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＜ 学会発表一覧 ＞

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V．研究成果の刊行物（論文別刷）

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LETTER TO THE EDITOR

Decreased insulin secretion in patients receiving tacrolimus as GVHD prophylaxis after allogeneic hematopoietic SCT

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As it has been reported that hyperglycemia is associated with a higher risk of non-relapse mortality after allogeneic hematopoietic SCT (HSCT), the efficient control of hyperglycemia has become an important consideration for safer HSCT.[1,3] A characteristic feature of this field is the use of calcineurin inhibitors, including tacrolimus (TAC), which may cause hyperglycemia as suggested in organ transplant settings, possibly by decreasing insulin secretion.[4] To evaluate this possibility, we serially monitored fasting glucose levels and serum immunoreactive insulin, and calculated homeostasis model assessment (HOMA)-IR and HOMA-β with the HOMA model[5] as recommended by Wallace *et al.*[6] HOMA-IR reflects insulin resistance and HOMA-β reflects the insulin secretion status.[5] If HOMA-IR increased after the administration of allogeneic HSCT, drugs that reduce insulin resistance, such as metformin or pioglitazone, might theoretically be effective. In contrast, if HOMA-β decreased, drugs that increase insulin secretion, such as glucagon-like peptide-1 analog or sulfonylureas, might be effective. The data from this study may help us to better understand how we should control glucose levels after HSCT.

Data obtained from 43 adult patients who received allogeneic HSCT from October 2006 to December 2007 were included in the analysis. The median age of the patients was 48 years (range: 19–66 years). When patients were not receiving s.c. long-acting insulin, systemic corticosteroid or parenteral nutrition, blood samples were obtained 1–2 months after HSCT. GVHD prophylaxis was started using CsA-based ($n=13$) or TAC-based regimens ($n=30$), with an additional short course of MTX in 35 patients. At the time of subsequent blood sampling, 15 patients were receiving CsA and 28 patients were receiving TAC, with no significant difference in various factors including age, gender, disease and intensity of the conditioning regimen (conventional vs reduced intensity), except that the TAC group included more HSCT with unrelated BM than the CsA group (89 vs 27%, respectively). The results regarding fasting glucose level, immunoreactive insulin and the HOMA model are summarized in Table 1.

We found that HOMA-β was significantly reduced in the TAC group compared with that in the CsA group, which was consistent with earlier studies in an organ transplant setting.[4] Clinically, it has been reported that GVHD prophylaxis with TAC is generally associated with a reduced incidence of acute GVHD compared with CsA. In contrast, hyperglycemia was associated with a higher risk of non-relapse mortality after allogeneic HSCT.[1,3] In our earlier study, patients with severe hyperglycemia had a significantly higher incidence of acute GVHD compared with normoglycemic patients.[3] Therefore, it is possible that hyperglycemia related to the use of TAC could offset the potential benefit of TAC, and drugs that increase insulin secretion, including the glucagon-like peptide-1 analog, may reverse the suppression of the insulin level.[7] Whether intensive glucose control could reduce the risk of acute

Table 1 Pretransplant and posttransplant glycemic status

Variable	N *(%)/ Median (range)*			
	Tacrolimus (n = *28*)		*CsA* (n = *15*)	
Fasting glucose level (mg per 100 ml)				
Pretransplant	87 (80–129)	$P=0.08$	89 (79–154)	$P=0.55$
Posttransplant	95 (79–129)		91 (80–116)	
Immunoreactive insulin level (μU/ml)				
Pretransplant	6.1 (1.6–17.3)	$P=0.60$	6.6 (2.9–13.5)	$P=0.25$
Posttransplant	6.5 (1.5–18.0)		5.3 (2.4–10.1)	
HOMA-IR				
Pretransplant	1.4 (0.3–4.6)	$P=0.75$	1.4 (0.6–5.13)	$P=0.40$
Posttransplant	1.5 (0.3–4.2)		1.3 (0.5–2.2)	
HOMA-β				
Pretransplant	90.9 (30.3–193.7)	$P=0.04$	65.4 (38.7–160.0)	$P=0.43$
Posttransplant	69.9 (15.8–202.5)		61.7 (28.5–180.0)	

Abbreviations: HOMA = homeostasis model assessment; IR = insulin resistance.

GVHD in patients using TAC should be evaluated by prospective randomized control trials.

In conclusion, this is the first study to assess the change in the glycemic status with the HOMA model in patients undergoing HSCT with CsA or TAC. We showed that GVHD prophylaxis with TAC was associated with decreased insulin secretion and a resultant tendency for hyperglycemia. It is possible that measures to keep insulin and glucose levels within their respective normal ranges are effective for reducing morbidity and mortality after HSCT.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

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S Fuji[1], S-W Kim[1], S Mori[1], K Furuta[2], R Tanosaki[1], Y Heike[1], Y Takaue[1] and T Fukuda[1]

[1]*Division of Stem Cell Transplantation, National Cancer Center Hospital, Tokyo, Japan and*

[2]*Division of Laboratory Medicine, National Cancer Center Hospital, Tokyo, Japan*

E-mail: tafukuda@ncc.go.jp

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ORIGINAL ARTICLE

Intensive glucose control after allogeneic hematopoietic stem cell transplantation: a retrospective matched-cohort study

S Fuji[1], S-W Kim[1], S Mori[1], S Kamiya[2], K Yoshimura[3], H Yokoyama[1], S Kurosawa[1], B Saito[1], T Takahashi[1], S Kuwahara[2], Y Heike[1], R Tanosaki[1], Y Takaue[1] and T Fukuda[1]

[1]*Department of Hematology and Stem Cell Transplantation, Tokyo, Japan;* [2]*Division of Nutritional Management, National Cancer Center Hospital, Tokyo, Japan and* [3]*Biostatistics and Epidemiology Section, Center for Cancer Control and Information Services, National Cancer Center Hospital, Tokyo, Japan*

