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Allografting

Comparison between reduced intensity and conventional myeloablative allogeneic stem-cell transplantation in patients with hematologic malignancies aged between 50 and 59 years

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Summary:

To evaluate the efficacy of reduced-intensity stem-cell transplantation (RIST), we retrospectively compared outcomes of 207 consecutive Japanese patients aged between 50 and 59 years with hematologic malignancies who received RIST ($n=70$) and conventional stem-cell transplantation (CST) ($n=137$). CST recipients received total body irradiation (TBI)-based or busulfan/cyclophosphamide-based regimens. RIST regimens were purine analog-based ($n=67$), 2 Gy TBI-based ($n=2$), and others ($n=1$). Most CST recipients (129/137) received calcineurin inhibitors and methotrexate as graft-versus-host (GVHD) prophylaxis, while 32 RIST recipients received cyclosporin. In all, 23 CST and five RIST recipients died without disease progression within 100 days of transplant. Grade II to IV acute GVHD occurred in 56 CST and 38 RIST recipients. There was no significant difference in overall survival (OS) and progression-free survival between CST and RIST. On multivariate analysis on OS, five variables were significant: preparative regimens (CST *vs* RIST) (hazard ratio = 1.92, 95% confidence interval, 1.25–2.97; $P=0.003$), performance status (2–4 *vs* 0–1) (2.50, 1.51–4.16; $P<0.001$), risk of underlying diseases (1.85, 1.21–2.83; $P=0.004$), acute GVHD (2.57, 1.72–3.84; $P<0.001$), and CML (0.38, 0.21–0.69; $P=0.002$). We should be careful in interpreting results of this small-sized retrospective study; however, reduced regimen-related toxicity might contribute to better survival in RIST. The low relapse rates following RIST suggest a strong antitumor activity through allogeneic immunity.
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Allogeneic hematopoietic stem-cell transplantation (autologous stem-cell transplantation (allo-SCT)) is a therapeutic option for advanced hematologic malignancies. A small but significant proportion of these patients can be cured with allo-SCT.[1] Conditioning regimens have been developed to maximize dose intensity, escalating the dose-limiting toxicity in nonhematopoietic tissues.[2] Conventional stem-cell transplantation (CST) using a myeloablative preparative regimen is associated with severe regimen-related toxicities (RRT), resulting in high nonrelapse mortality (NRM) especially for old patients.[3] NRM tends to be higher in patients with refractory or advanced diseases, who have been treated heavily, compared with those who have achieved remission.[3] Considering that high-dose chemotherapy followed by allo-SCT is ineffective for these patients,[4] and that intensification of preparative regimens usually leads to severe RRT and high NRM,[5] it remains unknown whether myeloablative preparative regimens are beneficial to improve survival of patients with advanced chemorefractory leukemia.

A new strategy for transplantation using a reduced-intensity stem-cell transplantation (RIST) or nonmyeloablative preparative regimen has been developed to reduce RRT while preserving an adequate antileukemia effect.[4,6] This strategy decreases the risk of NRM and allows

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transplantation in elderly patients or those with organ dysfunction. RIST appears to be promising for a variety of hematologic diseases, if disease activity is controlled prior to transplant.[7] Most physicians believe that RIST is insufficient in controlling advanced hematologic malignancies, and that intensification of preparative regimens is required to improve their prognosis. Small pilot studies showed that RIST had been unsuccessful for advanced hematologic malignancies,[5,8] yet, efficacy of RIST has not been fully evaluated. Few comparative studies have been reported between RIST and CST for hematologic malignancies.[9]

Patients older than 50 years are regarded as candidates for RIST, yet, patients younger than 60 years frequently undergo CST. Either RIST or CST is offered to patients aged between 50 and 59 years according to doctors' preferences or based on patients' conditions. To evaluate the efficacy of RIST for hematologic malignancies in the elderly patients, we retrospectively compared the outcomes of 207 consecutive patients aged between 50 and 59 years with hematologic malignancies who had received either RIST ($n=70$) or CST ($n=137$).

Patients and methods

Data collection

We conducted a nation-wide retrospective survey of 207 adult Japanese patients aged between 50 and 59 years who received allo-HSCT from an HLA-identical sibling for the treatment of acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), and myelodysplastic syndrome (MDS) from February 1998 to November 2002 in 55 participating hospitals. Patients with a history of previous transplantation were excluded from this study.

