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

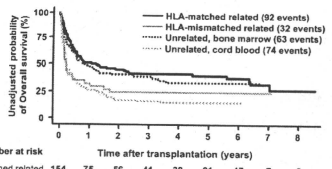

Figure 1. Unadjusted probability of overall survival according to type of graft source. The unadjusted Kaplan-Meier estimates of overall survival stratified according to type of graft source are shown.

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–

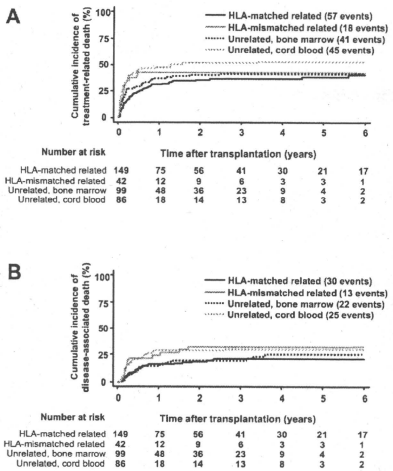

Figure 2. Cumulative incidence of treatment-related mortality and disease-associated mortality according to type of graft source. The unadjusted cumulative incidence curves for treatment-related mortality (A) and disease-associated mortality (B) stratified according to type of graft source are shown 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

Outcome	Univariable analysis			Multivariable analysis	
	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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ORIGINAL ARTICLE

Hematopoietic stem cell transplantation for therapy-related myelodysplastic syndrome and acute leukemia: a single-center analysis of 47 patients

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Abstract The prognosis of therapy-related myelodysplastic syndrome and acute leukemia (t-MDS/AL) remains poor. We retrospectively analyzed the data of 47 patients (31 AL and 16 MDS) who were treated at our institute. Thirty-three patients received disease-adapted chemotherapy, with a response rate of 73%, while 14 received no interventions due to an indolent course, such as MDS. The median follow-up of surviving patients was 1.9 years (range 0.1–10.5) after the diagnosis of t-MDS/AL, and the estimated 3-year overall survival (OS) for all patients was 55%. Twenty-seven patients underwent allogeneic hematopoietic stem cell transplantation (HCT), and the 3-year non-relapse mortality was 17%. Twenty patients did not undergo HCT due to various reasons including advanced age or comorbidities. The 3-year OS was better in patients who received HCT than in those who did not (71 vs. 31%; $p = 0.018$). A multivariate analysis revealed that HCT was associated with a better OS. Although this study has several limitations, including a potential selection bias due to the retrospective nature of the analysis and a small number of patients, the results show that modern HCT may be useful for inducing long-term survival in a fraction of patients suffering from t-MDS/AL. The present findings warrant future prospective studies.

Keywords Therapy-related myelodysplastic syndrome · Acute leukemia · Transplantation

1 Introduction

Therapy-related myelodysplastic syndrome and acute leukemia (t-MDS/AL) following exposure to cytotoxic agents have become increasingly common as a consequence of more intensive treatment and prolongation of the period at risk [1, 2]. Patients with t-MDS/AL generally have an inferior outcome due to a more progressive clinical course compared to patients with de novo disease [3, 4], with a lower complete remission (CR) rate and a shorter duration of CR [5–7], since they have a higher frequency of poor prognostic factors including unfavorable cytogenetic abnormalities, e.g., −7/del7q, −5/del5q, balanced translocation of 11q23, and complex abnormalities [4, 6, 8, 9]. Accumulated clinical and subclinical organ toxicities due to previous anti-cancer therapy are other risk factors that limit the success of subsequent therapy.

Allogeneic hematopoietic stem cell transplantation (HCT) from a suitably HLA-matched donor is a potential curative treatment for t-MDS/AL [10–14]. However, the clinical role of allogeneic HCT has not been well clarified, although previous reports have shown that patients with unfavorable-risk cytogenetics still have inferior outcomes [14–16]. In the case of t-AL, the need for remission induction chemotherapy before HCT has been questioned, although some reports support this strategy [12, 14]. Similarly, the timing of HCT should be optimized, since it has been reported that HCT at an early stage of the disease in

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patients with a lower marrow myeloblast count was associated with a higher probability of long-term survival [11, 13, 15].