Some studies have shown that intensive glucose control (IGC) improves outcome in the intensive care unit setting. However, it is the benefit of IGC in hematopoietic SCT (HSCT) that is not well defined. Between June 2006 and May 2007, IGC was maintained prospectively after allogeneic HSCT and clinical outcomes were compared with a cohort matched for conditioning regimen, source of stem cells, age and relation to donor. A stratified Cox regression model was used. There were no significant differences in baseline clinical characteristics. The median age was 43.5 years in both groups. The primary diagnosis was a hematologic malignancy. Patients in the IGC group had a lower glucose level (least-square mean, 116.4 vs 146.8 mg per 100 ml, $P<0.001$) compared to the standard glucose control group. The incidences of documented infections and bacteremia were significantly lower in the IGC group (14 vs 46%, $P=0.004$, 9 vs 39%, $P=0.002$, respectively). IGC tended to reduce the incidence of renal dysfunction (19 vs 37%, $P=0.36$) and the elevation of C-reactive protein (18 vs 38%, $P=0.13$). This study suggests that IGC has may have a beneficial effect after HSCT. IGC should be evaluated further in a large prospective, randomized study.
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Keywords: intensive glucose control; allogeneic transplantation; hyperglycemia; C-reactive protein

Introduction

Previous studies showed that intensive glucose control (IGC), in which the target blood glucose level was set within 80–110 mg per 100 ml, reduced infections, dysfunction of organs including the liver and kidney and mortality compared to patients who received standard glucose control.[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 IGC rather than to any pharmacological activity of administered insulin *per se*.[3,4]

Recipients of allogeneic hematopoietic SCT (HSCT), which is the most drastic therapeutic modality in patients with hematological malignancies, often suffer from serious complications including infectious diseases, GVHD and multiple organ failure. They are also at higher risk of hyperglycemia because of the use of steroids for the treatment of GVHD, the use of total parenteral nutrition (TPN), immunosuppressive drugs and infectious complications,[10,11] which makes them further susceptible to numerous serious complications including infectious diseases and multiple organ failure.[12–14] Our group previously reported that hyperglycemia during neutropenia was associated with an increased risk of acute GVHD and nonrelapse mortality (NRM) after myeloablative allogeneic HSCT,[15] and that hyperglycemia during neutropenia was associated with a higher incidence of subsequent acute GVHD. It is well known that an increase in the levels of circulating cytokines may aggravate hyperglycemia, and hyperglycemia itself could increase the levels of cytokines. This vicious cycle could lead to elevated cytokine levels, which could lead to subsequent acute GVHD. With this background, it can be hypothesized that IGC would reduce the incidence of infectious diseases, acute GVHD and organ dysfunctions after allogeneic HSCT. Therefore, we prospectively investigated the effect of IGC after allogeneic HSCT, and compared the clinical outcomes to those in a matched cohort to address whether IGC following allogeneic HSCT could improve the clinical course of patients, that is, reduction of infectious diseases and organ dysfunction, as has been shown in the intensive care unit (ICU) setting.

Correspondence: Dr Y Takaue, Department of Medical Oncology, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-Ku, Tokyo 104-0045, Japan.
E-mail: ytakaue@ncc.go.jp
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Patients and methods

Patients
From June 2006 to May 2007, a total of 73 patients received allogeneic HSCT at the National Cancer Center Hospital (Tokyo, Japan); 60 patients were eligible for participation in this trial. Finally, 22 patients (36.7%) were enrolled in this IGC study to keep the blood glucose level at 80–110 mg per 100 ml, as shown in Figure 1.

Study center and organization
The National Cancer Center Hospital in Tokyo holds 600 beds. The transplant team consists of 4 full-time physicians and 26 nursing staff who oversee 26 beds in the HSCT, and the entire ward is covered by high-efficiency particulate air-filters. We regularly perform 90–120 transplants per year: 80% allogeneic and 20% autologous.

Study design
This was a case–control study to investigate the clinical benefits of comprehensive nutritional support including IGC and parenteral nutrition (PN) management, which was approved by the Institutional Review Board. A matching control group was selected among patients who received HSCT from January 2002 to March 2007 (ratio of 1:2 compared to the study group) according to the following criteria: (1) conditioning regimen (conventional myeloablative or reduced intensity), (2) source of stem cells (BM, peripheral blood or cord blood), (3) age and (4) source of donor (related or unrelated). Criteria (1–4) were essential for inclusion. As a result, 42 matched controls were selected, and a total of 64 patients were subjected to further analysis (Table 1).

Exclusion criteria
Exclusion criteria were as follows: (1) patients who received a reduced-intensity conditioning regimen for an HLA-matched related donor, as we applied GVHD prophylaxis without short-term MTX in this setting, and they had much less need for TPN and less need for intense glucose control,[16] (2) those with a poor performance status (Eastern Cooperative Oncology Group) ⩾2, (3) those with uncontrolled infectious diseases at the beginning of the conditioning regimen and (4) those with preexisting neutropenia. We previously reported that the incidence of severe stomatitis (Common Terminology Criteria for Adverse Events (CTCAE) grade (3) was 0% after reduced-intensity SCT (RIST) from a related HLA-matched donor.[16] In this situation, the need for TPN and the incidence of hyperglycemia were quite low, compared to RIST from an unrelated donor, which included additional low-dose TBI or antithymocyte globulin (ATG) and short-term MTX or conventional SCT with a myeloablative regimen. Hence, we only included patients who received a RIST regimen from an unrelated donor, who had a higher probability of glucose-control intervention, to evaluate the beneficial effects of IGC.

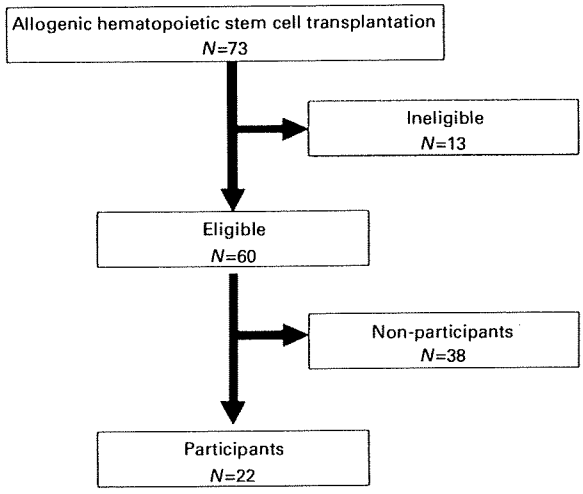

Figure 1 Trial profile.