All the CST and RIST recipients who were eligible in this study were included in each hospital. In Japan, approximately 2000 transplants are performed annually. The types of transplantations are autologous (40%), myeloablative allogeneic (45%), and reduced intensity or nonmyeloablative allogeneic transplantation (15%).[10] RIST recipients are generally treated as clinical studies in Japan. Most patients were incurable with conventional treatments and were considered inappropriate for conventional allo-SCT because they were age >50 years old and/or due to organ dysfunction (generally attributable to previous intensive chemo- and/or radiotherapy).

Data from participating centers were derived from questionnaires distributed to each center. Minimum data required for the inclusion of a patient in this study were age, performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG) criteria before conditioning, medical complications at transplant, diagnosis of underlying diseases, treatment prior to allo-HSCT, disease status at transplant, preparative regimens, GVHD prophylaxis, date of transplant, date of follow-up, disease status at follow-up, development of acute and/or chronic GVHD, date of acute and/or chronic GVHD, date of disease progression/death, and causes of death. We have not collected information on the types of chronic GVHD (limited *vs* extensive).

Definition

Reduced-intensity regimens were defined as reported previously.[11,12] The upper limits of busulfan, melphalan, and TBI were 8, 140 mg/m^2, and 2 Gy for consideration as reduced-intensity preparative regimens. Neutrophil recovery was defined as an absolute neutrophil count of more than 0.5×10^9/l for two consecutive days. Patients were divided into two groups based on their disease status at transplant. Low-risk patients were defined as those with acute leukemia in first remission, CML in chronic phase, and myelodysplastic syndrome refractory anemia. The others were classified into the high-risk group. NRM was defined as death without progression of the underlying disease. Overall survival (OS) was defined as the duration of survival between transplant and either death or last follow-up. Progression-free survival (PFS) was defined as the duration of survival after transplant without disease progression, relapse, and death.

End points and statistical analysis

The primary end points were 2-year OS and PFS. The secondary end points included NRM within 100 days and 1-year of transplant, incidence of acute GVHD, and relapse rates. These end points were compared between CST and RIST recipients. For the analysis of OS and PFS, patients were stratified according to the risk of the underlying disease.

OS and PFS were determined using the Kaplan–Meier method. The last follow-up was on 1st August 2003. Median follow-up of surviving patients was 26.6 months (range, 9.5–63.6). Surviving patients were censored on the last day of follow-up. Acute GVHD was analyzed in patients who achieved initial engraftment. Cumulative incidence of acute GVHD, relapse rates, and NRM was calculated using Gray's method, considering each other event as a competing risk.[13]

Clinical characteristics were compared between CST- and RIST recipients using Fisher's exact test or the Mann–Whitney test. A multivariate Cox proportional hazards model was used to identify independent and significant prognostic factors on OS. The variables entered in each analysis were patient age, sex, primary disease, their risks, PS, and type of preparative regimens (CST *vs* RIST). Acute and/or chronic GVHD was included as a time-dependent covariate. A significance level of 5% was set as the limit for inclusion in the model. Prognostic factors, significant at $P<0.05$ in the stepwise proportional model analysis, were considered to be of importance in influencing survival.

Results

Patient characteristics and transplantation procedures

Types of transplants were CST ($n=137$) and RIST ($n=70$). Patient characteristics and transplantation procedures are shown in Table 1. Between the two groups, there were significant differences in age, sex, types of stem cells, presence of infectious complications at transplant, and PS.

Table 1 Characteristics of patients

Variables	*CST (n = 137)*	*RIST (n = 70)*	*P-value*
Pretransplant factors			
Age			
Median (range)	52 (50–59)	57 (50–59)	<0.01*
Sex			
Male/female	93/44	35/35	0.012*
Underlying diseases			
AML	56 (41%)	33 (47%)	0.42
ALL	27 (20%)	8 (11%)	
CML	34 (25%)	16 (23%)	
MDS	20 (15%)	13 (19%)	
Risk of underlying diseases[a]			
Total: low/high	63/74	25/45	0.18
AML: low/high	19/37	7/26	
ALL: low/high	14/13	5/3	
CML: CP/BC/AP	19/3/4	12/3/2	
MDS: RA/RAEB/RAEB in T/CMMoL	0/0/0/1	1/1/1/1	
Stem cells[b]			
Peripheral blood/bone marrow	57/80	68/2	<0.01*
Complications			
Cardiac impairment	5	3	0.72
Liver dysfunction	10	6	0.78
Respiratory dysfunction	6	6	0.22
Infection	9	11	0.028*
Performance status (PS)			
0–1/2–4	123/12	54/13	0.033*
Sex mismatch			
Donor → Recipient; F → M	35	12	0.17
Transplantation procedures			
Conditioning regimen	12 Gy TBI-based	74 (54%)	
BU/CY-based	51 (37%)		
TBI/BU/CY	12 (9%)		
Cladribine-based		6 (9%)	
Fludarabine-based		61 (87%)	
2 GY TBI-based		3 (4%)	
GVHD prophylaxis			
CSP	3 (2%)	32 (46%)	
CSP + sMTX	124 (91%)	23 (33%)	
FK506 + sMTX	5 (4%)	8 (11%)	
Others	5 (4%)	7 (10%)	