Against this background, the aim of the present retrospective analysis was to examine the predictive variables associated with the outcome of patients with t-MDS/AL who were diagnosed at a single institution and received different modalities of therapy.

2 Patients and methods

2.1 Patients

We retrospectively reviewed the medical records of 47 consecutive adult patients with t-MDS/AL who were treated at the National Cancer Center Hospital between December 1996 and June 2007. Twenty-five patients had acute myeloid leukemia (AML: M1, $n = 3$; M2, $n = 11$; M3, $n = 2$; M4, $n = 4$; M5, $n = 5$) by the French–American–British (FAB) classification. Five patients had acute lymphoblastic leukemia (ALL), 1 had acute biphenotypic leukemia, and 16 had myelodysplastic syndrome (MDS) (Table 1). Patients with t-MDS were categorized according to the World Health Organization classification [17]: 3 refractory anemia (RA), 8 refractory cytopenia with multilineage dysplasia (RCMD), 3 refractory anemia with excess blasts (RAEB)-1 and 2 RAEB-2. The patients with RAEB in transformation according to the FAB classification were included as AML.

2.2 Definitions

We classified patients as having t-MDS/AL if they had received cytotoxic agents and/or radiation therapy (RT) prior to their diagnosis of t-MDS/AL. Cyclophosphamide, procarbazine, and nitrosoureas were included as alkylating agents. Similarly, to assess exposure to topoisomerase II (topo II) inhibitor, etoposide and anthracyclines were considered. Patients with therapy-related disease who had an MDS before progression into AML were categorized as having t-AML. Two patients with t-MDS after de novo acute promyelocytic leukemia (APL) were considered to develop t-MDS because their phenotypes and cytogenetic abnormalities were different from primary APL. In our study, ALL ($n = 5$) and acute biphenotypic leukemia ($n = 1$) were included as t-AL. Cytogenetic risk group assignment was made according to the Southwest Oncology Group (SWOG) cytogenetic risk category for AML patients [18]. The diagnosis and clinical grading of acute

Table 1 Patient characteristics

	All patients ($n = 47$)	HCT ($n = 27$)	No HCT ($n = 20$)
Male/female	18/29	12/15	6/14
Median age (range, years)[a]	51 (3–84)	48 (3–63)	63 (40–84)
Therapy-related disease			
t-AL	31 (66%)	18 (67%)	13 (65%)
AML M1	3	2	1
AML M2	11	6	5
AML M3	2	0	2
AML M4	4	3	1
AML M5	5	4	1
ALL	5	2	3
Acute biphenotypic leukemia	1	1	0
t-MDS	16 (34%)	9 (33%)	7 (35%)
RA	3	1	2
RCMD	8	4	4
RAEB-1	3	3	0
RAEB-2	2	1	1
Year of diagnosis of t-MDS/AL			
1996–2000	15 (32%)	7 (26%)	8 (40%)
2001–2007	32 (68%)	20 (74%)	12 (60%)
Cytogenetic risk group of t-AML[b]			
Favorable	6 (24%)	3 (20%)	3 (30%)
Intermediate	8 (32%)	5 (33%)	3 (30%)
Unfavorable	11 (44%)	7 (47%)	4 (40%)

HCT Hematopoietic stem cell transplantation, *AL* acute leukemia, *AML* acute myeloid leukemia, *ALL* acute lymphoblastic leukemia, *MDS* myelodysplastic syndrome, *RA* refractory anemia, *RCMD* refractory cytopenia with multilineage dysplasia, *RAEB* refractory anemia with excess blasts, *CR* complete remission, *NR* non-remission

[a] Age at diagnosis of t-MDS/AL

[b] Cytogenetic risk groups were categorized according to the Southwest Oncology Group cytogenetic risk category for AML patients

and chronic graft-versus-host disease (GVHD) were performed according to established criteria [19–21]. CR was defined as lower than 5% blasts in the bone marrow, with a neutrophil count >1,000/μL and a platelet count >100,000/μL in leukemia/MDS patients [22]. The overall survival (OS) was defined as the time between the diagnosis of t-MDS/AL and death due to any cause. Non-relapse mortality (NRM) was defined as death due to any cause without progression or relapse of t-MDS/AL.

