. Probabilities of acute and chronic GVHD, treatment-related mortality, and disease-associated mortality were estimated with the use of cumulative incidence curves to accommodate the following competing events[34]: death without GVHD for acute and chronic GVHD, disease-associated death for treatment-related mortality, and treatment-related death for disease-associated mortality. Data on patients who were alive at the time of last follow-up were censored. Cox proportional-hazards regression was used to evaluate variables potentially affecting overall survival, whereas Fine and Gray proportional-hazard model was used to evaluate variables affecting other outcomes.[35] The variables considered were recipient age group ($\leq$ 50 years or $>$ 50 years at transplantation); recipient sex; disease status before transplantation; type of conditioning regimen; type of GVHD prophylaxis; type of graft source; time from diagnosis to transplantation (within 6 months or longer than 6 months); and year of transplantation. Only factors differing in distribution among the graft source groups and factors associated with outcomes by univariable comparison were included in the final models. The effect of donor HTLV-I seropositivity on outcomes after related donor transplantation was also evaluated by univariable and multivariable analysis with the use of data on 156 patients given transplants from siblings or other related family members for whom data on the HTLV-I serostatus were available. Results were expressed as hazard ratios and their 95% confidence interval (CI). All tests were 2-sided, and a P value of less than .05 was considered to indicate statistical significance. All statistical analyses were performed with STATA software (Version 11; Stata Corporation).

Results

Patients

Table 1 shows characteristics of the patients and transplantation procedures. Compared with HLA-matched related bone marrow or

Table 1. Characteristics of allografted patients with ATL

Patient variables	No. of recipients by graft source type (%)				
	HLA-matched related bone marrow or peripheral blood (N = 154)	HLA-mismatched related bone marrow or peripheral blood (N = 43)	Unrelated bone marrow (N = 99)	Unrelated cord blood (N = 90)	*P*
Age range at transplantation, y					.001
30 or younger	4 (3)	1 (2)	2 (2)	1 (1)	
30-40	21 (14)	4 (9)	8 (8)	3 (3)	
40-50	56 (36)	12 (28)	44 (44)	21 (23)	
50-60	57 (37)	22 (51)	43 (43)	47 (52)	
Older than 60	16 (10)	4 (9)	2 (2)	18 (20)	
Sex					.257
Male	76 (49)	21 (49)	60 (61)	52 (58)	
Female	78 (51)	22 (51)	39 (39)	38 (42)	
Disease status					.001
Complete remission	50 (32)	7 (16)	35 (35)	26 (29)	
Not in complete remission	102 (66)	35 (81)	52 (53)	57 (63)	
Unknown	2 (1)	1 (2)	12 (12)	7 (8)	
Conditioning regimen					< .001
CY-TBI or BU-CY	51 (33)	6 (14)	43 (43)	14 (16)	
Purine analog–containing	72 (47)	23 (53)	37 (37)	64 (71)	
Others	31 (20)	14 (33)	19 (19)	12 (13)	
GVHD prophylaxis					< .001
Cyclosporine-based	146 (95)	11 (26)	29 (29)	60 (67)	
Tacrolimus-based	6 (4)	31 (72)	68 (69)	25 (28)	
Others	2 (1)	1 (2)	2 (2)	5 (6)	
Source of stem cells					< .001
Bone marrow	46 (30)	12 (28)	99 (100)	-	
Peripheral blood	106 (69)	31 (72)	-	-	
Bone marrow + peripheral blood	2 (1)	0 (0)	-	-	
Cord blood	-	-	-	90 (100)	
HLA compatibility*					
Matched	154 (100)	-	83 (84)	3 (3)	< .001
One-antigen mismatch		19 (44)	12 (12)	29 (32)	
Two-antigen mismatch		13 (30)	0 (0)	57 (63)	
Three-antigen mismatch		7 (16)	0 (0)	1 (1)	
Uncertain/missing		4 (9)	4 (4)	0 (0)	
Time from diagnosis to transplantation					< .001
6 months or less	92 (60)	26 (60)	22 (22)	49 (54)	
More than 6 months	52 (34)	16 (37)	75 (76)	41 (46)	
Uncertain/missing	10 (6)	1 (2)	2 (2)	0 (0)	
Year of transplantation					< .001
1995-1999	18 (12)	1 (2)	5 (5)	0 (0)	
2000-2002	66 (43)	15 (35)	26 (26)	12 (13)	
2003-2005	70 (45)	27 (63)	68 (69)	78 (87)	
Follow-up of survivors†					
Median mo (range)	40.5 (1.5-102.3)	36.7 (8.8-85.1)	40.2 (16.0-81.2)	48.9 (1.6-73.5)	.847

ATL indicates adult T-cell leukemia; HLA, human leukocyte antigen; GVHD, graft-versus-host disease; CY-TBI, cyclophosphamide with total-body irradiation; BU-CY, busulfan and cyclophosphamide; purine analog–containing, conditioning regimens containing fludarabine, cladribine, or pentostatin; cyclosporine-based, cyclosporine with or without other agents; and tacrolimus-based, tacrolimus with or without other agents.

*HLA compatibility was defined according to the results of serologic or low-resolution molecular typing for HLA-A, HLA-B, and HLA-DR antigens.

†Data are time interval in months.

peripheral blood recipients, HLA-mismatched bone marrow or peripheral blood recipients were more likely to receive tacrolimus for GVHD prophylaxis; unrelated bone marrow recipients took a longer time from diagnosis to transplantation, were more likely to have attained complete remission at transplantation, and were more likely to receive tacrolimus for GVHD prophylaxis; unrelated cord blood recipients were older, underwent transplantation more recently, and were more likely to receive purine analog–containing conditioning regimens. All unrelated cord blood recipients received a single cord blood unit that was not manipulated ex vivo. The median weight of unrelated cord blood recipients was 52.0 kg (range, 31.0-90.2 kg); the median dose of nucleated cells and $CD34^+$ progenitor cells in the grafts, measured before freezing, was 2.55×10^7 (range, $1.39\text{-}5.34 \times 10^7$) and 0.79×10^5 (range, $0.07\text{-}3.15 \times 10^5$) per kg of recipient body weight, respectively.

Engraftment and GVHD

Of 310 patients who survived 30 days after transplantation and were evaluable for engraftment, primary graft failure was reported in 2 (6%) of 35 recipients of HLA-mismatched related grafts and in 12 (17%) of 70 recipients of unrelated cord blood, whereas the remaining 296 patients had evidence of initial engraftment. Acute GVHD of grades II, III, or IV occurred in 158 (47%) of 333

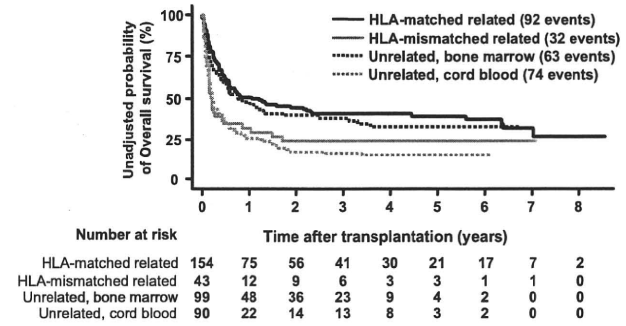

Figure 1. Unadjusted probability of overall survival according to type of graft source. The unadjusted Kaplan-Meier estimates of overall survival stratified according to type of graft source are shown.

evaluable patients; 69 (49%) of 140 HLA-matched related bone marrow or peripheral blood recipients, 20 (56%) of 36 HLA-mismatched related bone marrow or peripheral blood recipients, 40 (44%) of 91 unrelated bone marrow recipients, and 29 (44%) of 66 unrelated cord blood recipients. In a multivariable analysis, rates of grades II to IV acute GVHD did not significantly differ among the 4 groups (supplemental Table 1; available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article). Chronic GVHD occurred in 94 (48%) of 195 evaluable patients at a significantly lower rate among the unrelated cord blood recipients than among HLA-matched graft recipients (hazard ratio, 0.25; 95% CI, 0.10-0.61, $P = .002$).