*Statistically significant.
[a]We divided the risk of transplantation into two groups. The low-risk group was as follows: acute myeloid or lymphoid leukemia in first remission, chronic myelogeneous leukemia in chronia phase, and myelodysplastic syndrome refractory anemia.
[b]Four patients were infused both peripheral and bone marrow.
CST = conventional stem cell transplantation; RIST = reduced-intensity stem cell transplantation; TBI = total body irradiation; CY = cyclophosphamide; BU = busulfan; 2-CdA = cladribine; Flu = fludarabine; Mel = melpharan; CSP = cyclosporine; sMTX = short-term methotrexate; AML = acute myeloid leukemia; ALL = acute lymphoid leukemia; CML = chronic myelocytic leukemia; MDS = myelodysplastic syndrome; RA = refractory anemia; RAEB = refractory anemia with excess blasts; RAEB in T = refractory anemia with excess blasts in transformation; CMMoL = chronic myelomonocytic leukemia.

RIST recipients had poorer characteristics than CST recipients.

All the CST recipients received either TBI-based or busulfan/cyclophosphamide-based regimens. RIST regimens were purine analog based ($n = 67$), and 2 Gy TBI based ($n = 3$).

Most CST recipients (129/137) received a combination of calcineurin inhibitors (cyclosporin or tacrolimus) and short-term methotrexate as GVHD prophylaxis, while 32 of the 70 RIST received cyclosporin alone as GVHD prophylaxis (Table 1).

Engraftment

Six CST recipients (9%) died of NRM before engraftment. Neutrophils did not decrease below 0.5×10^9/l in 6 RIST recipients (9%). The other 131 CST recipients (96%) and 64 RIST recipients (91%) achieved primary neutrophil engraftment. The median intervals between transplant and neutrophil engraftment were 15 days (range, 5–27) and 12 days (range, 9–30) in CST and RIST, respectively.

Secondary graft failure developed in three patients (CST 2 and RIST 1) 3–9 months after transplant. All the three patients died of infectious complication during neutropenia.

NRM

In all, 23 CST (17%) and five RIST recipients (7%) died of NRM within 100 days of the transplant. Cumulative incidences of 100 days NRM following CST and RIST were 16% (95% confidence interval (CI), 10–22%) and 7% (95% CI, 1–14%), respectively ($P = 0.040$). As of August 2003, 46 CST (34%) and 16 RIST recipients (23%) died of NRM. The median onset of NRM following CST and RIST was day 95.5 (range, 2–967) and day 254 (range, 49–724), respectively. Cumulative incidences of 1-year NRM following CST and RIST were 31% (95% CI, 23–39%) and 15% (95% CI, 6–23%), respectively ($P = 0.0062$, Figure 1). Primary causes of NRM following CST and RIST are

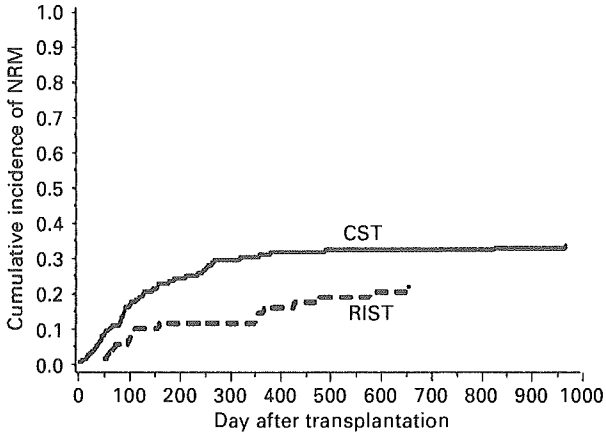

Figure 1 Cumulative incidences of NRM following CST and RIST. Cumulative incidences of NRM following CST and RIST were 31% (95% CI, 23–39%) and 15% (95% CI, 6–23%), respectively.

shown in Table 2. NRM attributable to RRT occurred in 12 and one patient following CST and RIST, respectively.