2.3 Statistical methods

Patients who were alive or lost to follow-up were censored at the time last seen alive. OS was calculated using the method of Kaplan and Meier [23]. The log-rank test was used to compare Kaplan–Meier curves. The incidence of NRM was estimated from the cumulative incidence of the curve at 3 years. Hazard ratios (HR) with 95% confidence intervals (CI) were obtained by the use of univariate Cox models. Multivariate Cox models were used to determine the variables that provided the most prognostic information and to estimate adjusted HR. The initial characteristics that were considered for a multivariate analysis included CR after induction therapy, disease type (t-MDS, t-AL), HCT (received or not), the interval between the diagnosis of primary disease and t-MDS/AL (<3 vs. ≥3 years), and patient's age (<50 or ≥50 years). We chose 50 years as a cut-off of patient's age group because this is generally used to determine whether to perform reduced-intensity or myeloablative regimen for HCT, and the median age of all patients was 51 years. In addition, we performed a multivariate analysis of 25 patients with t-AML after incorporating the cytogenetic risk. We considered two-sided p values of <0.05 to be statistically significant. Statistical analyses were performed with SAS version 8.2 (SAS Inc., Cary, NC, USA).

Table 2 Primary malignancy before the development of t-MDS/AL ($n = 47$)

	No. of patients
Primary disease	
Hematologic malignancies	19 (40%)
Follicular lymphoma	8
Diffuse large B-cell lymphoma	7
Precursor T lymphoblastic lymphoma	1
Mycosis fungoides	1
Acute promyelocytic leukemia	2
Solid tumors	28 (60%)
Breast	13
Brain	2
Lung	2
Germ cell tumor	2
Prostate	2
Others[a]	7
Treatment of primary disease	
Chemotherapy alone	26 (55%)
Alkylator alone	9
Topo II alone	6
Alkylator + topo II	8
Others[b]	3
Chemoradiotherapy	13 (28%)
Alkylator + irradiation	4
Alkylator + topo II + irradiation	9
Irradiation	5 (11%)
Autologous HCT	3 (6%)

t-MDS/AL therapy-related myelodysplastic syndrome and acute leukemia, *topo II* topoisomerase II inhibitor, *HCT* hematopoietic stem cell transplantation

[a] Others included retinoblastoma, thyroid cancer, esophageal cancer, uterine cervical cancer, multicentric Castleman's disease, colon cancer, and osteosarcoma

[b] Others included iodine-131, fluorouracil, or carboplatin + paclitaxel

3 Results

3.1 Patient characteristics

The median age of the patients at the time of diagnosis of t-MDS/AL was 51 years (range 3–84). The primary malignancies included malignant lymphoma ($n = 17$: 8 follicular lymphoma, 7 diffuse large B-cell lymphoma, 1 precursor T lymphoblastic lymphoma, and 1 mycosis fungoides), breast cancer ($n = 13$), APL ($n = 2$), germ cell tumor ($n = 2$), brain tumor ($n = 2$), lung cancer ($n = 2$), prostatic cancer ($n = 2$), and others (Table 2). All patients had been treated with various cytotoxic drugs including alkylating agents ($n = 33$), topo II inhibitors ($n = 26$), and/or RT ($n = 20$). Three patients developed t-MDS/AL after autologous HCT for malignant lymphoma. The median interval from the diagnosis of the primary disease was 3.8 years (range 0.6–18.2) for patients with t-AL, 5.9 years (range 1.9–18.7) for those with t-MDS, 7.0 years (range 0.7–18.7) for those who received alkylating agents, 3.9 years (range 2.7–5.0) for those who received topo II inhibitors, and 3.8 years (range 0.9–18.2) for those who received both alkylating agents and topo II inhibitors.

A cytogenetic analysis was performed in all patients and 37 (79%) had chromosomal abnormalities, including complex abnormalities in 15 patients, 5q−/−5 in 4, and 7q−/−7 in 4. According to a cytogenetic risk classification for t-AML ($n = 25$), 6 patients (24%) were categorized as favorable risk, 8 (32%) as intermediate risk, and 11 (44%) as unfavorable risk.

