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第 30 回日本造血細胞移植学会総会 2008 年 2 月 29 日～3 月 1 日 大阪



Comparable Antileukemia/Lymphoma Effects in Nonremission Patients Undergoing Allogeneic Hematopoietic Cell Transplantation with a Conventional Cytoablative or Reduced-Intensity Regimen

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Received February 1, 2007; accepted April 12, 2007

ABSTRACT

To evaluate the potential of allogeneic hematopoietic cell transplantation (HCT) with a reduced-intensity conditioning regimen (RIST) for the treatment of patients with hematologic malignancies not in remission, we retrospectively reviewed the medical records of 132 patients (89 leukemia or myelodysplastic syndrome, 40 malignant lymphoma, and 3 others) who received conventional myeloablative HCT (CST, $n = 52$) or RIST ($n = 80$). The median age of the RIST group was significantly higher than that of the CST group (53 years versus 40 years, $P < .01$). The RIST group also included a higher proportion of patients with an HCT-specific comorbidity index (HCT-CI) of 1 or more than the CST group (65% versus 37%, $P = .03$). The probabilities of achieving complete remission and the incidences of grades II-IV and III-IV acute graft-versus-host disease (aGVHD) in the CST and RIST groups were, respectively, 77% and 64%, 50% and 50%, and 23% and 28%, with no significant differences. Similarly, there was no difference in the 2-year probabilities of nonrelapse mortality (NRM, 36% and 38%), progressive disease or relapse (PD 51% and 49%), overall survival (OS, 31% and 38%), and progression-free survival (PFS, 28% and 29%). Multivariate analyses revealed that a higher HCT-CI score and transplant from donors other than HLA-matched relatives were associated with increased risks of NRM and poor OS, and patients who received chemotherapy within 2 months before HCT were associated with increased risks of PD, poor OS, and PFS after transplantation. After adjusting for these variables, the risks of NRM, PD, OS, and PFS in the RIST group were not significantly different from those in the CST group. In conclusion, these results suggest that the antileukemia/lymphoma effect associated with RIST is comparable to that associated with CST. RIST appears to be feasible for the treatment of hematologic malignancies not in remission.

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KEY WORDS

Transplantation • Leukemia • Lymphoma

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) has the potential to achieve long-term cure of hematologic malignancies by pretransplant conditioning and a graft-versus-leukemia/lymphoma (GVL) effect. It has been well established that the disease status

at the time of transplantation is the most important prognostic factor, and the rates of relapse and nonrelapse mortality (NRM) significantly increase in patients with hematologic malignancies who were not in remission. Therefore, conventional stem cell transplantation (CST) using a myeloablative conditioning

regimen has been universally used in the hope of maximally reducing the tumor burden before HCT in patients not in remission. However, CST may not be an option for many patients because of their older age or associated comorbidities. Alternatively, over the past few years, nonmyeloablative and reduced-intensity conditioning stem cell transplantation (RIST) have been offered to these patients undergoing HCT, on the assumption that RIST would be better tolerated [1-4].

There have been several reports that the outcome of older patients who underwent RIST while in remission was comparable to that of patients who received CST [5-9], which suggests that the GVL effect associated with RIST might be adequate for controlling chemosensitive or slowly progressing disease. On the other hand, it still remains controversial whether RIST is feasible for patients not in remission, although small pilot studies have shown that RIST was unsuccessful for advanced hematologic malignancies [3,10-14]. To address this issue, we retrospectively analyzed 132 patients who were not in remission at the time of CST or RIST.

PATIENTS AND METHODS

Study Patients

We retrospectively reviewed the medical records of 132 patients with various hematologic malignancies who underwent allogeneic HCT (CST, $n = 52$; RIST, $n = 80$) while not in remission at our institution from January 2000 to December 2004. Patients with chronic myelogenous leukemia (CML) in the chronic phase, myelodysplastic syndrome (MDS)-refractory anemia, and those with lymphoma in partial remission (PR) were not included because the response to treatment and the outcome of these patients is generally considered to be similar to those in patients who are in complete remission (CR). Bone marrow or granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood stem cells (PBSC) were harvested from donors according to protocols approved by the guidelines of the Japan Marrow Donor Program, the Japanese Society for Hematopoietic Cell Transplantation, and the Japanese Society of Blood Transfusion. Informed consent was obtained according to the Declaration of Helsinki.

Transplantation Procedures

The conditioning regimens used in CST included the combination of cyclophosphamide (CY; 60 mg/kg i.v. daily for 2 days) and fractionated total body irradiation (TBI; 12 Gy in 6 fractions over 3 days) in 34 patients, CY and oral busulfan (BU; 16 mg/kg divided over 4 days) in 13 patients, and other combinations in 5 patients (Table 1). Targeted dose adjustment of BU

was not performed. Patients who underwent RIST were older than 50 years of age or those who had comorbidities or prior transplantation. The conditioning regimens for RIST consisted of fludarabine (30 mg/m² i.v. daily for 6 days) or cladribine (0.11 mg/kg i.v. daily for 6 days) plus 8 mg/kg of oral BU [15] with ($n = 27$) or without ($n = 53$) 4 Gy TBI. In Japan, only bone marrow is permitted as a stem cell source in transplantation from an unrelated healthy volunteer donor. In the setting of nonmyeloablative stem cell transplantation from an unrelated donor, the sustained engraftment rate has been reported to be lower for recipients of bone marrow than for those given PBSC [13]. Therefore, low-dose TBI was also added to the conditioning regimen for RIST from an unrelated donor to facilitate engraftment.

Day 0 was defined as the day of stem cell infusion. G-CSF was administered after transplantation in all patients until neutrophil engraftment. Most patients who underwent CST were given cyclosporine (CSP) with methotrexate (MTX) [16], and all patients who underwent RIST were given CSP with or without MTX for graft-versus-host disease (GVHD) prophylaxis (Table 1). GVHD was treated with 1 to 2 mg/kg/day prednisolone equivalents, resumption of full-dose CSP administration if applicable, or both. Initial doses of corticosteroids and tapering schedules of immunosuppressive medications were modified at the discretion of the attending physicians according to the presence or absence of malignant cells and the severity of GVHD. Treatment for relapse after transplantation was left to the discretion of the attending physicians.

All patients received ciprofloxacin (200 mg orally 3 times daily) for bacterial prophylaxis until neutrophil engraftment. Fluconazole (100 mg once daily) was administered for fungal prophylaxis. Patients who had positive serologic test results for herpes simplex virus or varicella zoster virus received prophylactic low-dose acyclovir until the cessation of immunosuppressive agents [17]. Prophylaxis against *Pneumocystis jirovecii* infection was provided with trimethoprim-sulfamethoxazole from the first day of conditioning to day -3 of transplantation, and from day 28 until day 180 or the cessation of immunosuppressive agents. Patients were monitored with weekly cytomegalovirus (CMV) pp65 antigenemia testing, and positive antigenemia was treated with ganciclovir as described previously [18,19].