Graft-versus-host disease

A total of 130 CST and 68 RIST recipients were evaluable. There was no difference in the cumulative incidences of grade II–IV acute GVHD between CST and RIST (Figure 2).

In CST, grade II–IV and grade III–IV acute GVHD occurred in 56 (43%) and 24 patients (18%), respectively. The median onset of grade II–IV acute GVHD was day 23 (range, 3–146 days). GVHD was fatal in 13 of the 56 patients. Of the 104 patients who survived longer than 100 days, 60 patients (58%) developed chronic GVHD.

In RIST, grade II–IV and grade III–IV acute GVHD developed in 38 (56%) and 16 (24%), respectively. The median onset of grade II–IV acute GVHD was day 44 (range, 7–109). GVHD was fatal in 11 of the 38 patients. Of the 57 patients who survived longer than 100 days, 37 (65%) developed chronic GVHD.

Survival

As of August 1, 2003, median follow-ups of surviving patients following CST and RIST were 31.6 months (range, 9.5–63.6) and 20.3 months (range, 9.5–38.4), respectively. Disease-specific outcomes are shown in Table 3.

In all, and low-risk patients, significant differences were not observed in OS between CST and RIST ($P=0.25$, $P=0.69$) (Figures 3 and 4). Among the high-risk patients, there was a significant difference between the two groups ($P=0.044$). The 2-year OS following CST and RIST was 27 and 37%, respectively (Figure 5). There was no significant difference in PFS between CST and RIST among all and low-risk patients ($P=0.39$, $P=0.77$). Among high-risk patients, there was a trend toward better PFS after RIST ($P=0.063$). The 2-year PFS following CST and RIST was 30 and 56%, respectively.

Underlying diseases relapsed in 38 CST and 23 RIST recipients. There was no significant difference in the cumulative incidence of 1-year relapse rates between the two groups; CST 24% (95% CI, 17–32%) and RIST 29% (95% CI, 19–40%) ($P=0.21$, Figure 6).

Risk factors

A univariate analysis revealed that CML ($P<0.0001$), risk of underlying diseases ($P=0.0002$), PS ($P<0.0001$), and

Table 2 Causes of deaths

	CST	*RIST*
Relapse	28	16
Graft-versus-host disease	13	11
Infection	4	0
Bacteria	5	0
Virus	4	1
Fungi		
Idiopathic pulmonary syndrome	5	0
Thrombotic microangiopathy	5	1
Hepatic venoocclusive disease	2	0
Secondary malignancy	2	1
Cardiac failure	1	1
Cerebral infarction	1	0
Others	4	1

CST = conventional stem cell transplantation; RIST = reduced-intensity stem cell transplantation.

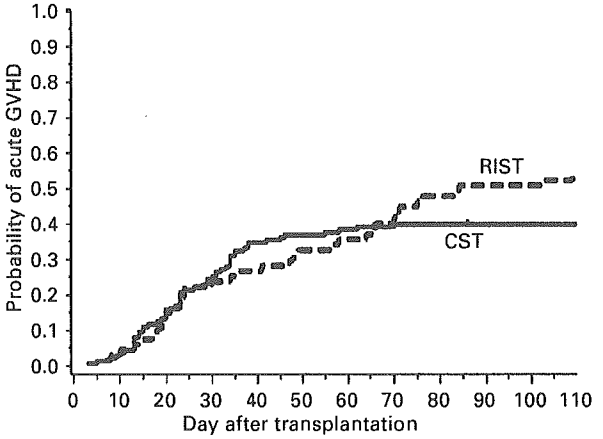

Figure 2 Cumulative incidences of grade II–IV acute GVHD. There was no difference in the cumulative incidences of grades II–IV acute GVHD between CST and RIST.

Table 3 Disease-specific outcomes

Underlying disease	*Type of transplant*	*Number of patients*	*Nmber of patients who died of TRM*	*Number of patients who developed disease progression*	*2-year overall survival*[a]
AML	CST	56	19	20	38.7 (25.8–51.6)
	RIST	33	8	12	69.3 (53.4–85.2)
ALL	CST	27	11	10	33.3 (15.5–51.1)
	RIST	8	2	3	50.0 (15.3–84.7)
MDS	CST	34	8	5	45.0 (23.2–66.8)
	RIST	16	5	3	53.8 (26.8–80.8)
CML	CST	20	8	3	73.4 (58.5–88.3)
	RIST	13	1	5	93.3 (80.8–100)

[a]Each column denotes a rate of 2-year overall survival and its 95% confidence interval.
AML = acute myeloid leukemia; ALL = acute lymphoid leukemia; MDS = myelodysplastic syndrome; CML = chronic myelocytic leukemia; TRM = transplant-related mortality; CST = conventional stem-cell translantation; and RIST = reduced intensity stem cell transplantation.