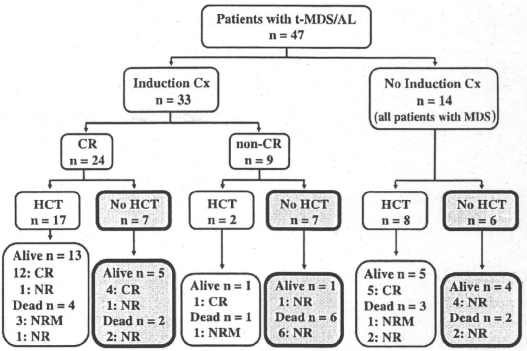

Fig. 1 Summary of treatment strategies and outcomes of t-MDS/AL. *Cx* chemotherapy, *CR* complete remission, *HCT* hematopoietic stem cell transplantation, *NR* non-remission, *NRM* non-relapse mortality

3.2 Treatment of t-MDS/AL

Treatment strategies and outcomes of t-MDS/AL are summarized in Fig. 1. Among the 47 patients, 33 received disease-adapted induction chemotherapy. The regimens for patients with t-MDS RAEB-2 ($n = 2$) or t-AML ($n = 25$) consisted of an anthracycline with standard-dose cytosine arabinoside, and regimens for patients with ALL ($n = 5$) or acute biphenotypic leukemia ($n = 1$) consisted of combination chemotherapy including alkylating agents and anthracyclines. Of the 33 patients who received disease-adapted induction chemotherapy, 24 (73%) achieved CR, and 17 of them subsequently underwent allogeneic HCT (AML, $n = 13$; ALL, $n = 2$; acute biphenotypic leukemia, $n = 1$; MDS, $n = 1$). Of the 9 who failed to achieve CR, 2 underwent HCT (all with AML).

The remaining 14 patients (all with MDS-RA, RCMD or RAEB-1) were elected to receive no induction chemotherapy due to an indolent clinical course: 8 subsequently underwent HCT (RA, $n = 1$; RCMD, $n = 4$; RAEB-1, $n = 3$) and 6 did not (RA, $n = 2$; RCMD, $n = 4$).

3.3 HCT for t-MDS/AL

Table 3 summarizes the transplant characteristics. The median age of the 27 patients who underwent allogeneic HCT was significantly younger than that of those who did not (48 vs. 63 years, $p = 0.001$). The median time from the diagnosis of t-MDS/AL to HCT was 6.3 months (1.4–20.4). Donor type was either related ($n = 12$) or unrelated ($n = 15$). The conditioning regimens were either myeloablative ($n = 18$) including cyclophosphamide plus total body irradiation (TBI, $n = 9$) or busulfan ($n = 9$), or a reduced-intensity regimen that mostly included a fludarabine plus busulfan-based regimen ($n = 9$) as previously described [24]. The sources of stem cells were bone marrow ($n = 15$), peripheral blood stem cells ($n = 10$), or umbilical cord blood ($n = 2$). GVHD prophylaxis consisted of cyclosporine with or without methotrexate (MTX) in 14 patients, and tacrolimus with or without MTX in 13 patients. Infection prophylaxis and therapy, transfusion support, and other supportive care were provided according to standard procedures as previously described [25]. At the time of HCT, 17 patients with t-MDS/AL were in CR1 (AL, $n = 16$; RAEB-2, $n = 1$), 1 AML was in CR3, 1 AML was in non-remission (NR), and 8 had untreated t-MDS (all patients with RA, RCMD, or RAEB-1).

All of the patients who underwent HCT achieved donor cell engraftment. The median time to reach a neutrophil count of 500/μL was 15 days (range 11–45) after HCT. Fifteen patients (56%) developed acute GVHD, and 5 of them developed grade III disease. Thirteen patients (48%) developed chronic GVHD, and 10 of them developed an extensive grade.

Twenty patients (43%) did not undergo HCT due to various reasons including advanced age (>65 years, $n = 11$) since they were treated before the introduction of reduced-intensity conditioning, an indolent clinical course such as MDS-RA and RCMD ($n = 4$), progression of the primary malignancy ($n = 4$) or t-AL ($n = 3$), and patient's refusal ($n = 2$).