Table 1 Patients' characteristics

Variable	N *(%)/median (range)*		P-*value*
	Intensive glucose control (n = *22*)	*Standard glucose control* (n = *42*)	
Age (years)	43.5 (17–64)	43.5 (20–66)	
<40	8 (36)	18 (43)	0.62
⩾40	14 (64)	24 (57)	
Sex			
Male	9 (41)	22 (52)	0.38
Female	13 (59)	20 (48)	
Disease risk[a]			
Standard	6 (27)	16 (38)	0.39
High	16 (73)	26 (62)	
Conditioning			
CST	14 (64)	27 (64)	
BU/CY	9 (40)	18 (43)	
CY/TBI (12 Gy)	4 (18)	6 (14)	
Other	1 (5)	3 (7)	
RIST	8 (36)	15 (36)	0.96
2CdA/BU	1 (5)	1 (2)	
Flu/BU	7 (32)	14(33)	
Low-dose TBI (2–4 Gy)	3 (14)	7 (17)	
Low-dose ATG	5 (23)	10 (24)	0.92
GVHD prophylaxis			
Cyclosporin-based	7 (32)	27 (64)	
Tacrolimus-based	15 (68)	15 (36)	0.01
Short-term MTX (+)	22 (100)	40 (95)	0.30
Relation to donor			
Related	6 (27)	12 (29)	
Unrelated	16 (73)	30 (71)	0.91
Stem cell source			
Bone marrow	15 (68)	30 (71)	
PBSC	5 (23)	10 (24)	
Cord blood	2 (9)	2 (5)	0.19
HLA match			
Match	11 (50)	28 (67)	
Mismatch	11 (50)	14 (33)	0.19

Abbreviations: ATG = antithymocyte globulin; 2CdA = cladribine; CST = conventional stem cell transplantation; Flu = fludarabine; RIST = reduced-intensity stem cell transplantation.
[a]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.

Transplantation procedures
Forty-one patients received a myeloablative conditioning regimen that included BU (orally 4 mg/kg per day × 4 days or i.v. 3.2 mg/kg per day × 4 days) plus CY (60 mg/kg per day × 2 days, $n=27$), CY plus 12 Gy TBI ($n=10$) or other ($n=4$). Twenty-three patients received a reduced-intensity conditioning regimen that included fludarabine (30 mg/m^2 per day × 6 days) or cladribine (0.11 mg/kg per day × 6 days) plus BU (oral 4 mg/kg per day × 2 days or i.v. 3.2 mg/kg per day × 2 days). Low-dose TBI (2 or 4 Gy, $n=10$) and/or low-dose ATG (total dose 5–10 mg/kg ATG-F or 5 mg/kg thymoglobulin, $n=15$) were added. GVHD prophylaxis included CYA- ($n=13$) and tacrolimus-based regimens ($n=51$), with an additional short course of MTX. 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 after the beginning of the conditioning regimen until neutrophil engraftment. Fluconazole (100 mg once daily) was administered for fungal prophylaxis after the beginning of the conditioning regimen. Low-dose acyclovir was given for prophylaxis against herpes simplex virus and VZV after the beginning of the conditioning regimen until immunosuppressive agents were discontinued. 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 or other cephalosporin, 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 ANC exceeded 0.5×10^9 per l.

Glucose management protocol
In the IGC group, the blood glucose level was routinely tested every morning to adjust the dose of insulin so as to keep the level within the range of 80–110 mg per 100 ml. Owing to the presence of fewer nursing staff in the HSCT unit than in the ICU, we replaced the continuous infusion of insulin with the addition of Humulin R to the bottle of PN to control the glucose level within the target range. In TPN, we universally added at least 1 unit of Humulin R per 10 g glucose. In patients who had an elevated blood glucose level, we also added Humulin R to the bottle of PN. We monitored the glucose level at least once a day in the morning as long as the level remained within the target range of 80–110 mg per 100 ml. When the glucose level became elevated, we increased the frequency of monitoring up to 2–4 times daily. In most patients, we adjusted the dose of insulin added to the bottle of PN as described in Table 2. When the blood glucose level was >180 mg per 100 ml or the dose of insulin was high, we manually adjusted the dose of Humulin R and administered insulin subcutaneously according to the attending physician's discretion. S.c. insulin administration usually consisted of 3–5 units at the beginning, and, if this was insufficient, the dose was manually adjusted by 2–4 units. When the patients received high-dose systemic steroid such as methylprednisolone 1–2 mg/kg per day for GVHD, we used the preprandial s.c. injection of insulin Aspart (NovoRapid) three times daily to avoid postprandial hyperglycemia and adjusted the dose according to the amount of food intake and the postprandial glucose level. When patients exhibited nausea, anorexia or vomiting, the amount of food intake became unstable. In such situations, insulin Aspart was injected immediately after the meal. When food intake was <50%, the dose was reduced or discontinued. Routine glucose monitoring was continued until PN was stopped, whereas the blood glucose level was maintained within the target range. Daily caloric intake was calculated by the dietitians. We tried to maintain oral intake as much as possible by using a suitable diet in jelly or liquid form. A dietitian adjusted the dose of supplemental PN to maintain the total caloric intake over 1.0 × basal energy expenditure (BEE), and if the glucose level was stable, the nutritional intake could be increased up to 1.5 × BEE. The glucose concentration in PN was usually started at 7.5% glucose as supplemental PN. The concentration was gradually increased to 12%, and, if necessary, this was further increased up to 18% to meet the target caloric intake. A lipid emulsion was also used to supply 10–30% of total caloric intake. The minimal total nutritional intake was set at 1.0 × BEE because a retrospective analysis at our institute showed that caloric intake of more than 1.0 × BEE was not associated with clinically significant wt loss.[17] To improve the glucose control, this level was set to be slightly lower