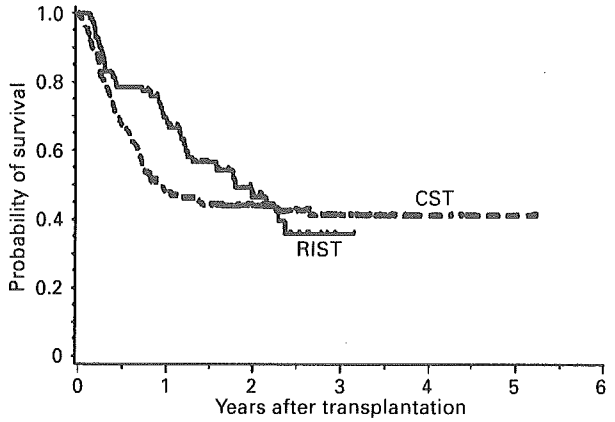

Figure 3 Overall survival (OS) following CST and RIST in all patients. There was no significant difference in OS between CST and RIST ($P=0.25$).

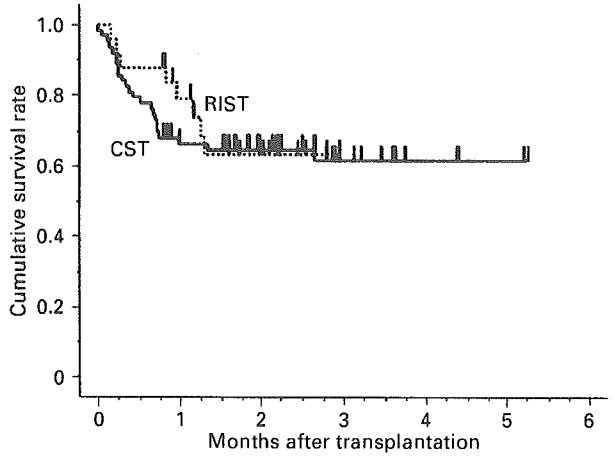

Figure 4 OS following CST and RIST in patients with low-risk diseases. There was no significant difference in OS between CST and RIST ($P=0.69$).

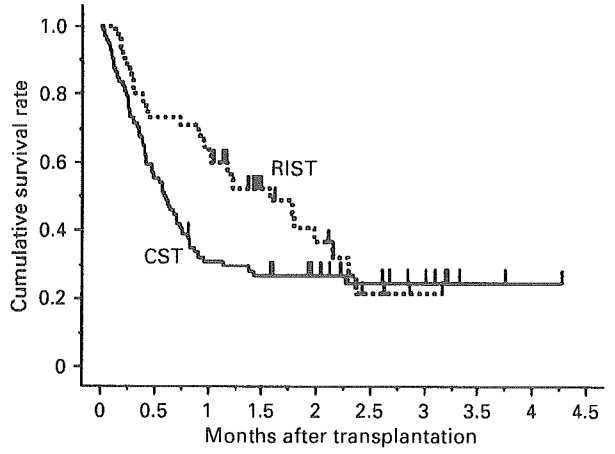

Figure 5 OS following CST and RIST in patients with high-risk diseases. There was a significant difference in OS between CST and RIST ($P=0.044$). The 2-year OS following CST and RIST were 27 and 37%, respectively.

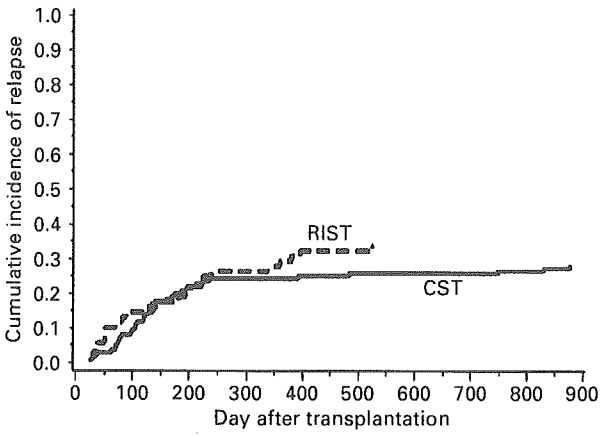

Figure 6 Cumulative incidences of relapse following RIST and CST. There was no significant difference in cumulative incidences of relapse between RIST and CST.