Definitions

Chemotherapy within 2 months before HCT was defined as chemotherapy to control the disease except for rituximab alone for lymphoma and imatinib mesylate alone for CML. Pretransplantation comorbidities were determined by the HCT-specific comorbidity index (HCT-CI) [20] with a minor modification [21]. Neutrophil engraftment was defined as the first

Table 1. Patient Characteristics

	CST	RIST	P-Value
No. of patients	52	80	
Sex, male/female	25/27	50/30	
Median age, years (range)	40 (3-55)	53 (20-68)	<.01
Disease status at conditioning, N (%)			
AML	20 (38)	15 (19)	
Relapse 1	12	6	
Relapse ≥ 2	5	5	
Primary refractory	3	4	
MDS (including overt AML)	15 (29)	24 (30)	
Relapse 1	1	2	
Untreated	6	11	
Primary refractory	8	11	
ALL	5 (10)	2 (3)	
Relapse 1	4	1	
Relapse 2	1	1	
CML	5 (10)	3 (4)	
Accelerated phase	3	0	
Blastic crisis	2	3	
NHL	7 (13)	33 (40)	
Relapse 1	2	6	
Relapse ≥ 2	2	16	
Primary refractory	3	11	
Others*	0	3 (4)	
Chemotherapy within 2 months before HCT, N (%)	33 (63)	52 (65)	
Leukemia/MDS	30	23	
Lymphoma	3	26	
Others*	0	3	
HCT-CI score, N (%)			.03
0	33 (63)	28 (35)	
1-2	11 (21)	31 (39)	
≥ 3	8 (16)	21 (26)	
Conditioning regimen, N (%)			
TBI/CY	34 (65)	0	
BU/CY	13 (25)	0	
Fludarabine-based (\pm TBI)†	0	68 (85)	
Cladribine-based (\pm TBI)‡	0	12 (15)	
Others	5 (10)	0	
Donor type, N (%)			.1
HLA-matched related donor	17 (33)	41 (51)	
HLA-mismatched related donor	5 (9)	7 (9)	
Unrelated donor	30 (58)	32 (40)	
Stem cell source, N (%)			<.01
G-CSF mobilized PBSC	21 (40)	49 (61)	
BM	27 (52)	20 (25)	
CB	4 (8)	11 (14)	
GVHD prophylaxis, N (%)			<.01
Cyclosporine§	1 (2)	52 (65)	
Cyclosporine/MTX¶	49 (94)	28 (35)	
Tacrolimus	1 (2)	0	
Tacrolimus/MTX	1 (2)	0	
Prior HCT, N (%)	4 (8)	8 (10)	.65

CST indicates conventional stem cell transplantation; RIST, reduced-intensity stem cell transplantation; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; NHL, non-Hodgkin's lymphoma; HCT, hematopoietic cell transplantation; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; TBI, total-body irradiation; CY, cyclophosphamide; BU, busulfan; HLA, human leukocyte antigen; G-CSF, granulocyte colony-stimulating factor; PBSC, peripheral blood stem cell; BM, bone marrow; CB, cord blood; GVHD, graft-versus-host disease; MTX, methotrexate.

*Others included 1 chronic lymphocytic leukemia and 2 multiple myeloma patients.

†Twenty-three patients received 4 Gy TBI.

‡Four patients received 4 Gy TBI.

§Including 7 with antithymocyte globulin.

¶Including 10 with antithymocyte globulin.

of 3 consecutive days after transplantation that the absolute neutrophil count exceeded $0.5 \times 10^9/L$ of peripheral blood. The diagnosis and clinical grading of acute and chronic GVHD (aGVHD, cGVHD) were performed according to established criteria [22-24]. CR was defined as lower than 5% blasts in the bone marrow, with a neutrophil count $>1.5 \times 10^9/L$ and a platelet count $>100 \times 10^9/L$ in leukemia/MDS patients, and according to the International Workshop Criteria [25] in lymphoma patients.

Statistical Analysis

The endpoints of the study were progressive disease/relapse (PD), NRM, overall survival (OS), and progression-free survival (PFS). OS, NRM, and PD were defined as the time between stem cell infusion to the event. PFS was defined as the time between stem cell infusion to PD or death from any cause, whichever occurred earlier. OS and PFS were estimated by the Kaplan-Meier method [26]. NRM and PD were estimated by the cumulative incidence. The chi-square test or Fisher's exact test was used to evaluate the differences in the clinical characteristics of the CST and RIST groups. The log-rank test and the generalized Wilcoxon test were used to compare the probabilities of survival, NRM, and PD after HCT over time across patient subgroups.

Multiple Cox regression models were used for multivariate risk factor analysis for PD, NRM, OS, and PFS after HCT. Clinical factors evaluated in the PD, NRM, OS, and PFS analyses were patient age at the time of HCT (continuous), HCT-CI (0, 1-2, 3 or more), conditioning (CST, RIST), donor (HLA-matched related, HLA-mismatched related or unrelated), disease type (leukemia/MDS, lymphoma), and chemotherapy within 2 months before HCT (yes, no). Logistic regression analysis was performed to identify prognostic factors that were associated with the achievement of CR. In addition to the variables examined in the Cox analysis, blast percentage ($\geq 20\%$, $<20\%$) in the bone marrow or peripheral blood and the serum lactate dehydrogenase (LDH) level (normal, elevation) before HCT were included for the analysis of CR in patients with leukemia/MDS and those with lymphoma, respectively. We considered 2-sided *P*-values of $<.05$ to be statistically significant. Statistical analyses were performed with the SAS version 8.2 (SAS Inc, Cary, NC).

RESULTS

Patient Characteristics

The characteristics of all patients who underwent CST ($n = 52$) or RIST ($n = 80$) are summarized in Table 1. The median age of the RIST group was significantly higher than that of the CST group (53

years versus 40 years, $P < .01$). A large number of patients in both groups had acute myeloid leukemia (AML) or MDS (CST 67%, RIST 49%), and the RIST group included a higher population of patients with malignant lymphoma (CST 13%, RIST 40%). All malignant lymphomas ($n = 40$) were non-Hodgkin's lymphoma, including aggressive ($n = 16$), highly aggressive ($n = 15$), and indolent ($n = 9$) lymphomas. The distribution of lymphoma subtypes was similar between the 2 groups. Disease status at transplantation included primary refractory ($n = 42$), refractory relapse ($n = 65$), blastic crisis, or accelerated phase of CML ($n = 8$) and untreated disease ($n = 17$). The distribution of disease status and the proportion of patients who received chemotherapy within 2 months before HCT were similar between the 2 groups. The RIST group contained higher proportions of patients with an HCT-CI score of 1 or more (CST 37%, RIST 65%) and those who received G-CSF-mobilized PBSC (CST 40%, RIST 61%) than the CST group.

In the leukemia/MDS patients ($n = 89$), the median percentage of blasts (82 patients in bone marrow and 7 patients in peripheral blood) in both groups were similar (CST 29%, RIST 30%). In patients with malignant lymphoma, serum LDH was elevated above the upper normal limit in 3 of 7 (43%) in the CST group compared to 23 of 33 (70%) in the RIST group.

Engraftment and GVHD

The clinical course and response are detailed in Table 2. The median duration of follow-up in surviving patients is 1123 days (range: 367-2044 days) in the CST group and 899 days (range: 334-1961 days) in the RIST group. Neutrophil engraftment was observed in 48 patients (92%) and 75 patients (94%), at a median of 17 days and 12 days, respectively. Engraftment was not confirmed in the remaining 9 patients because of death or PD within 28 days after HCT. The incidences of grade II-IV and grade III-IV aGVHD were similar in the CST and RIST groups (50% versus 50% and 23% versus 28%, respectively). The incidences of cGVHD and chronic extensive GVHD were also similar (46% versus 49% and 34% versus 38%, respectively).

Disease Response

The probabilities of achieving CR as the best response were similar after CST and RIST (77% and 64%, respectively) (Table 2). To examine the possible risk factors for achieving CR, we separately analyzed patients with leukemia/MDS and those with lymphoma using a logistic regression analysis (Table 3). Conditioning regimen (RIST) did not influence the CR rate in patients with leukemia/MDS (odds ratio [OR] 1.11, 95% confidence interval [CI] 0.40-3.07,

Table 2. Clinical Course and Response

	CST (N = 52)	RIST (N = 80)
Median follow-up of surviving patients, days	1123 (367-2044)	899 (334-1961)
Engraftment of neutrophils, N (%)	48 (92)	75 (94)
Median day (range)	17 (10-35)	12 (5-43)
Acute GVHD, N (%)		
Grade II-IV	26 (50)	40 (50)
Grade III-IV	12 (23)	22 (28)
CR*, N (%)	40 (77)	51 (64)
Leukemia/MDS (n = 89), CR/total	35/45	35/44
Lymphoma (n = 40), CR/total	5/7	14/33
Causes of NRM, N (%)	15 (29)	26 (33)
GVHD	6	11
Infection		
fungus	0	4
CMV	0	1
bacterial	4	7
Interstitial pneumonitis	2	1
Others†	3	2

CST indicates conventional stem cell transplantation; RIST, reduced-intensity stem cell transplantation; GVHD, graft-versus-host disease; MDS, myelodysplastic syndrome; CR, complete remission; NRM, nonrelapse mortality; CMV, cytomegalovirus.