Relapse and disease progression

Of 333 patients who survived 30 days after transplantation, 136 patients experienced relapse or progression of ATL at a median of 76 days (range, 1-1964 days) after transplantation. ATL recurred or progressed in 52 (37%) of 141 recipients of HLA-matched related grafts, in 19 (51%) of 37 recipients of HLA-mismatched related grafts, in 27 (32%) of 85 recipients of unrelated bone marrow, and 38 (54%) of 70 recipients of unrelated cord blood. Of 113 patients who were evaluable for the date of relapse or disease progression, the median time from transplantation to relapse or progression of ATL was 65.5 days (range, 1-1964 days) for HLA-matched related bone marrow or peripheral blood recipients, 63 days (range, 22-269 days) for HLA-mismatched related bone marrow or peripheral blood recipients, 152 days (range, 42-819 days) for unrelated bone marrow recipients, and 83 days (range, 7-596 days) for unrelated cord blood recipients.

Overall survival

Of 386 patients included in the study, a total of 125 patients were alive and 101 patients were alive in continuous complete remission after a median follow-up of 41 months (range, 1.5-102 months). The unadjusted 3-year probability of overall survival was 33% (95% CI, 28%-38%) for the whole cohort; 41% (95% CI, 33%-49%) in HLA-matched related graft recipients; 24% (95% CI, 12%-38%) in HLA-mismatched related graft recipients; 39% (95% CI, 29%-49%) in unrelated bone marrow recipients; and 17% (95% CI, 9%-25%) in unrelated cord blood recipients (Figure 1). The median overall survival time after transplantation was 9.8 months for HLA-matched related bone marrow or peripheral blood recipients, 2.5 months for HLA-mismatched related bone marrow or peripheral blood recipients, 9.6 months for unrelated bone marrow recipients, and 2.6 months for unrelated cord blood recipients. Patients who received transplants in complete remission had a higher probability of survival than those who received transplants not in complete remission (51% [95% CI, 41%-60%] vs 26% [95% CI, 20%-31%], $P < .001$). Multivariable analyses revealed 4 factors that adversely affected overall survival: older recipient age (> 50 years; hazard ratio, 1.56; 95% CI, 1.14-2.12, $P = .005$), male recipient (hazard ratio, 1.37; 95% CI, 1.07-1.77, $P = .014$), lack of complete remission at transplantation (hazard ratio, 2.01; 95% CI, 1.50-2.71, $P < .001$), and transplantation of unrelated cord blood. Hazard ratios for death among recipients of HLA-mismatched related transplants, unrelated bone marrow transplants, and unrelated cord blood transplants, compared with that among recipients of HLA-matched related transplants, were 1.55 (95% CI, 0.98-2.45, $P = .063$), 1.24 (95% CI, 0.82-1.88, $P = .312$), and 2.08 (95% CI, 1.43-3.02, $P < .001$), respectively (Table 2).

Treatment-related mortality and disease-associated mortality

Overall, 161 (43%) of 376 evaluable patients succumbed to treatment-related complications. Cumulative incidence of treatment-related mortality at 3 years after transplantation was 37% (95% CI, 29%-45%) in HLA-matched related bone marrow or peripheral blood recipients, 43% (95% CI, 28%-57%) in HLA-mismatched related bone marrow or peripheral blood recipients, 42% (95% CI, 32%-51%) in unrelated bone marrow recipients, and 52% (95% CI, 41%-62%) in unrelated cord blood recipients (Figure 2A). When adjusted by multivariable analysis, patients given unrelated cord blood (hazard ratio, 1.77; 95% CI, 1.10-2.86, $P = .019$) had higher treatment-related mortality rates (Table 2).

Deaths from progression of ATL occurred in 90 (24%) patients. Cumulative incidence of disease-associated mortality at 3 years after transplantation was 21% (95% CI, 14%-28%) in HLA-matched related bone marrow or peripheral blood recipients, 32% (95% CI, 19%-47%) in HLA-mismatched related bone marrow or peripheral blood recipients, 19% (95% CI, 12%-28%) in unrelated bone marrow recipients, and 30% (95% CI, 21%-40%) in unrelated cord blood recipients (Figure 2B). In multivariable analysis, patients given transplants not in remission (hazard ratio, 2.55; 95% CI 1.50-4.33, $P = .001$) or male recipients (hazard ratio, 1.86; 95% CI, 1.17-2.95, $P = .008$) had higher rates of disease-associated mortality (Table 2).

Causes of death after transplantation are summarized in Table 3. Of the 161 patients who died of treatment-related complications, 51 (32%) succumbed to infection and 53 (33%) to organ failure. Treatment-related events were principal causes of early death, whereas death from relapse or progression of ATL was more common later than 100 days after transplantation, irrespective of types of graft source.

Effect of donor HTLV-I serostatus on outcomes

Data on donor HTLV-I serostatus were available for analysis in 156 of 197 patients given related transplants; 68 received transplants from an HTLV-I–seropositive donor and 88 from an HTLV-I–seronegative donor. Patients who received transplants from HTLV-I–seropositive donors and those from HTLV-I–seronegative donors had similar background characteristics (supplemental Table 2). Among 113 patients who had data on donor HTLV-I serostatus and maintained or attained complete remission after transplantation, relapse of ATL was observed in 18 (38%) of 48 patients who received transplants from an HTLV-I–seropositive donor, and 16 (25%) of 65 patients who received transplants from an HTLV-I–seronegative donor with a median follow-up time for survivors of 40 months (range, 7.3-102 months). In univariable and

Table 2. Multivariable analysis of transplantation outcomes

Variables	Overall survival			Treatment-related mortality			Disease-associated mortality		
	Number*	Hazard ratio (95% CI)	*P*	Number*	Hazard ratio (95% CI)	*P*	Number*	Hazard ratio (95% CI)	*P*
Age group, y									
50 or younger	109/177	1.00	Reference	70/173	1.00	Reference	35/173	1.00	Reference
Older than 50	152/209	1.56 (1.14-2.12)	.005	91/203	1.40 (0.96-2.05)	.084	55/203	1.22 (0.71-2.10)	.465
Sex of recipient†									
Female	105/177	1.00	Reference	68/171	-	-	31/171	1.00	Reference
Male	156/209	1.37 (1.07-1.77)	.014	93/205	-	-	59/205	1.86 (1.17-2.95)	.008
Disease status									
Complete remission	60/118	1.00	Reference	43/117	1.00	Reference	16/117	1.00	Reference
Not in complete remission	184/246	2.01 (1.50-2.71)	< .001	106/238	1.30 (0.92-1.84)	.137	70/238	2.55 (1.50-4.33)	.001
Unknown	17/22	2.01 (1.15-3.50)	.014	12/21	1.74 (0.89-3.40)	.105	4/21	1.42 (0.45-4.52)	.554
Conditioning regimen									
CY-TBI or BU-CY	68/114	1.00	Reference	45/112	1.00	Reference	21/112	1.00	Reference
Purine analog–containing	136/196	1.05 (0.75-1.48)	.777	79/191	0.86 (0.56-1.32)	.487	52/191	1.34 (0.72-2.48)	.360
Others	57/76	1.26 (0.86-1.84)	.240	37/73	1.23 (0.78-1.95)	.377	17/73	1.10 (0.56-2.13)	.784
GVHD prophylaxis‡									
Cyclosporine-based	160/246	1.00	Reference	99/241	1.00	Reference	56/241	1.00	Reference
Tacrolimus-based	91/130	1.09 (0.78-1.51)	.614	55/127	1.13 (0.72-1.75)	.599	33/127	1.05 (0.57-1.93)	.887
Others	10/10	1.74 (0.89-3.42)	.105	7/8	2.29 (1.14-4.62)	.020	1/8	0.32 (0.04-2.42)	.268
Type of graft source									
Matched related bone marrow or peripheral blood	92/154	1.00	Reference	57/149	1.00	Reference	30/149	1.00	Reference
Mismatched related bone marrow or peripheral blood	32/43	1.55 (0.98-2.45)	.063	18/42	1.12 (0.59-2.12)	.722	13/42	1.50 (0.67-3.37)	.329
Unrelated bone marrow	63/99	1.24 (0.82-1.88)	.312	41/99	1.19 (0.71-1.98)	.512	22/99	1.06 (0.46-2.48)	.888
Unrelated cord blood	74/90	2.08 (1.43-3.02)	< .001	45/86	1.77 (1.10-2.86)	.019	25/86	1.49 (0.80-2.80)	.211
Time from diagnosis to transplantation									
6 months or less	128/189	1.00	Reference	81/183	1.00	Reference	41/183	1.00	Reference
More than 6 months	125/184	1.03 (0.78-1.35)	.834	76/180	0.86 (0.61-1.22)	.395	45/180	1.32 (0.82-2.12)	.258
Uncertain/missing	8/13	1.01 (0.49-2.09)	.971	4/13	0.64 (0.25-1.60)	.340	4/13	1.93 (0.77-4.87)	.163
Year of transplantation									
1995-1999	18/24	1.00	Reference	11/24	1.00	Reference	7/24	1.00	Reference
2000-2002	85/119	1.01 (0.58-1.74)	.979	56/113	1.13 (0.59-2.13)	.716	23/113	0.61 (0.26-1.46)	.269
2003-2005	158/243	0.73 (0.41-1.32)	.296	94/239	0.75 (0.37-1.51)	.416	60/239	0.70 (0.29-1.73)	.442

CI indicates confidence interval; GVHD, graft-versus-host disease; CY-TBI, cyclophosphamide with total-body irradiation; BU-CY, busulfan and cyclophosphamide; purine analog–containing, regimens containing fludarabine, cladribine or pentostatin; cyclosporine-based, cyclosporine with or without other agents; tacrolimus-based, tacrolimus with or without other agents; and Reference, reference category in regression models.