Table 4 Risk factors for overall survival following allogeneic hematopoietic stem-cell tranplantation

	Hazard ratio	*95% confidence interval*	*P-value*
Factors			
Univariate analysis			
Pretransplant factors			
Sex: Female	0.85	0.58–1.25	0.40
Age: 56–59 *vs* 50–51 years	1.11	0.72–1.70	0.63
Donor: female to male recipient	1.22	0.80–1.88	0.35
Disease	1.00		0.0002
CML	0.29	0.15–0.58	
ALL	1.30	0.73–2.31	
AML	0.91	0.55–1.51	
Risk of underlying diseases; high	2.30	1.58–3.37	<0.0001*
PS: 2–4	3.49	2.16–5.64	<0.0001*
Preparative regimen; CST	1.26	0.85–1.88	0.25
Posttransplant factor			
Grade II–IV acute GVHD; presence	2.58	1.76–3.79	<0.0001*
Variables			
Multivariate analysis			
Preparative regimen; CST *vs* RIST	1.92	1.25–2.97	0.003*
PS; 2–4 *vs* 0–1	2.50	1.51–4.16	<0.001
Disease; CML	0.38	0.21–0.69	0.002
Risk of underlying diseases; high	1.85	1.21–2.83	0.004
Grade II–IV acute GVHD; presence	2.57	1.72–3.84	<0.001*

*Statistically significant.
AML = acute myeloid leukemia; CML = chronic myelogeneous leukemia; MDS = myelodysplastic syndrome; ALL = acute lymhoid leukemia; PS = performance status; CST = conventional stem-cell transplantation; GVHD = graft-versus host disease.

development of GVHD ($P<0.001$) were significant risk factors for OS (Table 4). On multivariate analysis, five variables were significant: preparative regimens (CST *vs* RIST) (hazard ratio (HR) = 1.92, 95% CI, 1.25–2.97; $P=0.003$), PS (2–4 *vs* 0–1) (HR = 2.50, 95% CI,

1.51–4.16; $P<0.001$), risk of underlying diseases (HR = 1.85, 95% CI, 1.21–2.83; $P=0.004$), development of grade II–IV acute GVHD (HR = 2.57, 95% CI, 1.72–3.84; $P<0.001$), and CML (HR = 0.38, 95% CI, 0.21–0.69; $P=0.002$).

Discussion

This study suggests that patients with hematologic malignancies aged between 50 and 59 years can achieve remission following RIST as well as CST. There was no significant difference in OS and PFS between RIST and CST (Figure 3). Follow-up of this study was too short to draw a definite conclusion; however, short-term survivals tended to be better in RIST recipients than in CST recipients in the high-risk group (Figure 5). These situations were in contrast to the low-risk group, in which OS and PFS were similar between the two groups (Figure 4). Myeloablative preparative regimens might have been intolerable for high-risk elderly patients. Patients with more progressive diseases might have received CST rather than RIST.

Most physicians believe that it is difficult to control advanced hematologic malignancies with RIST.[5,7] Yet, feasibility of myeloablative preparative regimens has not been fully investigated in patients aged between 50 and 59 years. It is questionable whether intensification of preparative regimens is beneficial for controlling advanced or chemoresistant hematologic malignancies in these patients, because patients with high-risk hematologic malignancies frequently have organ damage due to repeated cytotoxic chemotherapies prior to transplantation.[14] These patients are at high risk of NRM.[15,16] As shown in this study, a myeloablative preparative regimen is not necessarily beneficial in allo-HSCT for elderly patients with high-risk hematologic diseases. In contrast, patients aged between 50 and 59 years in good physical condition are able to tolerate a high-dose preparative regimen. Variables such as CML, low-risk underlying disease, and good PS were independent good prognostic factors for OS. We should tailor preparative regimens considering the patient's condition and risk of the underlying disease.