*CR as the best response after transplantation.

†Others included acute myocardial infarction, subarachnoid hemorrhage, and pulmonary alveolar haemorrhage in the CST group, and cerebral hemorrhage and unknown in the RIST group.

$P = .84$) or in those with lymphoma (OR 0.29, 95% CI 0.05-1.75, $P = .18$). In the leukemia/MDS patients, those who received chemotherapy within 2 months before HCT (OR 0.32, 95% CI 0.09-1.05, $P = .06$) and transplant from donors other than an HLA-matched relative (OR 0.28, 95% CI 0.08-1.06, $P = .06$) tended to have a lower CR rate, whereas the

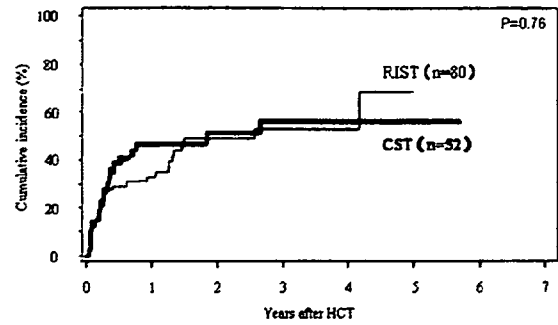


Figure 1. Cumulative incidence of PD. The 2-year probabilities of PD in the CST (51%) and RIST (49%) groups were not significantly different ($P = .76$).

blast percentage ($\geq 20\%$) of bone marrow or peripheral blood was not associated with the CR rate. In lymphoma patients, chemotherapy within 2 months before HCT was the only factor that was significantly associated with a low CR rate (OR 0.04, 95% CI 0.005-0.40, $P < .01$), whereas serum LDH elevation did not influence the CR rate.

As shown in Figure 1, the cumulative incidence of PD was not significantly different between the CST and RIST groups. The 2-year probabilities of PD were 51% in the CST group and 49% in the RIST group, which were not significantly different ($P = .76$). Cox regression analysis was performed to identify factors that were associated with PD. Multivariate analyses in all patients showed that those who received chemotherapy within 2 months before HCT were associated with an increased risk of PD (hazard ratio [HR] 3.93, 95% CI 1.97-7.83, $P < .01$) (Table 4). After adjusting for these variables, the intensity of conditioning (CST or RIST) did not influence the rate of PD in any of the patients. To further evaluate the association between risk factors and outcome, we performed a subset analysis in patients who underwent CST or RIST. As a result, chemotherapy within 2

Table 3. Logistic Analysis of CR Rate in Leukemia/MDS and Lymphoma Patients

		Leukemia/MDS (N = 89)		Lymphoma (N = 40)	
		Odds Ratio (95% CI)	P	Odds Ratio (95% CI)	P
HCT-CI	0	1.00		1.00	
	1-2	1.44 (0.43-4.87)	.56	3.33 (0.66-16.7)	.14
	3 or more	0.96 (0.28-3.35)	.95	2.22 (0.40-12.3)	.36
Age		1.00 (0.97-1.04)	.70	1.02 (0.97-1.07)	.49
Conditioning	RIST	1.11 (0.40-3.07)	.84	0.29 (0.05-1.75)	.18
Donor	Alternative*	0.28 (0.08-1.06)	.06	0.95 (0.26-3.42)	.93
Chemotherapy within 2 months before HCT	Yes	0.32 (0.09-1.05)	.06	0.04 (0.005-0.40)	<.01
Blasts†	$\geq 20\%$	0.62 (0.21-1.80)	.38		
Serum LDH level	Elevation			0.35 (0.09-1.34)	.12

MDS indicates myelodysplastic syndrome; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; RIST, reduced-intensity stem cell transplantation; LDH, lactate dehydrogenase; CI, confidence interval.

*Non-HLA-matched related donor.

†Blast counts in bone marrow (N = 82) or peripheral blood (N = 7).

Table 4. Multivariate Analysis of PD, NRM, OS, and PFS in All Patients

Covariates*	N	PD		NRM		OS		PFS	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Conditioning									
CST	52	1.00		1.00		1.00		1.00	
RIST	80	0.91 (0.53-1.55)	.72	0.99 (0.51-1.96)	.99	0.95 (0.60-1.51)	.83	0.95 (0.63-1.43)	.79
HCT-CI score									
0	65			1.00		1.00		1.00	
1-2	38			3.25 (1.43-7.40)	<.01	1.76 (1.08-2.89)	.02		
3 or more	29			6.61 (2.88-15.2)	<.01	2.62 (1.51-4.56)	<.01	1.63 (1.02-2.62)	.04
Donor									
MRD	58			1.00		1.00			
Alternative†	74			2.77 (1.39-5.54)	<.01	1.80 (1.15-2.82)	.01		
Chemotherapy within 2 months before HCT									
No	47	1.00				1.00		1.00	
Yes	85	3.93 (1.97-7.83)	<.01			1.73 (1.10-2.72)	.02	2.23 (1.44-3.45)	<.01

PD indicates progressive disease or relapse; NRM, nonrelapse mortality; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CST, conventional stem cell transplantation; RIST, reduced-intensity stem cell transplantation; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; MRD, HLA-matched related donor; HCT, hematopoietic cell transplantation.

*Factors analyzed included age at the time of HCT (continuous), HCT-CI (0, 1-2, 3, or more), conditioning (CST, RIST), donor (MRD, Alternative), disease type (leukemia/MDS, lymphoma) and chemotherapy within 2 months before HCT (yes, no).

†Non-HLA-matched related donor.

months before HCT was associated with an increased risk of PD only in the RIST group, and not in the CST group (Table 5).

NRM

Major causes of NRM for patients in both groups were GVHD and infection (Table 2). More patients died of fungal infection in the RIST group compared to the CST group, but the 2-year probabilities of NRM were not significantly different (36% and 38%, *P* = .50, Figure 2). A Cox regression analysis was performed to identify factors associated with NRM. Multivariate analyses in all patients showed that a higher HCT-CI score (1 or more) and transplant from an HLA-mismatched related or unrelated donor (al-

ternative donor) were associated with an increased risk of NRM (Table 4). After adjusting for these variables, the intensity of conditioning (CST or RIST) did not influence the rate of NRM in any of the patients. A subset analysis revealed that a higher HCT-CI score (1 or more) was associated with increased NRM in the CST group, but not in the RIST group (Table 5). In contrast, transplant from an alternative donor was associated with increased NRM in the RIST group, but not in the CST group.

Survival

The 2-year probabilities of OS and PFS were not significantly different between the CST and RIST groups (31% and 38%, *P* = .98, for OS; 28% and

Table 5. Multivariate Analysis of Outcomes after HCT in the CST and RIST Groups

Covariates	CST (N = 52)		RIST (N = 80)	
	HR (95% CI)	P	HR (95% CI)	P
PD				
Chemotherapy within 2 months before HCT		NS	6.16 (2.15-17.7)	<.01
NRM				
HCT-CI (1-2)	4.48 (1.26-16.0)	.02		NS
HCT-CI (3 or more)	10.2 (2.91-35.7)	<.01	2.41 (1.14-5.10)	.02
Alternative donor*		NS	4.63 (1.96-10.9)	<.01
OS				
HCT-CI (1-2)	2.69 (1.23-5.90)	.01		NS
HCT-CI (3 or more)	4.84 (1.97-11.9)	<.01		NS
Alternative donor*		NS	3.04 (1.73-5.35)	<.01
PFS				
HCT-CI (3 or more)	2.26 (1.01-5.04)	.04		NS
Chemotherapy within 2 months before HCT	2.10 (1.05-4.19)	.03	2.10 (1.19-3.70)	.01
Alternative donor*		NS	1.79 (1.06-3.00)	.03

PD, indicates progressive disease or relapse; NRM, nonrelapse mortality; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CST, conventional stem cell transplantation; RIST, reduced-intensity stem cell transplantation; HCT, hematopoietic cell transplantation; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; NS; not significant.