*Number of events/number of evaluable patients.

†Sex of recipient was not included as a confounder in the multivariable final model for treatment-related mortality because it was not found to be a significant factor in univariable comparison.

‡GVHD prophylaxis other than cyclosporine- or tacrolimus-based regimen was not considered as a significant variable associated with treatment-related mortality because of the small number of patients in this group.

multivariable analysis, patients who received transplants from an HTLV-I–seropositive donor had a higher risk of disease-associated mortality compared with those who received transplants from an HTLV-I–seronegative donor, whereas they had similar overall survival and treatment-related mortality rates (Table 4).

Discussion

The aim of this nationwide registry-based study was to compare overall survival after allogeneic HSCT with the use of various graft sources as treatment for ATL, and to identify factors that may influence transplantation outcomes. Despite the retrospective nature of the study, the validity of our analysis is strengthened by the fact that our cohort included most of the related transplants and nearly all unrelated transplants for ATL performed over a decade in our country.

We found that a substantial proportion of patients with ATL, including those who did not achieve complete remission, could enjoy long-term survival after allogeneic HSCT, validating the results of earlier observations.[18,19] However, our analysis in this cohort also revealed a high rate of treatment-related mortality. In particular, frequent incidence of fatal infectious complications may reflect preexisting profound immunodeficiency observed in patients with ATL.[4,5] Improved supportive care for opportunistic infection might be especially important for reducing treatment-related mortality in allografting for ATL.

Multivariable analysis revealed 4 factors that affected survival: recipient age, recipient sex, disease status before transplantation, and type of graft source. Although higher age of the recipient was associated with lower posttransplantation survival, most of the patients with ATL were older than age 50 years and were less likely to be candidates for fully ablative conditioning. Recently, 2 small prospective trials have demonstrated the feasibility and efficacy of allogeneic stem cell transplantations using reduced-intensity conditioning.[26,29] Although we observed no significant differences in overall survival between patients who received conventional conditioning regimens and those who received purine analog–

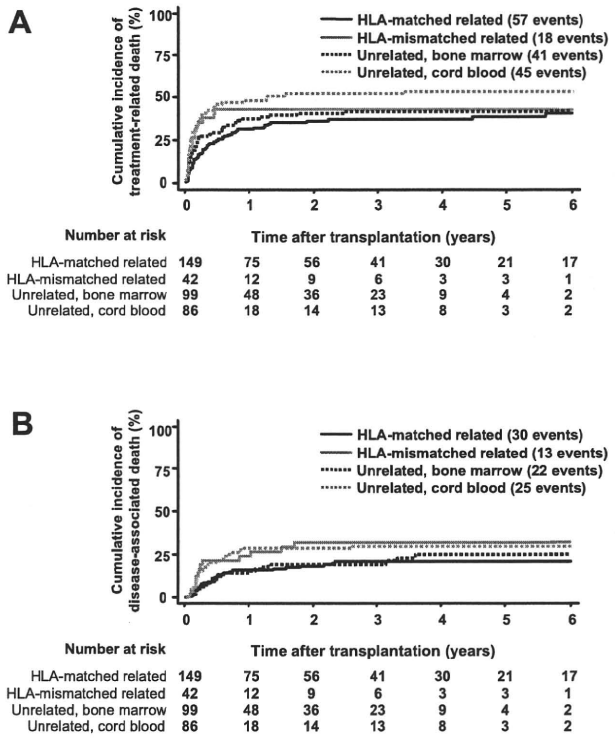

Figure 2. Cumulative incidence of treatment-related mortality and disease-associated mortality according to type of graft source. The unadjusted cumulative incidence curves for treatment-related mortality (A) and disease-associated mortality (B) stratified according to type of graft source are shown after allogeneic hematopoietic stem cell transplantation in patients with adult T-cell leukemia.

based regimens in the present study, it was difficult to evaluate the effect of conditioning dose intensity because data on doses of agents or total-body irradiation used in these regimens were not fully available in our cohort. Further studies are warranted to identify unfit or elderly ATL patients who can benefit from allogeneic stem cell transplantation with the use of less toxic conditioning.

A further novel finding in this study was that female patients with ATL had a more favorable outcome after allogeneic stem cell transplantation compared with male patients. Incidence of ATL in Japan is generally higher in male than in female populations, which was partly explained by the difference in routes of HTLV-I transmission between males and females. Sexual transmission of the virus can also occur, predominantly from males to females in adult life, thereby lowering the apparent incidence of ATL among female HTLV-I carriers.[7] However, the estimated ATL mortality among a prospective cohort of perinatally infected HTLV-I carriers was still higher for male patients,[36] suggesting that female sex itself might have a protective role against ATL development. Although much of the underlying mechanism for male predominance in ATL remains to be elucidated,[37] unidentified biologic or immunologic aspects of sex difference may contribute not only to development of ATL in HTLV-I carriers, but also to outcomes in allografted patients with ATL.

Despite the high risk for relapse after transplantation, survival rates observed in patients who received transplants not in complete remission were encouraging. Intriguingly, withdrawal of immunosuppressive agents or donor lymphocyte infusion can induce remission in relapse of ATL after allogeneic HSCT, implying the presence of a graft-versus-ATL effect.[19-23] Because several antigens have recently been identified as putative targets for cytotoxic T-cell responses against ATL,[38,39] future development of cellular immunotherapy targeting these molecules would reduce the incidence of relapse and improve survival in patients with residual ATL after allogeneic transplantation. Further investigations are warranted to elucidate the association between the occurrence of GVHD and disease response among allografted patients with ATL because our preliminary analysis using a similar cohort[40] suggested that patients who developed mild acute GVHD had a better posttransplantation survival compared with those who did not develop acute GVHD (J.K., M. Hishizawa, A.U., S.T., T.E., Y. Moriuchi, R.T., F.K., Y. Miyazaki, M.M., K.N., M. Hara, M.T., S. Kai, Y.A., R.S., T.K., K.M., T.N.-I., S. Kato, H.S., Y. Morishima, J.O., T.I., and T.U., manuscript in preparation).

Finally, the use of unrelated cord blood was associated with lower survival, most likely a result of higher treatment-related mortality. Two major causes of early treatment-related death were infection and organ failure. Because the development of ATL usually worsens preceding immunodeficiency associated with HTLV-I infection, it is imperative to establish effective measures to manage posttransplantation infections in allografted patients with ATL. In addition, the use of more intense conditioning for refractory disease in relatively elderly recipients may increase the risk of regimen-related toxicities especially in the setting of unrelated donor transplantation. However, direct comparison of

Table 3. Cause of death according to type of graft source

	Deaths within 100 days per graft source (%)				Deaths later than 100 days per graft source (%)			
Cause of death	HLA-matched related bone marrow or peripheral blood	HLA-mismatched related bone marrow or peripheral blood	Unrelated bone marrow	Unrelated cord blood	HLA-matched related bone marrow or peripheral blood	HLA-mismatched related bone marrow or peripheral blood	Unrelated bone marrow	Unrelated cord blood
Primary disease	11 (28)	9 (35)	6 (18)	15 (30)	19 (37)	4	16 (53)	10 (42)
Treatment-related								
GVHD	3 (8)	1 (4)	2 (6)	2 (4)	4 (8)	1	2 (7)	1 (4)
Infection	7 (18)	5 (19)	9 (27)	12 (24)	9 (17)	0	4 (13)	5 (21)
Organ failure	12 (30)	3 (12)	13 (39)	11 (22)	9 (17)	1	4 (13)	0 (0)
Others	6 (15)	7 (27)	3 (9)	10 (20)	7 (13)	0	4 (13)	4 (17)
Undetermined	1 (3)	1 (4)	0 (0)	0 (0)	4 (8)	0	0 (0)	4 (17)
Total no. of deaths	40 (100)	26 (100)	33 (100)	50 (100)	52 (100)	6	30 (100)	24 (100)
Patients at risk	154	43	99	90	113	17	66	39

HLA indicates human leukocyte antigen; GVHD, graft-versus-host disease.