3.4 Survival

The median follow-up time of surviving patients was 1.9 years (range 0.1–10.5) after the diagnosis of t-MDS/AL. The estimated 3-year OS for all 47 patients was 55%. The 3-year OS in patients who received allogeneic HCT was better than that in patients who did not (71 vs. 31%; $p = 0.018$; Fig. 2a). Among the 27 patients who received

Table 3 Transplant characteristics ($n = 27$)

	No. of patients
Donor type	
Related	12 (44%)
HLA-identical	9
HLA-nonidentical	3
Unrelated	15 (56%)
HLA-identical	14
HLA-nonidentical	1
Source of stem cells	
Bone marrow	15 (56%)
PBSC	10 (37%)
Cord blood	2 (7%)
Conditioning regimens	
Myeloablative	18 (67%)
BU + CY	9
CY + TBI	9
Reduced-intensity conditioning	9 (33%)
Flu + BU	3
Flu + BU + ATG	3
Others[a]	3
GVHD prophylaxis	
CSP ± MTX	14 (52%)
TAC ± MTX	13 (48%)
GVHD	
Acute GVHD	15 (56%)
I	2
II	8
III	5
IV	0
Chronic GVHD	13 (48%)
Limited	3
Extensive	10

HLA human leukocyte antigen, *PBSC* peripheral blood stem cell, *BU* busulfan, *CY* cyclophosphamide, *TBI* total body irradiation, *Flu* fludarabine, *ATG* anti-human T-lymphocyte immunoglobulin, *CSP* cyclosporine, *MTX* methotrexate, *TAC* tacrolimus, *GVHD* graft-versus-host disease

[a] Others included Flu + melphalan + TBI, cladribine + BU, or cladribine + BU + TBI

HCT, 8 (30%) died, and 4 of them had recurrent t-MDS/AL before death. The remaining 4 patients died of non-relapse causes including fungal infection, bacterial infection, sinusoidal obstructive syndrome of the liver, and bronchiolitis obliterans. The cumulative incidence of NRM at 3 years was 17%.

Of the 20 patients who did not undergo HCT, 10 died in NR status of t-MDS/AL. The direct causes of death were primary malignancies ($n = 2$), t-MDS/AL ($n = 1$), and bacterial infection ($n = 7$). Of the remaining 10 surviving patients, 6 were alive in NR status at the time last seen

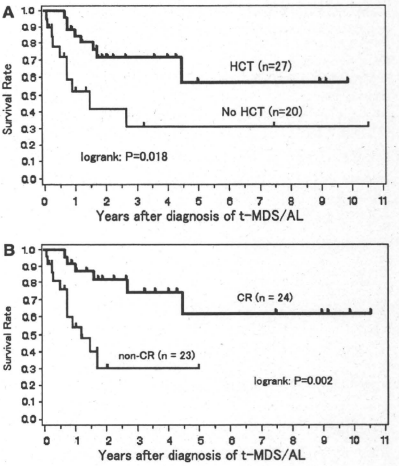

Fig. 2 Overall survival after the diagnosis of t-MDS/AL stratified according to the application of HCT (**a**) and achievement of CR after induction therapy (**b**)

alive (AL, $n = 2$; MDS-RA or RCMD, $n = 4$) with median follow-up of 167 days, and 4 patients who underwent induction chemotherapy were alive in CR status at that time (APL, $n = 2$; ALL, $n = 1$; MDS RAEB-2, $n = 1$). Of the 4 patients alive in CR, 3 were alive beyond 3 years. The likely explanations for their long-term survival were the achievement of CR after induction therapy and the long interval from the diagnosis of the primary disease (median 9.9 years). Whereas 18 (67%) of the 27 HCT patients remained alive in CR, 4 (20%) of the 20 no HCT patients were alive in CR.

To assess the therapeutic effect of HCT, we performed a 6-month landmark analysis that addressed potential selection bias between the patients who underwent HCT and those who did not. We chose 6 months as a landmark time because the median time from the diagnosis of t-MDS/AL to HCT was 6.3 months. Among the 20 no HCT patients, 5 were excluded from the analysis because of death within 6 months (AML, $n = 3$; ALL, $n = 1$; MDS RCMD, $n = 1$). Some specific clinical features that resulted in denial of the application of the HCT were observed in these patients. As all these 5 patients were elderly at the time of diagnosis of t-MDS/AL (median 68 years; range 64–84), they were not pursued for HCT at the discretion of the attending physicians. The interval from the diagnosis of the primary disease was short (median 2.0 years; range 0.6–3.4), and all of them

were in NR status of t-MDS/AL. The 6-month landmark analysis continued to show a better 3-year OS in HCT patients than that in no HCT patients, although this difference was not significant (71 vs. 44%; $p = 0.39$).