*Non-HLA-matched related donor.

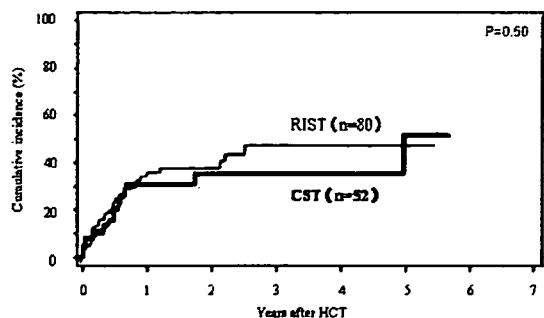


Figure 2. Cumulative incidence of NRM. The 2-year probabilities of NRM in the CST (36%) and RIST (38%) groups were not significantly different ($P = .50$).

29%, $P = .89$, for PFS), as shown in Figure 3 and Figure 4. The 2-year probabilities of PD, OS, and PFS were not significantly different between patients who developed grade III-IV aGVHD and those who did not (37% and 44%, $P = .39$, for PD; 33% and 50%, $P = .07$, for OS; 27% and 41%, $P = .24$, for PFS). On the other hand, the 2-year probability of NRM in patients who developed grade III-IV aGVHD was significantly higher than that in those who did not (56% and 21%, $P = .004$). We also evaluated outcomes in patients who had AML or MDS (CST, $n = 35$; RIST, $n = 39$). There was no significant difference in the 2-year probabilities of PD (50% and 51%), OS (37% and 33%), and PFS (34% and 22%) between the CST and RIST groups. On the other hand, the 2-year probability of NRM in the RIST group was significantly higher than that in the CST group (52% and 23%, $P = .03$).

Multivariate analyses in all patients showed that a higher HCT-CI score (1 or more) and transplant from an alternative donor were associated with poor OS, and patients who received chemotherapy within 2 months before HCT were associated with poor OS and PFS (Table 4). After adjusting for these variables, the risks of OS and PFS were not significantly different between the CST and RIST groups. Disease type (leukemia/MDS or lymphoma) was not a significant

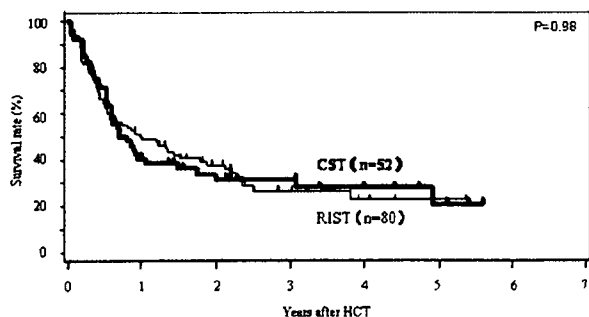


Figure 3. Estimated OS according to the conditioning regimen. The 2-year probabilities of OS in the CST (31%) and RIST (38%) groups were not significantly different ($P = .98$).

factor for OS or PFS. Furthermore, subset analyses revealed that a higher HCT-CI score (1 or more) was associated with poor OS and PFS in the CST group, but not in the RIST group (Table 5). In contrast, transplant from an alternative donor was associated with increased NRM in the RIST group, but not in the CST group. Patients who received chemotherapy within 2 months before HCT had a poor PFS in both groups.

DISCUSSION

Our results suggest that the antileukemia/lymphoma effect of RIST might be comparable to that of CST for hematologic malignancies that are not in remission. We found that a higher HCT-CI score and transplant from an alternative donor were associated with increased risks of NRM and poor OS, and patients who received chemotherapy within 2 months before HCT because of the acceleration of disease progression were associated with increased risks of PD, poor OS, and PFS. The estimated rates of NRM, PD, OS, and PFS in the RIST group were not significantly different from those in the CST group even though the patients who received RIST were significantly older and had significantly higher HCT-CI scores than those who received CST. Several reports have described a similar OS rate in older patients who underwent RIST and CST because the lower NRM rate was offset by a higher PD [5,27,28]. In contrast, Scott et al. [7] found no significant differences in OS, PFS, PD, or NRM between CST and RIST in patients with MDS/AML.

In this study, disease response to the transplantation procedure was similar between the CST and RIST groups when the CR rate is considered the best response, as were the rate and timing of PD. Whereas some reports have shown that PD after HCT was increased in patients who underwent RIST compared to CST [3,5,11], others have found no significant difference [6-8,29]. This discrepancy might result from the differences in disease status at the time of

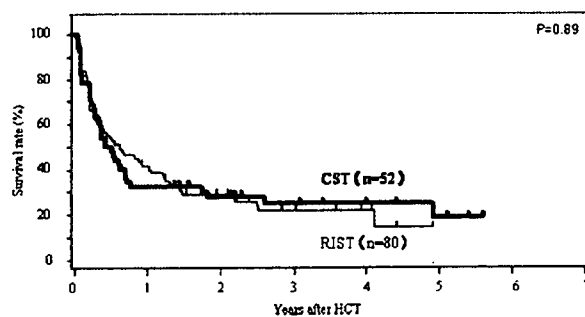


Figure 4. Estimated PFS according to the conditioning regimen. The 2-year probabilities of PFS in the CST (28%) and RIST (29%) groups were not significantly different ($P = .89$).

transplantation and the intensity of the conditioning regimens. In our study, the median percentage of blasts in leukemia/MDS patients and the distribution of serum LDH levels in lymphoma patients were comparable between the CST and RIST groups. The proportion of patients who required chemotherapy within 2 months before HCT was similar in the 2 groups. Overall, the risk of disease progression was comparable. The lack of a significant difference in PD between the CST and RIST groups in our study may be because the reduced-intensity regimens used in our study were more intense than those in previous reports. Nevertheless, our results suggest that RIST has a comparable antileukemia/lymphoma activity through a GVL effect compared to CST.

Our study found that chemotherapy within 2 months before HCT was the only factor that significantly predicted a lower CR rate in lymphoma patients and tended to be associated with a lower CR rate in leukemia/MDS patients. Furthermore, chemotherapy within 2 months before HCT was also associated with a worse prognosis not only with regard to PD but also for OS and PFS. A subset analysis showed that this negative impact of recent chemotherapy was only seen in RIST patients, and not in CST patients, which suggests that the tempo of the progression of the disease before HCT is especially important in RIST patients. Wong et al. [30] reported that high peripheral blast counts ($\geq 30\%$) in patients with AML/MDS were associated with poor event-free survival and OS after HCT regardless of the conditioning regimen. In our study, however, $\geq 20\%$ of blasts in the bone marrow or peripheral blood and serum LDH level elevation did not have a significant impact on the CR rate in leukemia/MDS and lymphoma patients, respectively.

In our study, there was no significant difference in NRM between the CST and RIST groups, which was in contrast to previous reports showing that reduced-intensity regimens were associated with less organ damage, and thus contributed to less NRM [1,4,5,9,27,31-34]. There are several possible explanations for this discrepancy. First, the patients who received RIST were older and had a higher HCT-CI score than those in the CST group. Second, the reduced-intensity conditioning (RIC) we used was more toxic than "truly nonmyeloablative" conditioning. Finally, we tapered immunosuppressive medications rapidly, especially in the RIST group, in an attempt to induce a more potent GVL effect, which resulted in more severe GVHD and subsequent infectious complications. However, our data showed that grade III-IV aGVHD did not contribute to a reduction in the rate of PD or to an overall improvement in survival, which was consistent with a previous report [14], although a high rate of NRM in patients with severe aGVHD may have masked its competing event (ie, PD).