Data are number of deaths to total deaths (%) after transplantation in the group according to type of graft source. Percentages are not provided for groups having fewer than 10 patients in total.

Table 4. Effect of donor HTLV-I serostatus on transplantation outcomes

		Univariable analysis		Multivariable analysis	
Outcome	Number*	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Overall survival†					
Donor HTLV-I antibody positive	43/68	1.00	Reference	1.00	Reference
Donor HTLV-I antibody negative	52/88	0.90 (0.60-1.35)	.603	0.83 (0.54-1.28)	.395
Treatment-related mortality‡					
Donor HTLV-I antibody positive	20/64	1.00	Reference		
Donor HTLV-I antibody negative	37/86	1.51 (0.88-2.58)	.133		
Disease-associated mortality§					
Donor HTLV-I antibody positive	19/64	1.00	Reference	1.00	Reference
Donor HTLV-I antibody negative	13/86	0.44 (0.22-0.89)	.022	0.43 (0.21-0.90)	.026

CI indicates confidence interval; and HTLV, human T-cell leukemia virus.

*Number of events/number of evaluable patients.

†Other variables considered in the multivariable analysis were disease status before transplantation, type of GVHD prophylaxis, and type of graft source. Variables significantly associated with overall survival were disease status before transplantation and type of GVHD prophylaxis: not in complete remission versus complete remission (hazard ratio, 1.95; 95% CI, 1.17-3.24, $P = .010$); tacrolimus- versus cyclosporine-based (hazard ratio, 4.22; 95% CI, 1.58-11.26, $P = .004$).

‡Multivariable analysis was not performed because no variable was significantly associated with treatment-related mortality by univariable analysis.

§Other variables considered in the multivariable analysis were disease status before transplantation, type of GVHD prophylaxis, and type of graft source. The only variable significantly associated with disease-associated mortality was disease status before transplantation: not in complete remission versus complete remission (hazard ratio, 2.88; 95% CI, 1.01-8.24, $P = .049$).

transplantation outcomes by graft source was not feasible because the selection of graft source is an individual process strongly influenced by donor availability and disease status of patients. It should also be noted that the study period encompassed the developmental phase of cord blood transplantation in adults. Because rates of disease-associated death were similar irrespective of type of graft source, new strategies to reduce early treatment-related mortality would improve the results of alternative donor transplantations for ATL.

Another concern related to selection of graft source involves the use of HTLV-I-seropositive-related donors. Sibling donors for patients with ATL are frequently infected with HTLV-I, because mother-to-child transmission by breastfeeding is a major route of HTLV-I acquisition.[5,6] The use of HTLV-I–seropositive donors raises the risk of ATL development in donor-derived HTLV-I–infected cells under immunosuppressive conditions after transplantation,[41] whereas it may enhance the therapeutic effect by the adoptive transfer of viral-specific immunocompetent cells.[21] However, the latter possibility seems less likely because transplantation from HTLV-I–seropositive donors was associated with higher risk for disease-associated mortality in our study cohort. Given that donor-derived HTLV-I–specific cytotoxic T-cell response can be observed in transplantation from an HTLV-I–seronegative donor,[21] it is important to note that the magnitude of specific T-cell responsiveness to HTLV-I might widely differ among healthy HTLV-I carriers. The impairment of HTLV-1–specific T-cell responses was observed not only in patients with advanced ATL but also in a subpopulation of asymptomatic carriers, which was associated with insufficient control of HTLV-I.[42] Although whether donor anti–HTLV-I immunity can harness graft-versus-ATL responses is still elusive, further investigations are clearly needed to resolve this issue.

This study had inherent limitations that are common among observational studies: eligibility for transplantation, as well as choice of transplantation protocol, including the selection of graft source, was determined by the treating physicians of each institution; the confounding effect of some variables, such as disease subtype, could not be fully evaluated because of missing data, although adjustment for other key risk factors enabled as controlled a comparison as possible.

In conclusion, allogeneic HSCT is an effective treatment that confers long-term survival in selected patients with ATL, but at the cost of substantial risk of treatment-related mortality. Posttransplantation outcomes are influenced by recipient age, recipient sex, and disease status at transplantation, as well as by type of graft source. More definitive conclusions on the role of allografting in the therapeutic algorithm for ATL will be drawn from future prospective studies that aim to compare the survival outcomes after transplantation with those after conventional chemotherapy.

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Authorship

Contribution: M. Hishizawa, J.K., T.I., and T.U. reviewed and analyzed data and wrote the paper; J.K., K.M., and T.I. performed statistical analysis; A.U., S.T., T.E., Y. Moriuchi, R.T., F.K., Y. Miyazaki, M.M., K.N., M. Hara, M.T., S. Kai, and J.O. interpreted data and reviewed and approved the final manuscript; Y.A., R.S., and H.S. collected data from the JSHCT; T.K. and Y. Morishima collected data from the JMDP; T.N.-I. and S. Kato collected data from the JCBBN; and T.I. and T.U. designed the research and organized the project.

T.U., the senior author, died after acceptance of the final manuscript.

In addition to authors, other members who contributed data on allogeneic hematopoietic stem cell transplantation for adult T-cell

leukemia to the JSHCT, JMDP, and JCBBN are listed in the supplemental Appendix.

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Allogeneic stem cell transplantation for adult Philadelphia chromosome negative acute lymphocytic leukemia: comparable survival rates but different risk factors between related and unrelated transplantation in first complete remission

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Allogeneic stem cell transplantation for adult Philadelphia chromosome–negative acute lymphocytic leukemia: comparable survival rates but different risk factors between related and unrelated transplantation in first complete remission

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To identify factors to improve the outcomes of related and unrelated allogeneic stem cell transplantations (allo-SCT) for Philadelphia chromosome–negative acute lymphocytic leukemia (Ph$^-$ ALL) in the first complete remission (CR1), we retrospectively analyzed 1139 Ph$^-$ ALL patients using the registry data, particularly the details of 641 patients transplanted in CR1. Overall survival was significantly superior among patients transplanted in CR1, but no significant difference was observed between related and unrelated allo-SCTs (related vs unrelated: 65% vs 62% at 4 years, respectively; $P = .19$). Among patients transplanted in CR1, relapse rates were significantly higher in related allo-SCT compared with unrelated allo-SCT, and multivariate analysis demonstrated that less than 6 months from diagnosis to allo-SCT alone was associated with relapse. On the other hand, nonrelapse mortality (NRM) was significantly higher in unrelated allo-SCT compared with related allo-SCT, and multivariate analysis demonstrated that 10 months or longer from diagnosis to allo-SCT, human leukocyte antigen mismatch, and abnormal karyotype were associated with NRM. In conclusion, our study showed comparable survival rates but different relapse rates, NRM rates, and risk factors between related and unrelated allo-SCTs. After a close consideration of these factors, the outcome of allo-SCT for adult Ph$^-$ ALL in CR1 could be improved. (*Blood.* 2010;116(20):4368-4375)

Introduction

The indication of allogeneic stem cell transplantation (allo-SCT) for Philadelphia chromosome–negative acute lymphocytic leukemia (Ph$^-$ ALL) is still controversial.[1,2] As for related allo-SCT, one prospective study suggested that related allo-SCT for Ph$^-$ ALL in first complete remission (CR1) could provide the most potent antileukemic therapy and considerable survival benefits.[3] As for unrelated allo-SCT, the largest retrospective study of Ph$^-$ ALL patients in CR1 showed worse overall survival (OS) rates because of higher incidences of nonrelapse morality (NRM) than those in related allo-SCT,[4] whereas another reported that there were no differences in OS rates and NRM rates between related and unrelated allo-SCTs for adult ALL in CR1.[5] These data indicated that unrelated allo-SCT could also be a treatment option for adult Ph$^-$ ALL patients in CR1 if NRM rates were low enough, although it is not yet routinely performed.