Table 2 Protocol for adjustment of Humulin R

Glucose level (mg per 100 ml)	*Adjustment of Humulin R*
BS ⩽ 40	i.v. 50% glucose 20 ml and recheck the glucose level Reduce the dose of Humulin R to 40–60% of the original dose
40 ⩽ BS < 60	i.v. 50% glucose 20 ml and recheck the glucose level Reduce the dose of Humulin R to 60–80% of the original dose
60 ⩽ BS < 80	i.v. 50% glucose 20 ml and recheck the glucose level Reduce the dose of Humulin R to 70–90% of the original dose
80 ⩽ BS ⩽ 110	No change
110 < BS < 130	Increase the dose of Humulin R to 110–120% of the original dose
130 ⩽ BS < 150	Increase the dose of Humulin R to 120–130% of the original dose
150 ⩽ BS < 180	Increase the dose of Humulin R to 130–150% of the original dose
BS ⩾ 180	Manually adjust the dose of Humulin R combined with sliding subcutaneous insulin administration

Abbreviation: BS = blood sugars.

than the recommendation in the HSCT setting (1.3–1.5 × BEE[18]). There are two beneficial aspects of this protocol: we could maintain the minimal caloric intake with supplemental PN and we could immediately start insulin as required after the introduction of PN. The SGC group was managed without a specific protocol for nutrition practice and glucose control, although we routinely monitored blood glucose at least three times weekly to avoid severe hyperglycemia (blood glucose >200 mg per 100 ml).

Outcome measures

Serially monitored glucose values were compared between the IGC group and the SGC group. We also analyzed the association between the mean glucose level during monitoring and the infection rate in both the SGC group and IGC group. Mean glucose levels were estimated for each patient and were categorized as follows: 80–110, 111–140, 141–179 and > 180. Glycemic variability, defined as the s.d. of the mean glucose value, was also analyzed. The outcome measures were time to the occurrence of documented infectious complications within 100 days after HSCT, time to each organ dysfunction defined as described below, time to grades II–IV and grades III–IV acute GVHD and time to NRM. These were calculated from the date of the start of the conditioning regimen. Organ dysfunction was defined with reference to van den Berghe[5–7] as follows: (1) hypercreatininemia; serum creatinine level ⩾2.0 mg per 100 ml or more than twice the baseline, (2) hyperbilirubinemia; serum total bilirubin level ⩾2.0 mg per 100 ml and (3) increased inflammatory markers; serum C-reactive protein (CRP) level ⩾15 mg per 100 ml. In our institute, the CRP level was routinely monitored at least three times a week, as we previously reported that the preengraftment CRP level may predict a subsequent occurrence of acute GVHD and NRM after allogeneic HSCT.[19] These results suggested that CRP might be useful not only as a marker of infectious diseases but also as a surrogate marker for produced cytokines. Therefore, the serial changes of CRP level were compared between the two groups. Acute GVHD was graded by the consensus criteria.[20]

Statistical analyses

Baseline characteristics were summarized using descriptive statistics. The Student's t, χ^2 and Wilcoxon rank-sum tests were used to compare clinical and patient characteristics. The probability of documented infectious complications and organ dysfunction were calculated using Kaplan–Meier estimates. A stratified Cox regression model, which accounts for the matched-cohort design, was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). On the basis of 64 patients, the study has an approximately 80% power to detect a HR of 0.5 for documented infections. The glucose values, measured repeatedly, were compared between groups using a repeated-measure analysis with a linear mixed-effect model. A level of $P<0.05$ was defined as statistically significant. All P-values are two-sided. All analyses were performed using SAS version 9.1.3 (Cary, NC, USA).

Results

Patient characteristics

Table 1 lists the patients' clinical and transplantation characteristics. Patients and transplantation characteristics were well balanced with the application of matching criteria. Nevertheless, in the IGC group, more patients received tacrolimus for GVHD prophylaxis (68 vs 36%, $P=0.01$) and more had a previous transplantation (32 vs 7%, $P=0.01$). The median duration of follow-up in surviving patients was 299 days (range, 78–607 days) in the IGC group and 1146 days (range, 329–1774 days) in the SGC group.

Glycemic control

Duration of monitoring and number of tests. The median duration of glucose monitoring and intervention in the IGC group was 38 days (range, 24–70 days) after the start of the conditioning regimen. The total number of glycemic monitorings was 867 and 1094 in the SGC group and IGC group, respectively.

Mean values and distribution of values. Patients in the IGC group had a lower glucose level (least-square mean, 116.4 vs 146.8 mg per 100 ml, $P<0.001$) than the SGC group. The trend of the glucose value is shown in Figure 2a. All glycemic results for the SGC and IGC groups were stratified into six levels: <40, 40–79, 80–110, 111–140, 141–179 and ⩾180, as shown in Figure 2b.

Hypoglycemia

In the IGC group, the incidence of mild hypoglycemia (CTCAE grades 1–2, glucose level 40–69 mg per 100 ml) was significantly higher than that in the SGC group (11 vs 3 patients, $P<0.001$). Although one patient (4.5%) in the IGC group who was diagnosed as type 2 diabetes mellitus developed severe hypoglycemia (CTCAE grade 3, glucose level 30–39 mg per 100 ml) with faintness, no patient developed seizure or loss of consciousness.

Glycemic variability

The mean glycemic variability in the SGC group and IGC group was 37.2 mg per 100 ml (range, 10.1–121.7 mg per 100 ml) and 27.5 mg per 100 ml (range, 11.3–46.6 mg per 100 ml), respectively, and glycemic variability in the IGC group tended to be lower than that in the SGC group ($P=0.07$).

TPN and insulin dosing

The percentage of patients who received TPN was 60% (25 patients) and 77% (17 patients) in the SGC group and the IGC group, respectively. The mean duration of TPN was 9 days (range, 0–35) and 13 days (range, 0–38) in the SGC group and IGC group, respectively. There was a tendency for more patients in the IGC group to receive TPN compared to the SGC group, but this difference was not statistically significant. The mean maximal dose of insulin (median (range), 51 (0–100) vs 2 (0–110) IU, $P<0.001$) and the mean maximal dose of insulin per 1 g parenteral glucose

were significantly higher in the IGC group (median (range), 0.22 (0–0.71) vs 0.003 (0–0.4) IU/g glucose, $P<0.001$).