We confirmed that HCT-CI was a significant risk factor for NRM and OS in patients not in remission. HCT-CI has recently been introduced to evaluate pretransplant comorbidities in HCT recipients, which predict well NRM and OS after allogeneic HCT [20]. In this study, the proportion of patients who were not in remission and were associated with comorbidities was 53%, which was higher than the value (42%) in our previous report [21], probably because these patients tended to be heavily pretreated and were forced to pursue HCT in the hope of a rare cure. Interestingly, this negative impact of HCT-CI was only seen in patients who underwent CST, and not in those who underwent RIST. Our data imply that RIC may be preferable in patients with hematologic malignancies not in remission and with a high HCT-CI score by reducing early NRM after transplantation.

Transplant from an alternative donor was another prognostic factor for NRM and OS in this study, which is consistent with previous reports [12,35-38]. Furthermore, an increased risk of NRM and OS associated with alternative donors was observed only in patients who underwent RIST. There are several possible explanations. First, the Japan Marrow Donor Program allows the donation of bone marrow, but not PBSC, from volunteer donors, which has been reported to be associated with poor engraftment and worse outcomes after nonmyeloablative stem cell transplantation [13]. Second, our conditioning regimen including low-dose TBI for RIST from an alternative donor was more toxic than that for RIST from an HLA-matched related donor. Further studies are required to establish optimized conditioning regimens and GVHD prophylaxis for RIST in unrelated pair settings.

In 27 patients who had all of these risk factors (ie, chemotherapy within 2 months before HCT, HCT-CI score of 1 or more, and transplant from an alternative donor), the 2-year probabilities of NRM, PD, and OS were 56%, 44%, and 21%, respectively, with no significant differences between the CST and RIST groups (data not shown). Therefore, the indications for transplantation in patients with multiple risk factors should be carefully determined.

This study has several inherent limitations. First, the eligibility requirements for CST and RIST were different. Most patients who received RIST were considered ineligible for CST because of age or comorbid conditions. Second, factors other than the conditioning regimen were not entirely comparable between the 2 groups, that is, patient age, underlying diagnosis (leukemia/MDS and lymphoma), donor selection, stem cell source, and GVHD prophylaxis. Third, some of the conventional cytoreductive conditioning regimens we used (ie, use of oral BU and lack of its pharmacologic monitoring) may no longer be considered optimal. Fourth, because the reduced-intensity

regimens used in our study were more intense than those in previous reports, our data may not be generalized to the concept of "reduced-intensity regimen" and there may be circumstances where PD would be more marked. Finally, the follow-up of patients in this study was too short to draw any definite conclusions. Nevertheless, the observed data may still be useful in evaluating the impact of RIST on disease control in patients suffering from a higher risk of disease progression after transplantation.

In conclusion, our results suggest that the antileukemia/lymphoma effect associated with RIST might be comparable to that of CST for hematologic malignancies not in remission, particularly when patients do not require chemotherapy within 2 months before HCT or they had a higher HCT-CI score. To determine the ultimate utility of specific conditioning regimens, controlled prospective trials are needed, with enrolled patients being stratified according to disease activity, hematopoietic stem cell source, and associated comorbidities.

ACKNOWLEDGMENTS

This work was supported in part by grants from the Ministry of Health, Labor and Welfare, Japan. This paper was presented in part as a poster presentation at the 47th Annual Meeting of the American Society of Hematology, Atlanta, GA, December 2005. We thank the medical, nursing, data processing, and laboratory staffs at National Cancer Center Hospital for their important contributions to this study through dedicated care of the patients. We also thank Yukio Kobayashi, Takashi Watanabe, Fusako Ohara, and Kazuaki Yokoyama for their helpful discussions.

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Hyperglycemia During the Neutropenic Period Is Associated With a Poor Outcome in Patients Undergoing Myeloablative Allogeneic Hematopoietic Stem Cell Transplantation

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Background. Recipients of allogeneic hematopoietic stem cell transplantation (HSCT) frequently require support with parenteral nutrition and immunosuppressive drugs, which introduce the risk of hyperglycemia. Van den Berghe et al. showed that the strict glucose control improved the outcome of patients treated in the intensive care unit, and this point was evaluated in this study in a HSCT setting.

Methods. A cohort of 112 consecutive adult patients treated by myeloablative allogeneic HSCT between January 2002 and June 2006 was reviewed retrospectively. Twenty-one patients were excluded due to graft failure, preexisting infectious diseases, preexisting neutropenia or previous allogeneic HSCT. The remaining 91 patients were categorized according to mean fasting blood glucose (BG) level in the neutropenic period after conditioning: normoglycemia (BG <110 mg/dL, n=28), mild hyperglycemia (110 to 150 mg/dL, n=49), and moderate/severe (>150 mg/dL, n=14). The primary endpoint was the occurrence of febrile neutropenia (FN) and documented infection during neutropenia, and the secondary endpoints included organ dysfunction according to the definition used by van den Berghe, acute graft-versus-host disease (GVHD), overall survival, and nonrelapse mortality (NRM).

Results. Although the incidence of FN or documented infections was similar between the three groups, hyperglycemia was significantly associated with an increased risk of organ dysfunction, grade II–IV acute GVHD, and NRM.

Conclusions. While the results suggested an association between the degree of hyperglycemia during neutropenia and an increased risk of posttransplant complications and NRM, the possibility that intensive glucose control improves the outcome after HSCT can only be confirmed in a prospective randomized trial.

Keywords: Allogeneic transplantation, Hyperglycemia, Nonrelapse mortality, Acute graft-versus-host disease.

(*Transplantation* 2007;84: 814–820)

Van den Berghe et al. showed with patients nursed in the intensive care unit (ICU) that the rigid control of hyperglycemia with intensive insulin therapy to keep the blood glucose level at 80–110 mg/dL reduced morbidity, including infec-

tions, and mortality compared to patients who received standard care maneuvers that maintained the level at <200 mg/dL (1–3). Although these results have been confirmed in several subsequent studies (4–7), the precise mechanism that underlies this association is unclear. In animal models, it has been shown that insulin itself has a direct inhibitory effect on the inflammation process (8, 9). However in human studies, it has been suggested that these benefits could be directly attributed to intense glucose control rather than to any pharmacological activity of administered insulin per se (3, 4).

Recipients of allogeneic hematopoietic stem cell transplantation (HSCT) suffer from serious complications including infection, graft-versus-host disease (GVHD) and organ dysfunction. They are also at higher risk of hyperglycemia due to the use of steroids for the treatment of graft-versus-host disease (GVHD), prolonged total parenteral nutrition (TPN), immunosuppressive drugs, and infectious complications (10, 11). This makes them susceptible to numerous serious complications, including multiple organ failure (12–14). In this study, we evaluated whether hyperglycemia during the cytopenic pe-

Supported in part by grants from the Ministry of Health, Labor and Welfare, Japan.

This paper was presented in part as a poster presentation at the tandem Meeting of ASBMT and IBMTR, Keystone, Colorado, February 2007.

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Received 12 June 2007. Revision requested 10 July 2007.

Accepted 18 July 2007.

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ISSN 0041-1337/07/8407-814

DOI: 10.1097/01.tp.0000282790.66889.a5

riod after conditioning for HSCT could be a significant risk factor for the subsequent clinical course.