Although the analyses of the outcome of allo-SCT alone have some biases, such as excluding death during chemotherapy, and there may be potential differences in the baseline characteristics of patients between related and unrelated allo-SCTs, the comparison of transplantation outcomes and risk factors between related and unrelated allo-SCTs for adult Ph$^-$ ALL could indicate strategies to improve transplantation outcomes for this disease. We particularly focused on allo-SCT in CR1 because this is the area of controversy.

Methods

Collection of data and data sources

The recipients' clinical data were provided by the Japan Society for Hematopoietic Cell Transplantation (JSHCT) and the Japan Marrow Donor Program (JMDP). Both JSHCT and JMDP collect recipients' clinical data at 100 days after allo-SCT. The patient's data on survival, disease status, and long-term complications, including chronic graft-versus-host disease (GVHD) and second malignancies, are renewed annually by follow-up forms. More than 99% of unrelated allo-SCT in Japan was captured in the JMDP database, and approximately 75% of related allo-SCT was captured in the JSHCT database. This study was approved by the data management committees of JSHCT and JMDP. Informed consent was obtained from both recipients and donors in accordance with the Declaration of Helsinki.

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Patients

Data of 1976 patients who underwent their first allo-SCT for Ph⁻ ALL between 1993 and 2007 were available in the registration database of JSHCT and JMDP. Excluding 662 patients whose age was 15 years or younger, 67 patients without data of GVHD prophylaxis and the interval from diagnosis to allo-SCT, 22 patients who underwent 2 or more human leukocyte antigen (HLA) loci mismatched related allo-SCT, and 86 patients who received reduced-intensity conditioning regimens, we analyzed 1139 adult Ph⁻ ALL patients (499 related and 640 unrelated). We particularly analyzed details of 641 patients transplanted in CR1, according to donor types (310 related and 331 unrelated). All but 4 patients were donated from Japanese donors harvested in Japanese harvest centers. Only bone marrow grafts were used in unrelated allo-SCT because peripheral blood stem cell donation from unrelated donors is not yet approved in Japan. HLA high-resolution molecular typing methods were performed for HLA-A, -B, -Cw, and -DRB1 for all patients in JMDP. Donor and recipient pairs were considered matched when HLA was matched at -A, -B, and -DRB1 loci in related allo-SCT and at -A, -B, -Cw, and -DRB1 loci in unrelated allo-SCT. Mismatches were defined as at least one disparity of these loci.

Definition

Neutrophil recovery was defined by an absolute neutrophil count of at least 0.5×10^9/L for 3 consecutive days; platelet recovery was defined by a count of at least 50×10^9/L without transfusion support. Acute and chronic GVHD was diagnosed and graded according to consensus criteria.[6,7] Relapse was defined as hematologic leukemia recurrence. NRM was defined as death during continuous remission. For analyses of OS, failure was death from any cause, and surviving patients were censored at the date of last contact. The date of allo-SCT was the starting time point for calculating all outcomes. Patients were classified at diagnosis by the Japan Adult leukemia Study Group (JALSG) risk stratification: low risk was defined as less than 30 years at diagnosis and white blood cell count less than 30 000/μL at diagnosis, high risk as 30 years or more at diagnosis and white blood cell count 30 000/μL or more at diagnosis, and intermediate risk as other.[8] To determine the cut-off for the upper limit of tolerability by age, we analyzed the cumulative incidence of NRM by categorizing the patients' age every 5 years. Because NRM rates of 45- to 49-year-old and 50-year-old or older categories showed higher incidences compared with other categories, we determined the best cut-off point as 45 years old.

Statistical analysis

The 2-sided χ^2 test was used for categorical variables. OS rates were estimated by the Kaplan-Meier method, and P values were calculated using a log-rank test.[9,10] Cumulative incidences of relapse, NRM, and GVHD were calculated by the Gray method.[11,12] Death without relapse was considered as a competing event for relapse, and relapse as a competing event for NRM. Univariate and multivariate analyses were performed using Cox proportional hazard regression model.[13] A significance level of P less than .05 was used for all analyses.

Results

Patient characteristics

Of 1139 patients, 641 received allo-SCT in CR1 (310 related and 331 unrelated), 199 in subsequent remission (56 related and 143 unrelated), and 299 in nonremission (133 related and 166 unrelated). The characteristics of the patients transplanted in CR1 are shown in Table 1. The frequencies of HLA mismatched donor and tacrolimus-based GVHD prophylaxis were higher, and the interval from diagnosis to allo-SCT was longer among patients who underwent an unrelated allo-SCT than among those who underwent a related allo-SCT. There was no significant difference in the age at allo-SCT, the white blood cell counts at diagnosis, JALSG risk stratification, and year of allo-SCT between related and unrelated allo-SCTs.

Survival

Median follow-up periods among survivors were 47.7 months (range, 1.3-162 months). OS rates at 4 years were 64% in CR1, 39% in subsequent CR, and 16% in non-remission ($P < .0001$). Although OS rates were significantly different among disease stages at allo-SCT, there were no significant differences in OS rates at 4 years between related and unrelated allo-SCTs in any disease stage (related vs unrelated: 65% vs 62% in CR1, $P = .19$; 44% vs 38% in subsequent CR, $P = .66$; and 17% vs 16% in non-remission, $P = .59$; respectively; Figure 1). There was no statistical difference in OS rates and NRM rates over transplantation years (data not shown). Among 641 patients transplanted in CR1, JALSG risk stratification did not have a significant impact on the OS after allo-SCT (68% in low risk, 62% in intermediate risk, and 58% in high risk, at 4 years, respectively; $P = .31$). To address our main issue, we performed the following analyses among patients transplanted in CR1 according to donor types.

Among 310 patients who underwent a related allo-SCT in CR1, multivariate analysis showed that age at allo-SCT and less than 6 months from diagnosis to allo-SCT were significant risk factors for OS. Among 331 patients who underwent an unrelated allo-SCT in CR1, multivariate analysis showed that abnormal karyotype [except for t(4;11) and t(1;19)], HLA mismatch, and 10 months or longer from diagnosis to allo-SCT were significant risk factors for OS (Table 2).

Relapse and NRM among patients transplanted in CR1

The cumulative incidence of relapse was significantly higher in patients who underwent a related allo-SCT compared with those who underwent an unrelated allo-SCT (related vs unrelated: 32% vs 22% at 4 years, $P = .03$; Figure 2A). Multivariate analyses according to donor type showed that less than 6 months from diagnosis to allo-SCT alone was associated with relapse among 310 patients who underwent a related allo-SCT in CR1, whereas only abnormal karyotype [except for t(4;11) and t(1;19)] was associated with relapse among 331 patients who underwent an unrelated allo-SCT in CR1 (Table 3).

The cumulative incidence of NRM was significantly higher in patients who underwent an unrelated allo-SCT compared with those who underwent a related allo-SCT (related vs unrelated: 14% vs 27% at 4 years, $P = .0002$; Figure 2B). Multivariate analyses according to donor type showed that age only 45 years or older at allo-SCT was associated with NRM among 310 patients who underwent a related allo-SCT in CR1, whereas abnormal karyotype [except for t(4;11) and t(1;19)], HLA mismatch, and 10 months or longer from diagnosis to allo-SCT were associated with NRM among 331 patients who underwent an unrelated allo-SCT in CR1 (Table 4).

Acute and chronic GVHD among patients transplanted in CR1

The cumulative incidence of grade II-IV acute GVHD was significantly higher in patients who underwent an unrelated allo-SCT compared with those who underwent a related allo-SCT (related vs unrelated: 30% vs 42% at day 100; $P = .0003$). The cumulative incidence of grade III-IV acute GVHD was significantly higher in patients who underwent an unrelated allo-SCT compared with those who underwent a related allo-SCT (related vs unrelated: 7% vs 16% at day 100; $P = .0006$).