The 3-year OS in those who achieved CR after induction therapy for t-MDS/AL was better than that in patients who did not (74 vs. 30%; $p = 0.002$; Fig. 2b). The 3-year OS was 100% for t-AML patients with favorable risk, 50% for those with intermediate risk, and 44% for those with unfavorable risk ($p = 0.19$). The 3-year OS of the 16 patients with t-MDS was 58%, which was not significantly different from that of the patients with t-AL (58 vs. 51%; $p = 0.67$).

The patients were registered over a decade, which resulted in difference in conditioning regimen modalities between early period (1996–2000) and late period (2001–2007). Whereas all patients who were diagnosed in early period received myeloablative regimen ($n = 7$), those who were diagnosed in late period received either myeloablative ($n = 11$) or reduced-intensity regimen ($n = 9$). The proportion of patients who underwent HCT was significantly higher in patients younger than 50 years than in those 50 years or older (77 vs. 40%, $p = 0.01$). However, the proportion of patients who underwent HCT was not significantly different between the early and late periods ($p = 0.31$). The 3-year OS of the early period group was not significantly different from that of the late period group (47 vs. 61%, $p = 0.53$). Furthermore, no significant difference was found between the 3-year OS of patients who underwent HCT with myeloablative and reduced-intensity regimen (70 vs. 65%, $p = 1.0$).

The HCT group included significantly younger patients and those who achieved CR, which were thought to be predictors for better OS. Therefore, to examine the role of HCT, we performed a multivariate analysis by adjusting other prognostic factors, which revealed that allogeneic HCT was associated with a significantly better OS [HR 3.8 (95% CI 1.1–12.4), $p = 0.03$] (Table 4). The other significant factors were the achievement of CR after induction therapy [HR 11.7 (95% CI 2.6–52.5), $p = 0.001$] and a longer interval between the diagnosis of the primary malignancy and t-MDS/AL [HR 3.9 (95% CI 1.0–15.6), $p = 0.04$]. Subgroup analysis of the 25 t-AML patients disclosed that allogeneic HCT and cytogenetic risk group were associated with a significantly better OS [HR 8.3 (95% CI 1.0–68.1), $p = 0.04$; HR 8.8 (95% CI 1.2–64.9), $p = 0.03$, respectively).

Table 4 Multivariate analysis of overall survival

Variable	HR (95% CI)	p
HCT for t-MDS/AL		
HCT	1.0	
No HCT	3.8 (1.1–12.4)	0.03
Disease status after induction therapy		
CR	1.0	
Non-CR	11.7 (2.6–52.5)	0.001
Interval between diagnosis of primary malignancy and t-MDS/AL		
≥3 years	1.0	
<3 years	3.9 (1.0–15.6)	0.04
Subgroup analysis of t-AML		
HCT for t-AML		
HCT	1.0	
No HCT	8.3 (1.0–68.1)	0.04
Cytogenetic risk group	8.8 (1.2–64.9)	0.03

Diagnosis and patient age at diagnosis of t-MDS/AL were not significant factors. According to subgroup analysis of t-AML, patient age at diagnosis, disease status after induction therapy, and interval between diagnosis of primary malignancy and t-AML were not significant factors

HR hazard ratio, *CI* confidence interval, *HCT* hematopoietic stem cell transplantation, *t-MDS/AL* therapy-related myelodysplastic syndrome and acute leukemia, *CR* complete remission, *AML* acute myeloid leukemia