PATIENTS AND METHODS

Patient Characteristics

A cohort of 112 consecutive adult patients who received myeloablative allogeneic HSCT between January 2002 and June 2006 at the National Cancer Center Hospital (Tokyo, Japan) was reviewed retrospectively. Twenty-one patients were excluded due to graft failure, pre-existing infectious diseases or neutropenia before HSCT, and previous allogeneic HSCT. The remaining 91 patients were subjected to further analysis, and their characteristics are listed in Table 1. Their median age was 36 years (range, 18–57 years), and their diagnosis included acute myeloid leukemia (AML, n=41), acute lymphoblastic leukemia (ALL, n=21), non-Hodgkin lymphoma (NHL, n=13), myelodysplastic syndrome (MDS, n=10), and chronic myelogenous leukemia (n=6). Standard-risk patients included those with acute leukemia in first complete remission, chronic leukemia in first chronic phase, MDS in refractory anemia, and NHL in complete remission, and the remaining patients were categorized as high-risk. Forty-

six and 45 patients received a graft from a related donor and an unrelated donor, respectively. Stem cell sources included bone marrow (n=46), peripheral blood (n=41), and cord blood cells (n=4). In this study, only two patients were diagnosed as type 2 diabetes mellitus before HSCT, which reflects the low prevalence of this condition in Japan, especially in younger patients who can be the target of allogeneic HSCT with a myeloablative conditioning regimen. These two diabetic patients were included in the moderate and severe hyperglycemia group. None of the patients, including these two patients, had major organ dysfunction or diabetic complications before HSCT. For the transplantation procedure, signed informed consent was obtained according to the Declaration of Helsinki.

Transplantation Procedures

All patients received a myeloablative conditioning regimen that included oral busulfan (BU) plus cyclophosphamide (CY, n=45), CY plus 12 Gy total body irradiation (TBI, n=43) or cytarabine (CA) plus CY plus TBI (n=3; Table 1). GVHD prophylaxis included cyclosporine- (n=62) and tacrolimus-based regimens (n=29), with an additional short course of methotrexate (MTX) in 89 patients. Granulocyte

TABLE 1. Patient characteristics

Variable	Normoglycemia (<110 mg/dl)	Mild hyperglycemia (110–150 mg/dl)	Moderate and severe hyperglycemia (>150 mg/dl)
N	28	49	14
Blood glucose, median mg/dl (range)	104 (81–109)	120 (110–150)	168 (150–211)
Age, median years (range)	31 (21–52)	36 (18–57)	45 (30–57)
<40	20 (71)	32 (65)	4 (29)
≥40	8 (29)	17 (35)	10 (71)
Sex			
Male	9 (32)	34 (69)	8 (57)
Female	19 (68)	15 (31)	6 (43)
Disease risk			
Standard	16 (57)	18 (37)	6 (43)
High	12 (43)	31 (63)	8 (57)
Conditioning			
TBI-containing	11 (39)	26 (53)	9 (64)
Non-TBI-containing	17 (61)	23 (47)	5 (36)
GVHD prophylaxis			
Cyclosporine-based	24 (86)	33 (67)	5 (36)
Tacrolimus-based	4 (14)	16 (33)	9 (74)
Relation to donor			
Related	19 (68)	24 (49)	3 (21)
Unrelated	9 (32)	25 (51)	11 (79)
Stem cell source			
Bone marrow	11 (39)	24 (49)	11 (79)
PBSC	16 (57)	22 (45)	3 (21)
Cord blood	1 (4)	3 (6)	0 (0)
HLA match			
Match	25 (89)	34 (69)	10 (71)
Mismatch	3 (11)	15 (31)	4 (29)

Data are n (%) unless noted.

TBI, total body irradiation; GVHD, graft-versus-host disease; PBSC, peripheral blood stem cells; HLA, human leukocyte antigen.

colony-stimulating factor (G-CSF) was administered in all patients from day +6 after transplantation until engraftment. Most patients received ciprofloxacin (200 mg orally three times daily) for bacterial prophylaxis until neutrophil engraftment. Fluconazole (100 mg once daily) was administered for fungal prophylaxis. Low-dose acyclovir was given for prophylaxis against herpes simplex virus and varicella zoster virus until the cessation of immunosuppressive agents. Prophylaxis against *Pneumocystis jiroveci* infection consisted of trimethoprim-sulfamethoxazole (400 mg of sulfamethoxazole once daily) from the first day of conditioning to day -3 of transplantation, and from day +28 until day +180 or the cessation of immunosuppressive agents. Patients who developed fever during the neutropenic period were treated with cefepime, and additional agents including vancomycin, aminoglycosides and amphotericin B were given as clinically indicated. Neutrophil engraftment was defined as the first of 3 consecutive days after transplantation that the absolute neutrophil count exceeded $0.5 \times 10^9/L$.

Grouping of Patients

Patients were categorized according to the mean blood glucose (BG) level in the preengraftment neutropenic period: normoglycemia BG maintained at <110 mg/dL (group 1, $n=28$), mild hyperglycemia at 110–150 mg/dL (group 2, $n=49$), and moderate/severe hyperglycemia at >150 mg/dL (group 3, $n=14$). Blood glucose level was routinely tested in the morning at least three times a week. Daily caloric intake was calculated by dietitian following the chart record.

Outcome Measures

The primary outcome measure was the occurrence of febrile neutropenia (FN) and documented infection including bacteremia, pneumonia and central venous catheter infection in the neutropenic period. Secondary outcome measurements were organ dysfunction in the neutropenic period, acute GVHD, overall survival (OS) and nonrelapse mortality (NRM). Organ dysfunction was defined with reference to van den Berghe (5–7) as follows: 1) hypercreatininemia: serum creatinine level ≥ 2.0 mg/dL or more than twice the baseline; 2) hyperbilirubinemia: serum total bilirubin level ≥ 2.0 mg/dL; and 3) increased inflammatory markers: serum C-reactive protein (CRP) level ≥ 15 mg/dL. Acute GVHD was graded by the Consensus Criteria (15).

Statistical Analyses

Standard descriptive statistics were used. The Student's *t*-test, chi-square, and Wilcoxon rank-sum tests were used to compare clinical and patient characteristics. Multiple logistic regression analysis was conducted to ascertain odds ratios (ORs) and 95% confidence intervals (CIs). OS was estimated using Kaplan-Meier curves. The cumulative incidences of NRM were estimated based on a Cox regression model for the cause-specific hazards by treating progressive disease or relapse as a competing event. Cox proportional hazard models were used for multivariate analysis of variables on NRM and OS after HCT. Clinical factors that were assessed for their association with NRM and OS included patient age, sex, conditioning regimen (TBI-based vs. non-TBI-based), donor [human leukocyte antigen (HLA)-matched vs. HLA-mismatched, related vs. unrelated], GVHD prophylaxis (cyclosporine-based

vs. tacrolimus-based) and disease risk (standard vs. high). Factors with $P < 0.10$ in the univariate analyses were subjected to a multivariate analysis. A level of $P < 0.05$ was defined as statistically significant. All *P* values are two-sided. All analyses were performed using SPSS 10.0 statistical software (Chicago, IL).

RESULTS

Patients and Transplantation Characteristics

The median ages of the patients in the normoglycemia, mild hyperglycemia, and moderate/severe hyperglycemia groups were, respectively, 31, 36, and 45 years. The percentages of patients who received graft from an unrelated donor were 32%, 51%, and 79%, and the percentages of patients who received GVHD prophylaxis with tacrolimus were 14%, 33%, and 74%. To clarify the risk factor to be included in moderate and severe hyperglycemia group, logistic analysis was performed, which showed older age and GVHD prophylaxis with tacrolimus were associated with moderate and severe hyperglycemia [$P=0.04$, OR 3.9 (1.1–14.0), and $P=0.01$, OR 5.5 (1.5–20.3), respectively], and there was a trend that patients who received stem cell from unrelated donor were associated with moderate and severe hyperglycemia [$P=0.07$, OR 3.6 (0.9–14.2)]. Multiple logistic analysis showed age more than 40 years old and GVHD prophylaxis with tacrolimus were associated with moderate and severe hyperglycemia [$P=0.042$, OR 4.1 (1.1–15.7), and $P=0.01$, OR 5.8 (1.5–22.1), respectively].