There are two types of complications associated with allo-HSCT. One is RRT, which often occurs within 30 days of transplantation.[3] The other is GVHD, which is frequently complicated with infections.[14,17] In the present study, there was a significant difference in NRM attributable to RRT between CST and RIST (16 *vs* 7%, $P=0.04$). Reduced-intensity regimens cause less organ damage, contributing to less NRM. These findings were comparable to previous reports.[4,16,18]

GVHD is the most significant concern after allo-HSCT. This study confirmed the previous studies on GVHD following RIST.[19,20] There was no significant difference in the incidence of GVHD between CST and RIST (43 *vs* 56%), and onset of GVHD was delayed in RIST compared with CST. Mortality of GVHD was similar between CST and RIST (23 *vs* 29%). Development of grade II to IV acute GVHD was an independent poor prognostic factor for OS (HR = 2.57, 95% CI, 1.72–3.84; $P<0.001$). These findings demonstrate that GVHD is a significant complication following RIST as well as CST, and that its optimal management awaits further investigation. Balancing GVHD and GVL effects is a delicate issue in allo-HSCT. The augmentation of GVHD prophylaxis may hamper GVL effects, and malignant cells cannot be eradicated by reduced-intensity conditioning alone. Augmentation of GVL effects such as prophylactic donor lymphocyte infusion, vaccination, and administration of cytotoxic T-cells[21] may be beneficial to control residual leukemia without increasing regimen-related mortality. At present, allo-HSCT recipients received uniform GVHD prophylaxis irrespective of the risk of underlying diseases and the patient's condition. In the future, management of GVHD should be optimized considering the risk of the underlying disease and patient conditions.

Relapse is another concern in RIST. This study did not show significant differences in relapse rates between CST and RIST (Figure 6). The unexpectedly low relapse rates following RIST suggest that it has a strong antitumor activity through allogeneic immunity. Augmentation of allogeneic immunity without increasing the intensity of the arative regimen is promising for controlling advanced hematological malignancies. However, late relapse might increase following RIST due to the lack of reduction of leukemic cells by the preparative regimen. It is too early to draw definite conclusions about the incidence of late relapse following RIST based on the results of this study, since allo-HSCT recipients have a considerable risk of relapse within 3 years of transplant[22] and median follow-up of surviving patients was only 26.7 months. Long-term follow-up is required to clarify the prognosis of RIST recipients.

This is a small-sized retrospective study, and we should be careful in interpreting results. The most important was a difference in patient backgrounds between CST and RIST recipients. To minimize unrecognized biases, patients enrolled in this study were limited to those aged between 50 and 59 years who had leukemia or MDS. Yet, RIST recipients were significantly older, and their disease status and PS were significantly worse than CST recipients. These variables influence survival following RIST[7,23] as well as CST.[24–26] Furthermore, there was a wide difference in GVHD prophylaxis between CST and RIST. Most RIST recipients received cyclosporin alone. Short-term methotrexate, and cyclosporin or tacrolimus were given to CST recipients. The median follow-up of surviving patients enrolled in this study was 26.6 months, and thus too short, requiring further observation. Considering these facts, it is difficult to make an accurate comparison between reduced-intensity and myeloablative preparative regimens in this study. We are now planning a prospective randomized study to compare RIST with CST for hematologic malignancies.