4 Discussion

Allogeneic HCT is a potential curative treatment for t-MDS/AL. However, to our knowledge, there has been no detailed comparison of the therapeutic benefits of allogeneic HCT and chemotherapy in patients with t-MDS/AL. The purpose of this study was to examine the predictive variables associated with the outcome of patients with t-MDS/AL who received different modalities of therapy. Although this study has several limitations, including a potential selection bias due to the retrospective nature of the analysis and a small number of patients, the results still suggest that HCT may induce long-term survival in a fraction of patients suffering from t-MDS/AL. However, similar published retrospective series of patients undergoing HCT for t-MDS/AL varied in their estimates of long-term survival, with values ranging from 20 to 40% [10–12, 14, 15], and no prospective trials have compared consolidation chemotherapy to HCT. The survival of patients with t-MDS/AL in our study compared very favorably with previously reported results with larger series of patients treated with standard therapy or allogeneic HCT [4, 8, 14–16]. The higher survival rate in our report may be due to application of the procedure at an earlier stage, i.e., during CR1 of AML or RA/RCMD of MDS. Notably, in our study the NRM after HCT was low (17%) in comparison with the data from other studies (30–60%) [10–14], which could be explained by the earlier application of HCT, the recent development of effective supportive measures, and the introduction of reduced-intensity conditioning regimens.

Our study confirmed that the achievement of CR by induction chemotherapy was a prognostic factor for a better OS. It has been reported that the CR rate associated with induction chemotherapy was low when applied to t-AML compared to de novo AML [26, 27]. In our study, the CR rate was 73%, which was higher than those in previous reports (around 60%). Additionally, patients with t-MDS/AL have a higher relapse rate than those with de novo MDS/AML, though they achieved CR or carried favorable cytogenetic features [4, 6, 28, 29], particularly when chemotherapy was the only therapeutic modality applied [30]. Consolidation with HCT after the achievement of CR by induction chemotherapy might be a suitable treatment option for maintaining CR.

In our study, survival was not significantly different between t-MDS and t-AL. It has been reported that patients with t-MDS, even if it is MDS-RA or RCMD, have a universally poor outcome with rapid progression to AML or bone marrow failure regardless of the initial morphologic classification of their disease [31]. On the other hand, HCT has been reported to offer the greatest potential for cure, particularly for younger patients and for those undergoing HCT earlier in the disease course [11–13, 15].

In a multivariate analysis, we confirmed that the cytogenetic risk group of t-AML was also a significant risk factor, as previously reported [4, 6, 14–16, 31]. Nevertheless, we feel that special consideration should be given to patients with favorable cytogenetic abnormalities, i.e., t(8;21), inv(16), and t(15;17). Among the 4 patients with t(8;21) or inv(16), 3 underwent allogeneic HCT in CR and 2 are still alive without recurrence. It has been reported that treatment with standard all-trans retinoic acid and chemotherapy in therapy-related APL (t-APL) produced results that were similar to de novo APL [32, 33]. In this study, no recurrence was noted without HCT in 2 such patients. It may be wise to treat t-APL similar to de novo APL. For t-AML patients with favorable cytogenetics, further studies with a larger number of patients will be required.

Another significant risk factor for OS was an interval longer than 3 years between the diagnosis of the primary malignancy and t-MDS/AL. This might be related to the fact that the shorter-interval group contained patients with more aggressive features including t-AL or topo II-related t-MDS/AL. Previous reports showed that patients who developed topo II-related t-MDS/AL earlier after primary malignancies had an inferior outcome even after allogeneic HCT [14, 34].

In our study, two-thirds of the patients had malignant lymphoma (36%) or breast cancer (28%) as the primary disease, which was similar to previous reports [2, 14, 15]. In general, it has been reported that t-MDS/AL occurs more often following autologous HCT, and the risk is increased with exposure to TBI or total lymphoid irradiation (TLI) [1, 35]. Although autologous HCT is infrequent (about 10 per year at our institution), t-MDS/AL that develops following autologous HCT is still extremely rare (3 cases). This might be because the conditioning regimen for autograft at our institute does not include TBI or TLI.

Our study consisted of a retrospective review of a small number of patients, and several factors could contribute to the bias. Clearly, a strong selection bias existed in patients who did not undergo HCT because of age, progression of the primary malignancy or t-AL, or the patient's refusal. In fact, the results from the landmark analysis showed a better 3-year OS in HCT patients than that in no HCT patients, although this difference was not significant. Nevertheless, the relatively large number of consecutive patients and their treatment at a single center argue that the results may be useful at least for designing hypotheses that can be further tested.

In conclusion, our study indicates that allogeneic HCT may be an effective therapeutic option for patients with t-MDS/AL. These results support a prospective study to examine the value of upfront HCT with stratification according to prognostic factors, including the cytogenetic risk group.

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