Although in practice we generally keep the parenteral glucose dose relatively low to avoid severe metabolic complications including hyperglycemia and hyperlipidemia during the acute phase of allogeneic HSCT, the possibility that the dose of parenteral nutrition affects the blood glucose level should be explored. We calculated the total caloric intake by combining both oral and parenteral nutrition. Although the mild hyperglycemia group received significantly more parenteral nutrition than the normoglycemia group (group 1 694+322 kcal/day vs. group 2 969+383 kcal/day), overall there was no essential difference in caloric intake between the three groups (1070+303 kcal/day, 1190+393 kcal/day, 1045+530 kcal/day, respectively). The median duration of the follow-up time in surviving patients was 809 days (range, 132–1530 days) in group 1, 369 days (105–1550 days) in group 2, and 587 days (170–774 days) in group 3. Described as hydrocortisone-equivalent dose, the median dose of corticosteroid used during neutropenia was 0 mg (0–1610 mg) in group 1, 100 mg (0–9700 mg) in group 2, and 375 mg (0–2468 mg) in group 3. Statistically more dose of corticosteroid was used in group 2 and group 3, compared with group 1.

Primary Endpoints

The incidence of FN and documented infections is summarized in Table 2. The incidences of FN and documented infections including bacteremia, pneumonia, and central venous catheter infection in groups 1, 2 and 3 were, respectively, 89% and 32% (25%, 4% and 11%), 88% and 20% (16%, 6% and 6%), and 98% and 43% (36%, 14% and 14%). Overall, no statistically significant difference was observed between the three groups in the incidence of infectious episodes, including FN and documented infections.

TABLE 2. Endpoints

Variable	Normoglycemia (<110 mg/dl)	Mild hyperglycemia ($110-150$ mg/dl)	Moderate and severe hyperglycemia (>150 mg/dl)
N	28	49	14
Febrile neutropenia	23 (89)	43 (88)	13 (98)
Documented infection	9 (32)	10 (20)	6 (43)
Bacteremia	7 (25)	8 (16)	5 (36)
Pneumonia	1 (4)	3 (6)	2 (14)
Central-venous catheter infection	3 (11)	3 (6)	2 (14)
Organ dysfunction			
Hypercreatininemia	1 (4)	4 (8)	4 (29)
Hyperbilirubinemia	3 (11)	11 (22)	6 (43)
Increased inflammatory markers	4 (14)	15 (31)	9 (64)

Data are n (%).

Hypercreatininemia, serum creatinine level ≥ 2.0 mg/dl or more than twice of baseline; hyperbilirubinemia, serum bilirubin level ≥ 2.0 mg/dl; increased inflammatory markers, serum C-reactive protein level ≥ 15 mg/dl.

Secondary Endpoints

The incidence of hypercreatininemia was 4% in group 1, 8% in group 2 and 29% in group 3, as summarized in Table 2, and that in group 3 was significantly higher than those in

TABLE 3. Multiple logistic regression analysis for organ dysfunction and multiple variate analysis for acute GVHD, nonrelapse mortality, and overall survival

Outcomes and variables	Odds/hazard ratio	95% CI	P value
Multiple logistic regression analysis			
Hypercreatininemia			
Hyperglycemia	5.2	1.1–24.6	0.039
Hyperbilirubinemia			
Hyperglycemia	4.9	1.6–14.9	0.005
Increased inflammatory markers			
Hyperglycemia	6.7	2.2–20.3	0.001
Tacrolimus-based	6.9	1.6–30.5	0.011
Multivariate analysis (Cox-proportional hazard model)			
Acute GVHD			
Hyperglycemia	2.3	1.2–4.3	0.013
Disease risk (high)	2.3	1.0–5.1	0.047
HLA mismatch	2.8	1.3–5.9	0.009
Nonrelapse mortality			
Hyperglycemia	2.9	1.2–6.6	0.013
Disease risk (high)	2.7	0.9–8.7	0.091
Overall survival			
Hyperglycemia	2.0	1.1–3.6	0.019
TBI-containing	2.3	1.1–5.0	0.035
Disease risk (high)	1.9	0.9–4.1	0.10

Odds ratios are presented for multiple logistic regression analysis; hazard ratios are presented for multivariate analysis.

GVHD, graft versus host disease; TBI, total body irradiation.

group 1 (OR 10.8, 95% CI 1.1–108.6; $P=0.018$) and group 2 (OR 4.5, 95% CI 1.0–21.1; $P=0.043$). The incidence of hyperbilirubinemia was, respectively, 11%, 22% and 43%, in the three groups, and that in group 3 was significantly higher than that in group 1 (OR 6.3, 95% CI 1.3–30.9; $P=0.017$). The incidence of increased inflammatory markers was, respectively, 14%, 31% and 64%, and that in group 3 was significantly higher than those in group 1 (OR 10.8, 95% CI 2.4–49.5; $P<0.001$) and group 2 (OR 4.1, 95% CI 1.2–14.3; $P=0.022$). Multiple logistic regression analysis showed that the degree of hyperglycemia was associated with hypercreatininemia, hyperbilirubinemia, and increased inflammatory markers (Table 3).

The cumulative incidence of grade II–IV acute GVHD is shown in Figure 1. The degree of hyperglycemia was associated with a higher incidence of grade II–IV acute GVHD

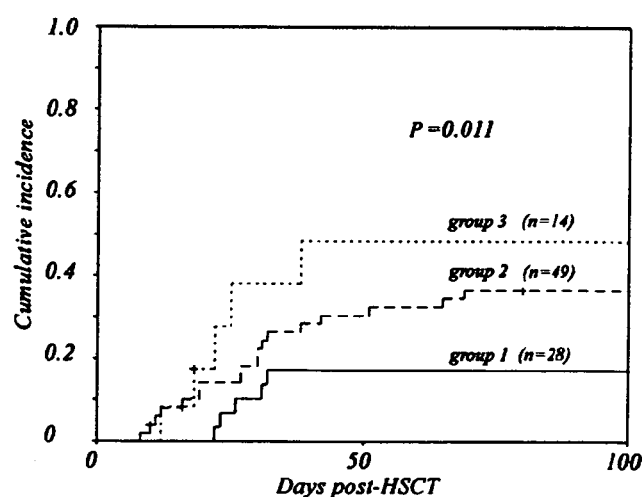


FIGURE 1. Cumulative incidence of acute GVHD grade II–IV stratified according to the mean glucose level during neutropenia. Group 1 included patients with normoglycemia, group 2 included patients with mild hyperglycemia, and group 3 included patients with moderate and severe hyperglycemia.

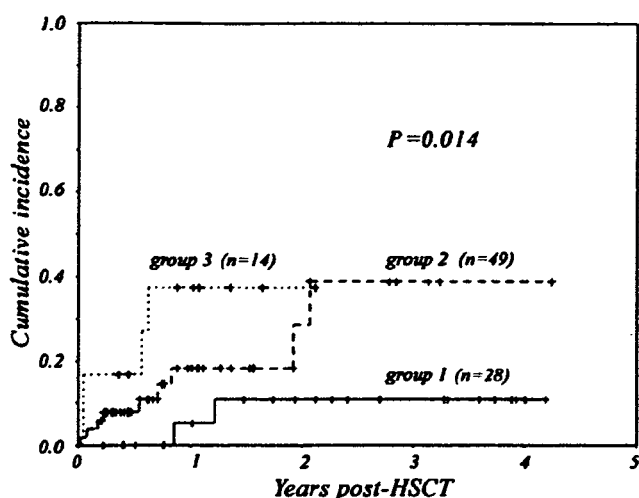


FIGURE 2. Cumulative incidence of treatment-related mortality stratified according to the mean glucose level during neutropenia.