Table 1. Characteristics of patients transplanted in CR1, according to donor type

	Related (n = 310)		Unrelated (n = 331)		
No. of patients	**No.**	**%**	**No.**	**%**	***P***
Median WBC count at diagnosis/μL (range)	10 250 (109-328 000)		11 000 (700-892 000)		.43
Median patient age at allo-SCT, y (range)	30 (16-66)		31 (16-59)		.95
16-20	66	21.3	77	23.3	
21-30	93	30.0	82	24.8	
31-40	71	22.9	86	26.0	
41-50	58	18.7	68	20.5	
51 or older	22	7.1	18	5.4	
Sex					.09
Male	157	50.6	190	57.4	
Female	153	49.4	141	42.6	
Source					< .0001
BM	212	68.4	331	100.0	
PB	98	31.6	0	0.0	
Lineage					.01
T	50	16.1	54	16.3	
B	218	70.3	203	61.3	
Other	42	13.5	74	22.4	
Cytogenetics					.07
Normal	193	62.3	208	62.8	
t(4;11)	11	3.5	5	1.5	
Other MLL/11q23 translocations	1	0.3	3	0.9	
t(1;19)	10	3.2	6	1.8	
t(8;14)	3	1.0	3	0.9	
14q32 translocations	1	0.3	0	0.0	
del(6q)	3	1.0	1	0.3	
del(7p)	2	0.6	1	0.3	
−7*	5	1.6	2	0.6	
+8*	2	0.6	0	0.0	
+X*	0	0.0	1	0.3	
del(9p)	3	1.0	9	2.7	
abnormality of 11q	0	0.0	3	0.9	
del(12p)	2	0.6	1	0.3	
del(13q)/−13	1	0.3	2	0.6	
del(17p)	0	0.0	1	0.3	
Complex	10	3.2	15	4.5	
Low hypodiploidy/near triploidy	2	0.6	0	0.0	
High hyperdiploidy	16	5.2	12	3.6	
Other abnormality (no t(9;22))†	45	14.5	58	17.5	
JALSG risk stratification					.21
Low	39	12.6	45	13.6	
Intermediate	163	52.6	192	58.0	
High	108	34.8	94	28.4	
HLA matching					< .0001
Match	285	91.9	192	58.0	
Class I 1 locus-mismatch	18	5.8	53	16.0	
Class II 1 locus-mismatch	7	2.3	32	9.7	
2 or more loci mismatch	0	0.0	54	16.3	
Time from diagnosis to transplantation, mo (range)	5.7 (1.9-36.6)		10.0 (4.0-43.0)		< .0001
< 6	169	54.5	23	6.9	
6-9	109	35.2	143	43.2	
10 or longer	32	10.3	165	49.8	
Preparative regimen					.004
CY + TBI	140	45.2	156	47.1	
CA + CY + TBI	66	21.3	84	25.4	
BU + CY + TBI	17	5.5	15	4.5	
VP + CY + TBI	23	7.4	32	9.7	
Other TBI myeloablative regimens	39	12.6	32	9.7	
BU + CY	17	5.5	12	3.6	
Other non-TBI myeloablative regimens	8	2.6	0	0.0	
GVHD prophylaxis					< .0001
Cyclosporine A with or without other	283	91.3	171	51.7	
Tacrolimus with or without other	27	8.7	160	48.3	

Table 1. Characteristics of patients transplanted in CR1, according to donor type (continued)

	Related (n = 310)		Unrelated (n = 331)		
No. of patients	**No.**	**%**	**No.**	**%**	***P***
Years of allo-SCT					.26
1993-1997	48	15.5	55	16.6	
1998-2002	132	42.6	120	36.3	
2003-2007	130	41.9	156	47.1	

WBC indicates white blood cell; BM, bone marrow; PB, peripheral blood; related HLA match, identical HLA-A, -B, and -DRB1 loci; unrelated HLA match, HLA-A, -B, -Cw, and -DRB1 loci; HLA mismatch, at least one disparity at one of these loci; CY, cyclophosphamide; TBI, total body irradiation; CA, cytarabine; BU, busulfan; and VP, etoposide.

*These groups exclude cases with low hypodiploidy and high hyperdiploidy.

†Abnormal karyotypes excluding those with any of the aforementioned abnormalities.

Among evaluable patients who survived at least 100 days after allo-SCT, no significant difference was observed between related and unrelated allo-SCTs in the incidence of chronic GVHD (related vs unrelated: 41% vs 41% at 2 years; $P = .76$). Extensive disease was observed in 60 (55%) of 109 with chronic GVHD after related allo-SCT and in 80 (74%) of 118 after unrelated allo-SCT ($P = .048$).

Causes of death among patients transplanted in CR1

Although relapse was the leading cause of death in both related and unrelated allo-SCTs, the proportion of relapse was significantly lower in those transplanted from unrelated donors ($P = .01$). Infection, GVHD, and organ failure were the major causes of NRM, and the incidence of interstitial pneumonia was higher in patients transplanted from unrelated donors ($P = .06$; Table 5).

Discussion

This study reports the largest series of adult Ph⁻ ALL patients who underwent allo-SCT. There was no significant survival difference between related and unrelated allo-SCTs in any disease stage. Among patients who underwent a related allo-SCT in CR1, a shorter interval from diagnosis to allo-SCT was associated with relapse, and age at allo-SCT was associated with NRM. On the other hand, among patients who underwent an unrelated allo-SCT, abnormal karyotype was associated with both relapse and NRM, and a longer interval from diagnosis to allo-SCT and HLA mismatch were associated with NRM. These results indicated that factors affecting transplantation outcomes were different according to donor type.

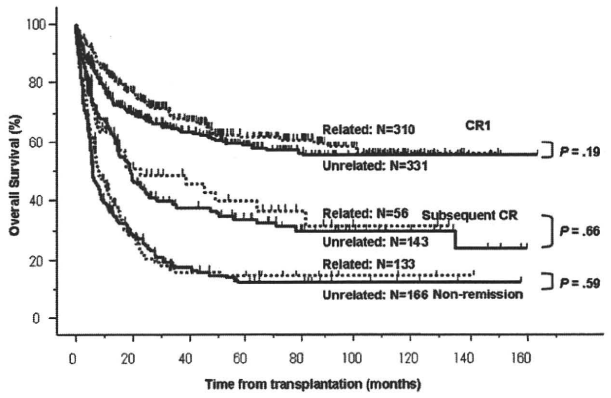

Figure 1. OS according to disease status and donor type. OS rates were significantly superior among patients transplanted in CR1. There was no significant difference between related and unrelated allo-SCTs (related vs unrelated: 65% vs 62% in CR1, $P = .19$; 44% vs 38% in subsequent CR, $P = .66$; and 17% vs 16% in nonremission, $P = .59$; respectively).

In our study, unrelated allo-SCT resulted in OS rates similar to those from related allo-SCT, which was compatible with the result of one prospective study for standard-risk hematologic malignancies.[14] The rates of OS, relapse, and NRM among patients who underwent a related allo-SCT in CR1 were 65%, 32%, and 14%, respectively, which were compatible with those observed in the United Kingdom Medical Research Council UKALL XII/Eastern Cooperative Oncology Group E2993 trial (53%, 24%, and 18%, respectively).[3] Some patients were transplanted from a 1-locus mismatched related donor because it was reported that the outcome of allo-SCT from a 1 locus-mismatched related donor was similar to that of matched unrelated allo-SCT in the Japanese population.[15] On the other hand, the rates of OS, relapse, and NRM among patients who underwent an unrelated allo-SCT were 62%, 22%, and 27%, respectively, which were better than those reported from the Center for International Blood and Marrow Transplant Research (39%, 20%, and 42%, respectively).[4] These differences in NRM could be explained by the lower incidence of acute GVHD in our population, which possibly resulted from the genetic homogeneity in the Japanese population.[16,17] Interestingly, abnormal karyotype was associated with NRM. This could be explained by the possibility that patients with abnormal karyotype received intensive chemotherapy before allo-SCT because of persistent minimal residual disease, which might result in increased NRM rates. Another possibility is that rapid taper of immunosuppressive treatment might also cause GVHD leading to NRM.