Infections

Table 3 summarizes the results. In the IGC group, dramatically fewer patients developed documented infections within 100 days compared to the SGC group, as shown in Figure 3.

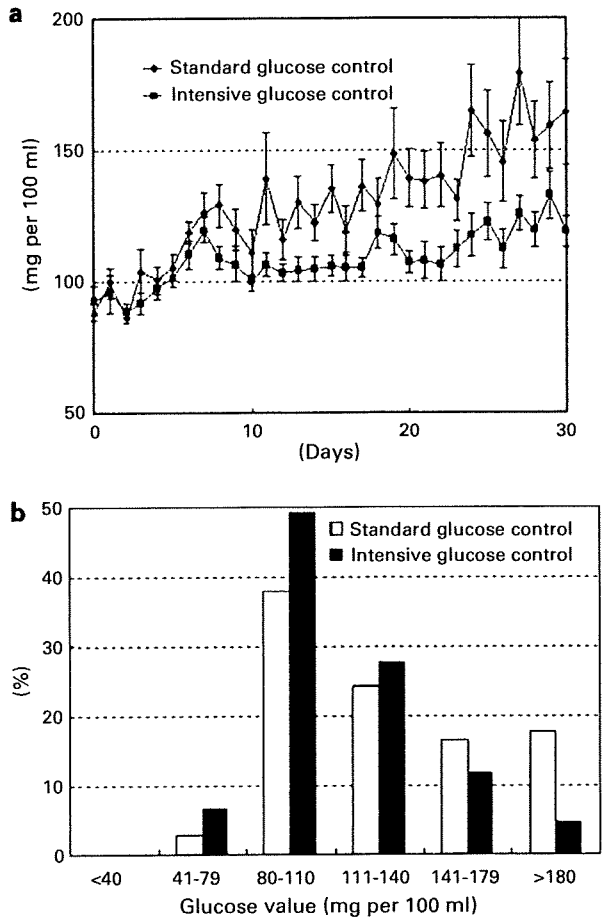

Figure 2 Serial changes in the mean glucose level in the intensive glucose control (IGC) and standard glucose control (SGC) groups. Values are mean + s.e. (**a**). The distribution of the glucose values in IGC and SGC is shown as a histogram (**b**).

Relation to mean glucose level

We also analyzed the association between the mean glucose level during monitoring and the infection rate in both the SGC and IGC groups. The incidence of infection was 34, 17, 67 and 40%, respectively, with mean glucose levels of 80–110, 111–140, 141–179 and ⩾180. When we compared a lower glucose-level group (mean glucose level of 80–140) with a higher glucose-level group (mean glucose level of >140), the incidence of infection was significantly higher in the latter group (28 vs 57%, $P=0.042$). When we assessed only patients with a lower glucose level, the IGC group tended to show a lower incidence of infectious diseases than the SGC group (14 vs 41%, $P=0.061$).

Relation to glycemic variability

We also analyzed the association between glycemic variability and the infection rate. The mean glycemic variability in patients with and without infection was 34.6 mg per 100 ml (range, 10.5–121.7 mg per 100 ml) and 33.3 mg per 100 ml (range, 10.1–110.6 mg per 100 ml), respectively, with no significant difference. As the importance of glycemic variability could vary among patients

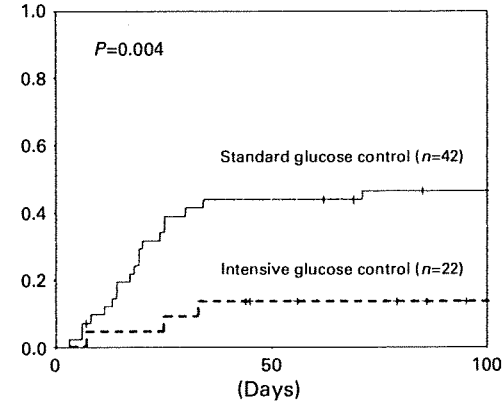

Figure 3 Probability of documented infections in the IGC and SGC groups.

Table 3 Incidence of infectious diseases and organ dysfunction

Variable	N *(%)/median (range)*			
	Intensive glucose control n = *22 (%)*	*Standard glucose control* n = *42 (%)*	*HR (95% CI)*	P-*value*
Documented infection	13	46	0.17 (0.04–0.75)	0.004
Bacteremia	9	39	0.10 (0.01–0.74)	0.002
Organ dysfunction				
Hypercreatininemia[a]	19	37	0.60 (0.19–1.88)	0.36
Hyperbilirubinemia[b]	28	31	1.05 (0.38–2.91)	0.93
Increased inflammatory markers[c]	18	38	0.45 (0.15–1.37)	0.13

Abbreviations: CI = confidence interval.
[a]Serum creatinine level ⩾2.0 mg per 100 ml or more than twice of baseline.
[b]Serum bilirubin level ⩾2.0 mg per 100 ml.
[c]Serum C-reactive protein level ⩾15 mg per 100 ml.

with different mean glucose levels,[21] we divided the patients into two groups based on mean glucose level 80–140 or 140+ and then determined whether glycemic variability was associated with an increased incidence of infections. However, there was no significant association between glycemic variability and the incidence of infections in both groups.

CRP levels

Figure 4 shows serial changes in the CRP level. Even though there was no difference in the CRP level between the two groups at the beginning of the conditioning regimen, the CRP level was significantly elevated in the SGC group compared to that in the IGC group 15 days after the beginning of the conditioning regimen, and this trend continued up to 40 days ($P<0.05$). The maximal CRP level during the neutropenic period in the IGC group was significantly lower than that in the SGC group (median (range), 6.9 (0.9–16.3) vs 11.5 (1.6–37.3), $P=0.007$).

Other clinical outcomes

The probability of grades II–IV acute GVHD within 100 days was 28 and 37% in the IGC and SGC groups (HR 1.05, 95% CI 0.38–2.91, $P=0.93$). The incidences of grades III–IV acute GVHD and NRM within 100 days were low in both groups (one and two patients, and one and one patient, in the IGC and SGC groups, respectively).