Acknowledgements

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References

1 Biggs JC, Horowitz MM, Gale RP *et al.* Bone marrow transplants may cure patients with acute leukemia never achieving remission with chemotherapy. *Blood* 1992; **80**: 1090–1093.
2 Ratanatharathorn V, Karanes C, Lum LG *et al.* Allogeneic bone marrow transplantation in high-risk myeloid disorders using busulfan, cytosine arabinoside and cyclophosphamide (BAC). *Bone Marrow Transplant* 1992; **9**: 49–55.
3 Bearman S, Appelbaum FR, Buckner C *et al.* Regimen-related toxicity in patients undergoing bone marrow transplantation. *J Clin Oncol* 1988; **6**: 1562–1568.
4 Slavin S, Nagler A, Naparstek E *et al.* Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. *Blood* 1998; **91**: 756–763.
5 Giralt S, Estey E, Albitar M *et al.* Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: harnessing graft-versus-leukemia without myeloablative therapy. *Blood* 1997; **89**: 4531–4536.
6 Saito T, Kanda Y, Kami M *et al.* Therapeutic potential of a reduced-intensity preparative regimen for allogeneic transplantation with cladribine, busulfan, and antithymocyte globulin against advanced/refractory acute leukemia/lymphoma. *Clin Cancer Res* 2002; **8**: 1014–1020.
7 Michallet M, Bilger K, Garban F *et al.* Allogeneic hematopoietic stem-cell transplantation after nonmyeloablative preparative regimens: impact of pretransplantation and post-transplantation factors on outcome. *J Clin Oncol* 2001; **19**: 3340–3349.
8 Nagler A, Slavin S, Varadi G *et al.* Allogeneic peripheral blood stem cell transplantation using a fludarabine-based low intensity conditioning regimen for malignant lymphoma. *Bone Marrow Transplant* 2000; **25**: 1021–1028.
9 Diaconescu R, Flowers CR, Storer B *et al.* Morbidity and mortality with nonmyeloablative compared with myeloablative conditioning before hematopoietic cell transplantation from HLA-matched related donors. *Blood* 2004; **104**: 1550–1558.
10 Imataki O, Kami M, Kim SW *et al.* A nationwide survey of deep fungal infections and fungal prophylaxis after hematopoietic stem cell transplantation in Japan. *Bone Marrow Transplant* 2004; **33**: 1173–1179.
11 Bacigalupo A. Second EBMT Workshop on reduced intensity allogeneic hemopoietic stem cell transplants (RI-HSCT). *Bone Marrow Transplant* 2002; **29**: 191–195.
12 Bacigalupo A. Third EBMT/AMGEN Workshop on reduced-intensity conditioning allogeneic haemopoietic stem cell transplants (RIC-HSCT), and panel consensus. *Bone Marrow Transplant* 2004; **33**: 691–696.
13 Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med* 1999; **18**: 695–706.
14 Yamamoto R, Kusumi E, Kami M *et al.* Late hemorrhagic cystitis after reduced-intensity hematopoietic stem cell transplantation (RIST). *Bone Marrow Transplant* 2003; **32**: 1089–1095.
15 Hogan WJ, Maris M, Storer B *et al.* Hepatic injury after nonmyeloablative conditioning followed by allogeneic hematopoietic cell transplantation: a study of 193 patients. *Blood* 2004; **103**: 78–84.
16 Fukuda T, Hackman RC, Guthrie KA *et al.* Risks and outcomes of idiopathic pneumonia syndrome after nonmyeloablative and conventional conditioning regimens for allogeneic hematopoietic stem cell transplantation. *Blood* 2003; **102**: 2777–2785.
17 Fukuda T, Boeckh M, Carter RA *et al.* Risks and outcomes of invasive fungal infections in recipients of allogeneic hematopoietic stem cell transplants after nonmyeloablative conditioning. *Blood* 2003; **102**: 827–833.
18 McSweeney PA, Niederwieser D, Shizuru JA *et al.* Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. *Blood* 2001; **97**: 3390–3400.
19 Nakai K, Mineishi S, Kami M *et al.* Antithymocyte globulin affects the occurrence of acute and chronic graft-versus-host disease after a reduced-intensity conditioning regimen by modulating mixed chimerism induction and immune reconstitution. *Transplantation* 2003; **75**: 2135–2143.
20 Mielcarek M, Martin PJ, Leisenring W *et al.* Graft-versus-host disease after nonmyeloablative versus conventional hematopoietic stem cell transplantation. *Blood* 2003; **102**: 756–762.
21 Fontaine P, Roy-Proulx G, Knafo L *et al.* Adoptive transfer of minor histocompatibility antigen-specific T lymphocytes eradicates leukemia cells without causing graft-versus-host disease. *Nat Med* 2001; **7**: 789–794.
22 Socie G, Stone JV, Wingard JR *et al.* Long-term survival and late deaths after allogeneic bone marrow transplantation. Late Effects Working Committee of the International Bone Marrow Transplant Registry. *N Engl J Med* 1999; **341**: 14–21.
23 Gomez-Nunez M, Martino R, Caballero MD *et al.* Elderly age and prior autologous transplantation have a deleterious effect on survival following allogeneic peripheral blood stem cell transplantation with reduced-intensity conditioning: results from the Spanish multicenter prospective trial. *Bone Marrow Transplant* 2004; **33**: 477–482.
24 Tallman MS, Kopecky KJ, Amos D *et al.* Analysis of prognostic factors for the outcome of marrow transplantation or further chemotherapy for patients with acute nonlymphocytic leukemia in first remission. *J Clin Oncol* 1989; **7**: 326–337.
25 Hansen JA, Gooley TA, Martin PJ *et al.* Bone marrow transplants from unrelated donors for patients with chronic myeloid leukemia. *N Engl J Med* 1998; **338**: 962–968.
26 Bolwell BJ. Are predictive factors clinically useful in bone marrow transplantation? *Bone Marrow Transplant* 2003; **32**: 853–861.

Appendix

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