In this study, NRM rates were higher in unrelated allo-SCT compared with related allo-SCT, whereas comparable NRM rates were reported in some recent reports,[18] suggesting that NRM rates after unrelated allo-SCT could be reduced with further efforts, such as better HLA matching. Because HLA-C was not routinely typed before 2003, most of the HLA-C data in this study were examined retrospectively, revealing that considerable numbers of patients had received class I allele-mismatched unrelated allo-SCT. Better HLA matching might reduce NRM after unrelated allo-SCT in the future. Although slower hematopoietic recovery after bone marrow transplantation compared with peripheral blood stem cell transplantation might affect the timing of deaths, there was no statistical difference in early mortality between the grafts (data not shown).

There was no statistical difference in the incidence of chronic GVHD between related and unrelated allo-SCTs, although acute GVHD was observed more frequently in unrelated allo-SCT. This was compatible with a past report in which the incidence of chronic GVHD was similar between related and unrelated allo-SCTs, whereas acute GVHD was observed more frequently in related allo-SCT.[14]

It was noteworthy that the interval from diagnosis to allo-SCT revealed a different effect on related and unrelated allo-SCTs. In Japanese clinical practice, the JALSG protocols have been common, where 1.5-month induction chemotherapy was followed by

Table 2. Univariate and multivariate analyses of factors influencing OS among patients transplanted in CR1, according to donor type

	Related (n = 310)					Unrelated (n = 331)				
		Univariate		Multivariate			Univariate		Multivariate	
Covariates	N	HR (95% CI)	P	HR (95% CI)	P	N	HR (95% CI)	P	HR (95% CI)	P
WBC count at diagnosis										
< 30 000/μL	224	1.00		—		230	1.00		—	
30 000/μL or more at diagnosis	86	1.19 (0.78-1.82)	.42	—		101	0.83 (0.56-1.25)	.38	—	
Lineage										
B	218	1.00		—		203	1.00		—	
T	50	0.73 (0.34-1.77)	.52	—		54	0.81 (0.44-1.48)	.35	—	
Other	42	0.94 (0.54-1.64)	.84	—		74	1.08 (0.70-1.67)	.72	—	
Karyotype										
Normal	193	1.00		—		208	1.00		—	
t(4;11) or t(1;19)	21	0.51 (0.14-1.54)	.19	—		11	1.49 (0.54-4.09)	.44	1.59 (0.58-4.36)	.37
Other (no t(9;22))	96	1.03 (0.67-7.14)	.89	—		112	1.49 (1.03-2.17)	.04	1.43 (1.13-2.40)	.01
JALSG risk stratification										
Low	39	1.00		—		45	1.00		—	
Intermediate	163	1.36 (0.87-2.12)	.18	—		192	1.06 (0.71-1.59)	.77	—	
High	108	1.77 (0.95-3.31)	.07	—		94	1.02 (0.56-1.88)	.94	—	
Age at allo-SCT										
< 45 y old	255	1.00		—		281	1.00		—	
45 y old or older at allo-SCT	55	2.04 (1.30-3.13)	.002	2.13 (1.36-3.34)	.0009	50	1.05 (0.63-1.73)	.86		
HLA										
Match	285	1.00		—		192	1.00		—	
Mismatch	25	0.95 (0.46-1.96)	.90	—		139	1.44 (1.01-2.06)	.04	1.45 (1.01-2.07)	.04
Stem cell source										
Bone marrow	212	1.00		—					—	
Peripheral blood	98	1.43 (0.94-2.13)	.09	1.40 (0.93-2.11)	.11					
Time from diagnosis to allo-SCT										
6 mo or longer	169	1.00		—		23	1.00		—	
< 6 mo	141	1.75 (1.16-2.63)	.007	1.80 (1.19-2.71)	.005	308	0.33 (0.10-1.04)	.06	—	
< 10 mo	278	1.00		—		166	1.00		—	
10 mo or longer	32	0.56 (0.26-1.20)	.14	—		165	1.54 (1.07-2.21)	.02	1.62 (1.12-2.34)	.01
Preparative regimen										
Non-TBI regimens	25	1.00		—		12	1.00		—	
TBI regimens	285	0.72 (0.38-1.35)	.30	—		319	0.59 (0.27-1.26)	.17	—	
GVHD prophylaxis										
Cyclosporine A with or without other	283	1.00		—		171	1.00		—	
Tacrolimus with or without other	27	2.02 (1.15-3.56)	.01	—		160	1.38 (0.96-1.97)	.08	—	

HR indicates hazard ratio; CI, confidence interval; WBC, white blood cell; —, not applicable; and TBI, total body irradiation.

6-month consolidation chemotherapy and 16-month maintenance chemotherapy.[8] Therefore, a shorter interval from diagnosis to allo-SCT, which was more common in related cases, might result in insufficient consolidation chemotherapy and worse survival because of increased relapse rates in related allo-SCT. Alternatively, effects from insufficient consolidation chemotherapy might be more prominent in related allo-SCT because graft-versus-leukemia effects might be weaker after related allo-SCT than unrelated allo-SCT.[19] On the other hand, a longer interval from diagnosis to allo-SCT, which was more common in unrelated cases, might result in the cumulative toxic sequelae of chemotherapy responsible for interstitial pneumonia indicated in the past reports.[20-25] Because the JALSG protocols do not define the timing of allo-SCT, it is possible that chemotherapy before allo-SCT might be prolonged because of persistent minimal residual disease. However, we could not confirm this because there were no data concerning minimal residual disease in the registry database.

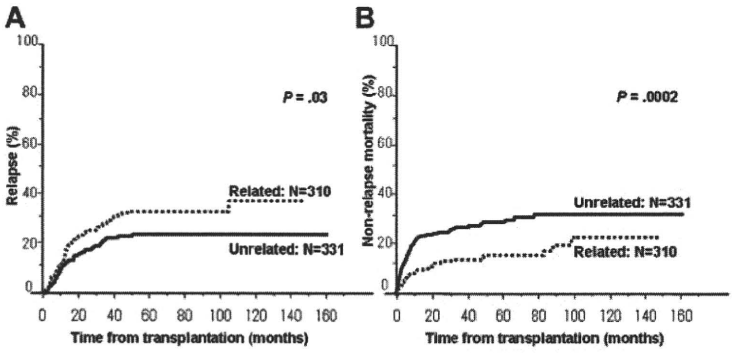

Figure 2. Cumulative incidence of relapse and NRM in patients transplanted in CR1 according to donor type. (A) Cumulative incidence of relapse among patients transplanted in CR1 was significantly higher in patients who underwent a related allo-SCT compared with those who underwent an unrelated allo-SCT (related vs unrelated: 32% vs 22% at 4 years, $P = .03$). (B) Cumulative incidence of NRM among patients transplanted in CR1 was significantly higher in patients who underwent an unrelated allo-SCT compared with those who underwent a related allo-SCT (related vs unrelated: 14% vs 27% at 4 years, $P = .0002$).

Table 3. Univariate and multivariate analyses of factors influencing relapse among patients transplanted in CR1, according to donor type

	Related (n = 310)					Unrelated (n = 331)				
		Univariate		Multivariate			Univariate		Multivariate	
Covariates	N	HR (95% CI)	P	HR (95% CI)	P	N	HR (95% CI)	P	HR (95% CI)	P
WBC count at diagnosis										
< 30 000/μL	224	1.00		—		230	1.00		—	
30 000/μL or more at diagnosis	86	0.88 (0.52-1.47)	.62	—		101	1.11 (0.62-1.98)	.72	—	
Lineage										
B	218	1.00		—		203	1.00		—	
T	50	0.54 (0.22-1.37)	.09	—		54	1.31 (0.57-3.02)	.62	—	
Other	42	1.21 (0.66-2.21)	.54	—		74	1.06 (0.53-2.11)	.87	—	
Karyotype										
Normal	193	1.00		—		208	1.00		—	
t(4;11) or t(1;19)	21	0.64 (0.19-2.12)	.36	—		11	1.97 (0.46-8.35)	.91	—	
Other (no t(9;22))	96	1.11 (0.68-1.82)	.67	—		112	2.15 (1.24-3.73)	.01	2.15 (1.24-3.73)	.01
JALSG risk stratification										
Low	39	1.00		—		45	1.00		—	
Intermediate	163	0.96 (0.59-1.55)	.87	—		192	1.04 (0.57-1.91)	.90	—	
High	108	0.81 (0.35-1.84)	.61	—		94	1.04 (0.43-2.52)	.94	—	
Age at allo-SCT										
< 45 y old	255	1.00		—		281	1.00		—	
45 y old or older at allo-SCT	55	0.82 (0.41-1.64)	.57	—		50	0.74 (0.42-1.32)	.08	—	
HLA										
Match	285	1.00		—		192	1.00		—	
Mismatch	25	0.82 (0.33-2.02)	.66	—		139	0.74 (0.42-1.32)	.31	—	
Stem cell source*										
Bone marrow	212	1.00		—					—	
Peripheral blood	98	1.07 (0.65-1.76)	.79	—					—	
Time from diagnosis to allo-SCT										
6 mo or longer	169	1.00		—		23	1.00		—	
< 6 mo	141	1.68 (1.05-2.69)	.03	1.68 (1.05-2.69)	.03	308	0.47 (0.11-1.92)	.29	—	
< 10 mo	278	1.00		—		166	1.00		—	
10 mo or longer	32	0.49 (0.18-1.34)	.16	—		165	0.92 (0.54-1.58)	.76	—	
Preparative regimen										
Non-TBI regimens	25	1.00		—		12	1.00		—	
TBI regimens	285	0.62 (0.31-1.25)	.18	—		319	0,47 (0.15-1.52)	.21	—	
GVHD prophylaxis										
Cyclosporine A with or without other	283	1.00		—		171	1.00		—	
Tacrolimus with or without other	27	1.62 (0.81-3.26)	.18	—		160	1.39 (0.81-2.38)	.24	—	