($P=0.002$). A Cox proportional hazard model showed that hyperglycemia, high-risk underlying disease, and HLA mismatch were risk factors for grade II-IV acute GVHD (Table 3).

The cumulative incidence of NRM was, respectively, 5%, 17%, and 35% at 1 year, and was significantly related to the degree of hyperglycemia ($P=0.014$; Fig. 2). The probability of OS was, respectively, 88%, 70%, and 56%, and was significantly associated with hyperglycemia ($P=0.008$; Fig. 3). A Cox proportional hazard model showed that the degree of hyperglycemia was associated with NRM and OS (Table 3).

DISCUSSION

In this study, we evaluated whether hyperglycemia during the cytopenic period after conditioning for HSCT could be a significant risk factor for the subsequent clinical course. Infectious diseases remain a major cause of morbidity and mortality in patients who receive HSCT, and we speculated that this might be exaggerated in the presence of hyperglycemia.

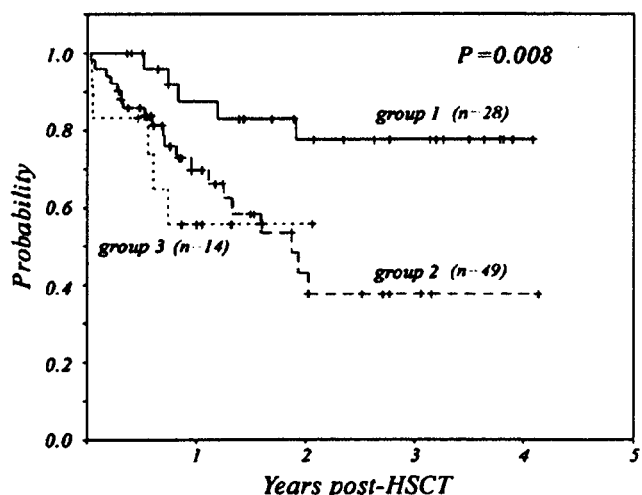


FIGURE 3. Overall survival stratified according to the mean glucose level during neutropenia.

Alternatively, hyperglycemia can be caused by infectious diseases and also aggravates infectious diseases to lead to a vicious cycle, with resultant morbidities that include organ dysfunction and mortality. Theoretically, strict glucose control should prevent this vicious cycle and help to reduce morbidity and mortality in patients after HSCT, as shown previously in ICU settings (1, 2). However, in this study the incidences of FN and documented infections were not different among the three groups. On the other hand, we found that hyperglycemia was associated with organ dysfunction and increased inflammatory markers, which was consistent with previous reports that demonstrated the impact of hyperglycemia on clinical outcomes of patients suffering from nonhematological diseases (1-3, 12-14). Additionally, a multivariate analysis showed that hyperglycemia was a risk factor for acute GVHD.

The reason for the association between early hyperglycemia and late complications needs to be clarified. The increase in the levels of circulating cytokines due to hyperglycemia may further aggravate hyperglycemia itself (16-21). Therefore, this condition which occurs during the critical period of neutropenia before engraftment may influence the afferent phase of acute GVHD, as suggested by Ferrara et al. Elevated cytokine levels during the afferent phase then lead to subsequent acute GVHD in the effector phase (22, 23). Teshima et al. reported that the effector phase of acute GVHD is not antigen-specific and inflammatory cytokines mediate target destruction (24), and other reports have shown that inflammatory cytokines were required in acute GVHD and these molecules can cause tissue damage (25-27). With these reports in mind, it is reasonable to speculate that the aggravated production of inflammatory cytokines by hyperglycemia may be a risk factor in the pathogenesis of acute GVHD and organ dysfunction.

This study has several limitations, including heterogeneous patient populations and a retrospective nature. First, hyperglycemia can be caused by infection itself and it has been previously shown that the level of hyperglycemia was correlated with the severity of illness (4). In this retrospective study, we could not confirm whether hyperglycemia directly influenced organ dysfunction or increased inflammatory markers. Furthermore, statistically more corticosteroid was used in the group of moderate and severe hyperglycemia, and statistically more parenteral nutrition was used in the group of mild hyperglycemia. However, the observation that hyperglycemia and the severity of illness were independently associated with a worse prognosis has been well confirmed in the ICU setting (4), and several prospective studies have shown that intensive glucose control reduced both morbidity and mortality (1, 2). Considering these findings, we suggest that our data still support the possibility that the degree of hyperglycemia was associated with morbidity and mortality in the allogeneic HSCT setting. Second, we must consider that the patients who developed moderate and severe hyperglycemia included older patients, those who received more unrelated grafts, and those who received tacrolimus compared to other groups. In terms of immunosuppressive drugs, tacrolimus has recently become a preferred immunosuppressive drug for GVHD prophylaxis in unrelated or HLA-mismatched HSCT, based on the results of two Japanese studies, which showed that, compared to cyclosporine, tacrolimus was associated with a lower incidence of acute GVHD and better overall survival, which were similar to those in related HSCT, even

after HSCT with alternative donors, including unrelated donors (28, 29). Therefore, the effect of unrelated graft and tacrolimus on the incidence of acute GVHD and NRM might not be significant in this study.

The effects of tacrolimus on hyperglycemia, hyperbilirubinemia, and hypercreatininemia need to be clarified. It is well known that hyperglycemia occurs more often in patients receiving tacrolimus than in those receiving cyclosporine (30–32). In the present study, patients receiving tacrolimus were more likely to have moderate to severe hyperglycemia. However, the association of hyperbilirubinemia with tacrolimus has not been previously reported and two other studies (33, 34) showed that cyclosporine was more likely to cause hyperbilirubinemia than tacrolimus after allogeneic HSCT or kidney transplantation. Although the relative nephrotoxicity attributed to tacrolimus compared to cyclosporine has been controversial (30, 33, 35), studies that have reported such nephrotoxicity used a higher target tacrolimus level (>20 ng/ml) (30, 35). On the other hand, it has been reported that the use of lower levels of tacrolimus (10–15 ng/ml in our hospital) was associated with reduced complications in allogeneic HSCT (36, 37), with no difference in the incidence of hypercreatininemia compared to cyclosporine (33). Based on a consideration of all of these results, we think that tacrolimus might not be the direct cause of hypercreatininemia in this study. Finally, due to the nature of this retrospective study, during the period evaluated we did not apply any consistent protocol for glucose control and nutritional support, although we tried to avoid severe hyperglycemia (BG \geq 200 mg/dl), which certainly biases the interpretation of the data, although it has been reported that the overall glucose level, rather than the dose of insulin administered, directly influenced the outcome of patients (3).

Even with these limitations, we believe that our observation is still of value in considering the clinical impact of the strict control of hyperglycemia during the early phase of HSCT. To confirm our preliminary observation, a prospective pilot study is underway to assess the effect of intensive glucose control after HSCT. If this pilot study shows a beneficial effect of intensive glucose control, a prospective randomized trial would be warranted to confirm the possibility that intensive glucose control improves the outcome after HSCT. Additionally, in this ongoing pilot study, we evaluate the diurnal blood glucose and insulin levels, including postprandial levels, to detect hyperglycemia more precisely before transplantation since the level of HgA1c is affected by both the blood glucose level and the turnover rate of red blood cells, and would not precisely correlate with the true mean blood glucose level in patients who received courses of blood transfusion for anemia.

In conclusion, the association of the degree of hyperglycemia during neutropenia and an increased risk of post-transplant complications and NRM was suggested, but the possibility that intensive glucose control improves the outcome after HSCT would only be confirmed in a prospective randomized trial.

ACKNOWLEDGMENTS

We thank the medical, nursing, data processing, laboratory, and clinical staffs at the National Cancer Center Hospital for their important contributions to this study through dedicated

care of the patients. The authors are indebted to Y. Iisaka and M. Kurita for their assistance with data collection. We also thank S. Saito for helping to prepare the manuscript.

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