Discussion

This is the first study to evaluate the outcomes in allogeneic HSCT patients who were treated with a glucose management protocol. A salient finding of this study is that the incidence of documented infections, especially the incidence of bacteremia, was significantly lower in the IGC group than in the SGC group, as in a previous report in the ICU setting.[1] Moreover, there tended to be fewer organ dysfunctions in the IGC group, albeit this difference was not statistically significant. Furthermore, the CRP level, which might be a surrogate marker for produced cytokines,[19] was significantly lower in the IGC group than in the SGC group, as shown in Figure 4. Even though this study did not have enough power to detect a decrease in acute GVHD and NRM, it could be anticipated that IGC could reduce the CRP level, which would lead to a reduced incidence of acute GVHD and NRM.

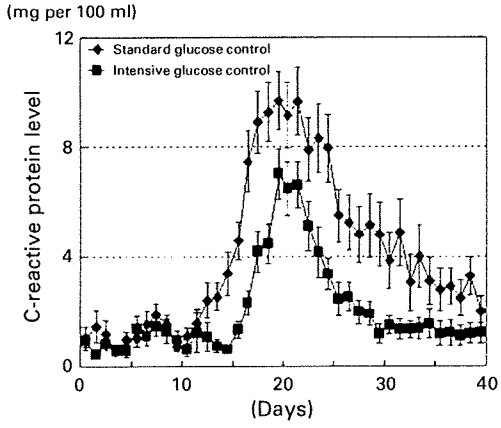

Figure 4 Serial change in the CRP level in the IGC and SGC groups. Values are mean + s.e.

This study has several limitations. One limitation is that only 64 patients were analyzed with no sufficient power to demonstrate any statistically significant changes in the incidences of organ dysfunctions, which was similar to the result in a previous report in the ICU.[1,2] An additional limitation was that the control of the glucose level could be suboptimal. This could be because of the glucose control protocol, which included monitoring of glucose level and the administration of insulin. With regard to the administration of insulin, we replaced the continuous infusion of insulin with the addition of Humulin R to the bottle of PN to control the glucose level within the target range because of the presence of fewer nursing staff in the HSCT unit than in the ICU. This could delay the normalization of hyperglycemia. Even though severe hyperglycemia (>180 mg per 100 ml) was reduced, a glucose value within the normal range (80–110 mg per 100 ml) could be achieved in only 49% of the IGC group as shown in Figure 1b. From a methodological point of view, it might be inappropriate to simply count the number of glucose value measurements, as patients with hyperglycemia were monitored more frequently, as defined in this protocol. Furthermore, as the mode of glucose monitoring was quite different between the IGC group and the SGC group, it could be inappropriate to compare the glucose values. A future protocol should include a more appropriate monitoring of glucose level and administration of insulin system that assures the fine tuning of glucose levels within the target range. Finally, there was a possible selection bias that may have affected the results, as this study was not a randomized-control study and there were many nonparticipants. However, the incidence of documented infections in nonparticipants within 100 days after allogeneic HSCT was 42%. Therefore, the reduction in the incidence of documented infections in the IGC group could not simply be explained by other causes such as the selection of antibiotics or catheter management.

With these limitations in mind, we took several steps to improve the quality of the study. First, we carefully matched patients and transplantation characteristics. Second, the IGC strategy was applied prospectively. Third, the low rate of patients who developed clinically significant hypoglycemia should be emphasized. As previously reported, the IGC procedure becomes very difficult in the medical ICU, especially in patients who have sepsis, a high APACHE score or mechanical ventilation.[1,2,22,23] The low rate of hypoglycemia could be because the medical acuity of our patients were relatively mild compared to those of patients in the medical ICU. Moreover, patients undergoing HSCT are younger and might have better β-cell function. The low rate of hypoglycemia could be important for maximizing the benefit of IGC because severe hypoglycemia could be associated with an increased risk of mortality.[23]

The biological plausibility of the intervention should be discussed. The reduction in infectious diseases by IGC may reflect the deleterious effects of hyperglycemia on macrophage or neutrophil function or insulin-induced protective effects on mucosal and skin barriers.[24–27] The improvement of innate immunity could be quite important, especially during the period of granulocytopenia after allogeneic HSCT. The protection of mucosal tissues could reduce bacterial translocation, which might lead to a reduced incidence of sepsis.

In conclusion, our results suggest that prospective IGC reduced the incidences of infectious diseases and organ dysfunction after allogeneic HSCT. To confirm these findings, a larger, prospective randomized-controlled trial is warranted.

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Possible Association between Obesity and Posttransplantation Complications Including Infectious Diseases and Acute Graft-versus-Host Disease

Shigeo Fuji,[1] Sung-Won Kim,[1] Ken-ichi Yoshimura,[2] Hideki Akiyama,[3] Shin-ichiro Okamoto,[4] Hiroshi Sao,[5] Junko Takita,[6] Naoki Kobayashi,[7] Shin-ichiro Mori[1] for the Japan Marrow Donor Program

Both obesity and malnutrition are considered risk factors for complications after bone marrow transplantation (BMT). To elucidate the impact of pretransplantation body mass index (BMI) on clinical outcome, we performed a retrospective cohort study with registration data from the Japan Marrow Donor Program (JMDP). Between January 1998 and December 2005, a total of 3935 patients received unrelated BMT through the JMDP; of these, 3827 patients for whom pretransplantation height and weight data were available were included in the study. Patients were stratified according to pretransplantation BMI values (low BMI: BMI < 18 kg/m^2, n = 295; normal BMI: 18 ≤ BMI < 25 kg/m^2, n = 2906; overweight: 25 ≤ BMI <30 kg/m^2, n = 565; obese: 30 kg/m^2 ≤ BMI, n = 61). In a univariate analysis, pretransplantation BMI was associated with a significantly greater risk of grade II-IV acute graft-versus-host disease (GVHD; P = .03). Multivariate analysis showed that pretransplantation BMI tended to be associated with an increased risk of grade II-IV acute GVHD (P = .07). Obesity was associated with an increased risk of infection compared with normal BMI (odds ratio = 1.9; 95% confidence interval = 1.1 to 3.2; P = .02). Our findings demonstrate a correlation between pretransplantation BMI and posttransplantation complications. Although BMI depends strongly on multiple factors, the effect of obesity on clinical outcome should be evaluated in a prospective study.