HR indicates hazard ratio; CI, confidence interval; WBC, white blood cell; —, not applicable; and TBI, total body irradiation.
*Stem cell source (peripheral blood) was not a significant risk factor for relapse in the multivariate analysis.

Although we mainly focused on patients in CR1, our results also indicated that some, but not all, patients with refractory disease could be rescued by allo-SCT. These patients could not have survived long with chemotherapy alone, and complete unresponsiveness, even to allo-SCT, was often assumed. These results were compatible with some reports showing that long-term survival could be achieved for patients receiving allo-SCT, even in refractory disease.[26-28]

Our study has several limitations. First, there might be some selection biases between related and unrelated allo-SCTs. It was possible that eligibility was more stringent in patients who received unrelated allo-SCT, and they might have had better pretransplantation conditions. Second, a time-censoring effect might impact the outcome. The longer interval from diagnosis to unrelated allo-SCT eliminates the effect of patients who die during that period. This bias might improve the outcome of unrelated allo-SCT. Third, we could not make the comparison between chemotherapy and allo-SCT in this study.

The time-censoring effect could be the major bias in this study, which resulted in lower relapse rates, especially in patients transplanted from unrelated donors. We tried to correct this bias by the previously described method.[29] In the JALSG ALL study, it was reported that approximately 80% and 75% of patients were alive 6 months and 10 months after enrollment, respectively.[8] Because 6 months and 10 months were the median interval from diagnosis to related and unrelated allo-SCTs, respectively, a crude way to apply a correction factor for the survival seen in our study is to lower the survival estimate at any given time point by 20% for related allo-SCT and 25% for unrelated allo-SCT, respectively. Thus, the corrected OS rates at 4 years were 52% ± 5% for related allo-SCT and 47% ± 4% for unrelated allo-SCT, which showed no statistical difference between related and unrelated allo-SCTs. Time-censoring effects would not change the results.

The change of transplantation indication for adolescents through the observation period might affect the outcome. In the JALSG protocol ALL202 (from September 2002), we treated patients less than 25 years old with a similar protocol performed for pediatric patients. Because allo-SCT was recommended only for high-risk patients, such as those with t(4;11) or MLL-rearrangement in the pediatric protocol, the outcome of young patients might be affected by the difference in the indication for allo-SCT between pediatric and adult protocols after 2002. However, the effect of this small population would not be so large.

Table 4. Univariate and multivariate analyses of factors influencing NRM among patients transplanted in CR1, according to donor type

	Related (n = 310)					Unrelated (n = 331)				
		Univariate		Multivariate			Univariate		Multivariate	
Covariates	n	HR (95% CI)	P	HR (95% CI)	P	N	HR (95% CI)	P	HR (95% CI)	P
WBC count at diagnosis										
< 30 000/μL	224	1.00		—		230	1.00		—	
30 000/μL or more at diagnosis	86	1.21 (0.63-2.34)	.57	—		101	0.79 (0.48-1.30)	.35	—	
Lineage										
B	218	1.00		—		203	1.00		—	
T	50	1.25 (0.41-3.81)	.53	—		54	0.62 (0.29-1.38)	.17	—	
Other	42	0.87 (0.34-2.26)	.78	—		74	1.08 (0.65-1.81)	.76	—	
Karyotype										
Normal	193	1.00		—		208	1.00		—	
t(4;11) or t(1;19)	21	0.77 (0.16-3.17)	.73	—		11	1.03 (0.25-4.30)	.63	1.11 (0.27-4.64)	.57
Other (no t(9;22))	96	0.92 (0.47-1.81)	.81	—		112	1.47 (0.94-2.29)	.09	1.67 (1.06-2.64)	.03
JALSG risk stratification										
Low	39	1.00		—		45	1.00		—	
Intermediate	163	1.85 (0.86-3.97)	.12	—		192	1.01 (0.62-1.65)	.96	—	
High	108	2.82 (1.09-7.31)	.03	—		94	1.03 (0.50-2.10)	.94	—	
Age at allo-SCT										
< 45 y old	255	1.00		—		281	1.00		—	
45 y old or older at allo-SCT	55	3.90 (2.09-7.25)	< .0001	3.90 (2.09-7.25)	< .0001	50	1.26 (0.72-2.20)		.42	
HLA										
Match	285	1.00		—		192	1.00		—	
Mismatch	25	1.64 (0.64-4.18)	.30	—		139	1.69 (1.10-2.60)	.02	1.69 (1.10-2.61)	.02
Stem cell source										
Bone marrow	212	1.00		—					—	
Peripheral blood	98	1.75 (0.94-3.28)	.08	—					—	
Time from diagnosis to allo-SCT										
6 mo or longer	169	1.00		—		23	1.00		—	
< 6 mo	141	1.64 (0.87-3.11)	.13	—		308	0.31 (0.08-1.25)	.10	—	
< 10 mo	278	1.00		—		166	1.00		—	
10 mo or longer	32	1.07 (0.42-2.72)	.89	—		165	1.90 (1.21-2.99)	.01	1.98 (1.26-3.13)	.003
Preparative regimen										
Non-TBI regimens	25	1.00		—		12	1.00		—	
TBI regimens	285	0.63 (0.25-1.61)	.34	—		319	0.67 (0.25-1.85)	.44	—	
GVHD prophylaxis										
Cyclosporine A with or without other	283	1.00		—		171	1.00		—	
Tacrolimus with or without other	27	1.66 (0.65-3.80)	.29	—		160	1.33 (0.86-2.05)	.52	—	

HR indicates hazard ratio; CI, confidence interval; WBC, white blood cell; —, not applicable; and TBI, total body irradiation.

In conclusion, comparable survival rates were observed between adult Ph$^-$ ALL patients who underwent related and unrelated allo-SCTs in CR1, although relapse rates, incidences of NRM, and risk factors for transplantation outcomes were different between them. Better outcomes could be achieved by performing allo-SCT at an appropriate timing and HLA compatibility according to donor type.

Table 5. Causes of death among patients transplanted in CR1, according to donor type

	Related (n = 310)		Unrelated (n = 331)		
	n	%	n	%	P
Relapse	44	44	32	26	.01
Infection	12	12	23	19	.20
Organ failure	12	12	17	14	.83
GVHD	9	8.9	16	13	.40
Interstitial pneumonia	5	5.0	15	12	.06
Hemorrhage	3	3.0	6	5.0	.52
Graft failure	2	2.0	3	2.5	1.0
ARDS	1	1.0	3	2.5	.63
Other	8	7.9	6	5.0	.42
Unknown	5	5.0	0	0.0	.02
Total	101	100	121	100	

ARDS indicates acute respiratory distress syndrome.

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Authorship

Contribution: S.N., Y.I., and K.M. designed the research and wrote the manuscript; S.N. and Y.I. performed the statistical analysis and interpreted the data; H.S., M. Kurokawa, H.I., H.O., T.F., Y.O., N.K., M. Kasai., T.M., K.I., T.Y., M.O., and

K.M. provided the patient data; and K.K., Y.M., R.S., and Y.A. collected the patient data.

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