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KEY WORDS: Obesity, Allogeneic transplantation, Infection, Acute graft-versus-host disease

INTRODUCTION

Both obesity and malnutrition are considered risk factors for complications and increased relapse and nonrelapse mortality in hematopoietic stem cell transplantation (HSCT). An inferior outcome after allogeneic HSCT has been reported in obese adult patients in both allogeneic [1,2] and autologous HSCT [3-5]. Furthermore, our group recently reported that hyperglycemia during the neutropenic period is associated with an increased risk of acute graft-versus-host disease (GVHD) and subsequent nonrelapse mortality [6]. Obesity obviously is associated with an increased risk of hyperglycemia [7], which can lead to an inferior outcome after allogeneic HSCT. Recently, obesity was reported to be associated with low-grade systemic inflammation and was identified as a possible risk factor for autoimmune diseases [8-10]. Alternatively, malnutrition has been reported to be associated with an increased risk of early death after allogeneic HSCT [11,12]. Several reports have noted an association between malnutrition and a high incidence of infectious disease in conventional chemotherapy settings [13-15].

Although we can speculate that these infectious complications may be associated with nonrelapse mortality in HSCT, there is currently no agreement

From the [1]Department of Hematology and Stem Cell Transplantation, National Cancer Center Hospital, Tokyo, Japan; [2]Department of Clinical Trial Management, Translational Research Center, Kyoto University Hospital, Kyoto, Japan; [3]Department of Hematology, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan; [4]Division of Hematology, Department of Medicine, Keio University School of Medicine, Tokyo, Japan; [5]Department of Hematology, Meitetsu Hospital, Nagoya, Japan; [6]Department of Pediatrics, Graduate School of Medicine, University of Tokyo, Tokyo, Japan; and [7]Department of Hematology, Sapporo Hokuyu Hospital, Sapporo, Japan.

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Correspondence and reprint requests: Shin-ichiro Mori, MD, Department of Hematology and Stem Cell Transplantation, National Cancer Center Hospital, Tokyo, Japan, 5-1-1, Tsukiji, Chuo-Ku, Tokyo 104-0045, Japan. (e-mail: shmori@ncc.go.jp).

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regarding a suitable target range of pretransplantation body mass index (BMI) for clinical management. Previous studies have included various kinds of stem cell sources, and some have included HSCT with T cell depletion. The aim of the present study was to retrospectively evaluate the impact of pretransplantation BMI on the clinical outcome after unrelated bone marrow transplantation (BMT) for hematologic malignancies, using registration data from the Japan Marrow Donor Program (JMDP). The results should provide insight into how to better manage nutritional support for patients undergoing HSCT.

PATIENTS AND METHODS

A total of 3935 patients with various hematologic malignancies underwent BMT through the JMDP between January 1998 and December 2005. Data from 3827 of these patients for whom pretransplantation height and weight data were available were included in the present study. Patient characteristics are summarized in Table 1. The median patient age was 39 years (range, 18 to 72 years), and diagnoses included acute myeloid leukemia (AML; n = 1165), acute lymphoblastic leukemia (ALL; n = 755), myelodysplastic syndrome/myeloproliferative disease (MDS/MPD; n = 597), malignant lymphoma (ML; n = 500) and chronic ML (CML; n = 576), other leukemia (n = 69), multiple myeloma (n = 71), and other (n = 94). Standard risk included acute leukemia in first complete remission (CR1), CML in first chronic phase, MDS in refractory anemia, and lymphoma in CR1. The rest of the patients were categorized as a high-risk group. Bone marrow was the sole stem cell source for transplantation. Total body irradiation (TBI) was used in 2849 patients. GVHD prophylaxis included cyclosporine (CSP)-based (n = 1520) and tacrolimus (TAC)-based regimens (n = 2155), or other combinations (n = 152), with the addition of low-dose antithymocyte globulin (ATG) in 205 patients. Alleles at the HLA-A, -B, and -DRB1 loci were identified by high-resolution DNA typing. The median follow-up period was 565 days. Informed consent was obtained from patients and donors in accordance with the Declaration of Helsinki, and the study design was approved by the JMDP's Institutional Review Board.

The study's primary endpoints were nonrelapse mortality at 100 days and 1 year, overall survival at 1 year, and progression-free survival at 1 year. For nonrelapse mortality, an event was death without disease progression after BMT. For overall survival, an event was death from any cause after BMT. For progression-free survival, an event was disease progression or death after BMT. Secondary endpoints were the incidence of infection (bacterial, viral, fungal, and others); incidence of lung organ toxicity including interstitial pneumonia, adult respiratory distress syndrome, bronchiolitis obliterans, pulmonary hemorrhage, and others, excluding pneumonia with obvious infectious diseases; and incidence of hepatic toxicity, including veno-occlusive disease and drug toxicity. Acute GVHD was classified as grade 0, I, II, III, or IV according to established criteria [16]. The probability of acute GVHD, nonrelapse mortality rate, overall survival, progression-free survival, and relapse rate were estimated using the Kaplan-Meier method. Death without acute GVHD was treated as censoring in the analysis of acute GVHD, and death without progression was treated as censoring in the analysis of relapse. Dichotomous variables between groups were compared using the χ^2 test, and survival times were compared using the log-rank test. An order-restricted version of the log-rank test (a log-rank trend test) was used to test ordered differences between the estimated survival curves. Multivariate analyses were performed using a logistic regression model or a Cox proportional hazards model, as appropriate. The following covariates were included in the univariate analysis: BMI (BMI < 18 kg/m^2, $18 \leq$ BMI < 25 kg/m^2, $25 \leq$ BMI < 30 kg/m^2, and 30 kg/m$^2 \leq$ BMI), sex (donor–recipient pairs), patient age (age < 30 years, $30 \leq$ age < 50 years, age ≥ 50 years), donor age (age < 40 years, age ≥ 40 years), type of disease, risk of leukemia relapse (standard vs high), conditioning (TBI-based vs non–TBI-based), GVHD prophylaxis (CSP-based vs TAC-based), genotypic HLA match versus HLA mismatch, ABO match versus mismatch (major mismatch vs minor mismatch vs major/minor mismatch vs match), cell dose in the graft (dose $< 3.0 \times 10^8$/kg, $3.0 \leq$ dose $< 5.0 \times 10^8$/kg, $\geq 5.0 \times 10^8$/kg), and use of ATG/antilymphocyte globulin (ALG) (ATG/ALG vs no ATG/ALG). All P values were 2-sided. A P value $< .05$ was considered statistically significant.

RESULTS

Patient Characteristics

Table 1 gives the BMI distribution of the study group. Patients were classified into 4 groups based on pretransplantation BMI values according to consensus weight designations from the World Health Organization [17] and the National Heart Lung and Blood Institute Expert Panel [18], as follows: low BMI (BMI < 18 kg/m^2; n = 295), normal BMI ($18 \leq$ BMI < 25 kg/m^2; n = 2906), overweight ($25 \leq$ BMI < 30 kg/m^2; n = 565), and obesity (30 kg/m$^2 \leq$ BMI; n = 61). The prevalence of obesity was quite low compared with that in previous reports from Western countries [1-4]. Significant differences in patient characteristics were observed with regard to age, sex disparity, total nucleated cells (TNCs) per body weight, and primary disease. The low-BMI group

Table 1. Patient Characteristics

	n (%)				
	BMI < 18 kg/m^2	18 ≤ BMI <25 kg/m^2	25 ≤ BMI < 30 kg/m^2	30 kg/m^2 ≤ BMI	
	(n = 295)	(n = 2906)	(n = 565)	(n = 61)	*P* value
Recipient age, years					
< 30	116 (39)	734 (25)	90 (16)	14 (23)	< .0001
30 ≤ age < 50	121 (41)	1473 (51)	322 (57)	36 (59)	
> 50	58 (20)	699 (24)	153 (27)	11 (18)	
Donor age, years					
< 40	217 (74)	2099 (72)	385 (68)	38 (62)	.27
≥ 40	75 (25)	741 (25)	162 (29)	18 (30)	
Sex, donor/recipient					
Match	181 (61)	1833 (63)	374 (66)	39 (64)	< .0001
Male/female	70 (24)	519 (18)	87 (15)	9 (15)	
Female/male	43 (16)	495 (17)	87 (15)	9 (15)	
TNC (× 10^{-8}/kg)					
TNC < 3.0	12 (4)	323 (11)	160 (28)	31 (51)	< .0001
3.0 ≤ TNC< 5.0	60 (20)	1085 (37)	267 (47)	16 (26)	
5.0 ≤ TNC	187 (63)	1191 (41)	78 (14)	1 (2)	
Year of transplantation					
1998	12 (4)	83 (3)	11 (2)	0 (0)	.18
1999	21 (7)	248 (9)	39 (7)	0 (0)	
2000	26 (9)	363 (12)	81 (14)	7 (11)	
2001	43 (15)	398 (14)	74 (13)	7 (11)	
2002	47 (16)	409 (14)	72 (13)	14 (23)	
2003	50 (17)	404 (14)	87 (15)	10 (16)	
2004	40 (14)	463 (16)	88 (16)	12 (20)	
2005	56 (19)	538 (19)	113 (20)	11 (18)	
Diagnosis					
Acute leukemia	186 (63)	1469 (51)	304 (54)	29 (48)	.02
CR1/CR2/>CR2	81/33/65	594/301/541	113/79/107	7/4/18	
Chronic leukemia	30 (10)	449 (15)	84 (15)	13 (21)	
CP1/CP2/AP/BC	16/5/5/3	251/66/65/53	53/8/12/11	5/3/3/2	
MDS/MPD	37 (13)	462 (16)	87 (15)	11 (18)	
RA/RAEB/others	7/12/10	99/155/166	25/33/20	7/3/1	
ML	35 (12)	400 (14)	62 (11)	4 (7)	
CR/>CR	10/19	138/230	24/33	1/3	
MM	5 (2)	56 (2)	10 (2)	0 (0)	
CR/>CR	1/1	10/33	1/7	0/0	
Disease stage*					
Standard	110 (37)	1034 (36)	202 (36)	19 (31)	.67
High	158 (54)	1686 (58)	324 (57)	38 (62)	
Blood type disparity					
Match	146 (49)	1477 (51)	276 (49)	28 (46)	.98
IA	8 (3)	103 (4)	18 (3)	2 (3)	
MA	71 (24)	650 (22)	127 (22)	13 (21)	
MI	65 (22)	586 (20)	121 (21)	14 (23)	
HLA disparity					
HLA allele match	185 (63)	1660 (57)	342 (61)	36 (59)	.01
HLA allele mismatch	70 (24)	857 (29)	149 (26)	18 (30)	
1 allele mismatch	59 (20)	728 (25)	118 (21)	11 (18)	
2 allele mismatch	10 (3)	116 (4)	31 (5)	6 (10)	
3 allele mismatch	1 (0)	13 (0)	0 (0)	1 (2)	
Conditioning regimen					
Conventional	235 (80)	2308 (79)	443 (78)	52 (85)	.25
Reduced-intensity	59 (20)	539 (19)	105 (19)	5 (8)	
TBI for conditioning					
No	80 (27)	654 (23)	146 (26)	12 (20)	.14
Yes	214 (73)	2188 (75)	402 (71)	45 (74)	
ATG for conditioning					
No	268 (91)	2670 (92)	517 (92)	55 (90)	.21
Yes	23 (8)	155 (5)	25 (4)	2 (3)	
GVHD prophylaxis					
CSP-based	137 (46)	1141 (39)	226 (40)	16 (26)	.19
TAC-based	153 (52)	1651 (57)	312 (55)	39 (64)	
Others	3 (1)	48 (2)	7 (1)	2 (3)	
Comorbidity					
Liver dysfunction					
No	239 (81)	2436 (84)	481 (85)	49 (80)	.78
Yes	41 (14)	360 (12)	66 (12)	7 (11)	

(Continued)

Table 1. (*Continued*)

	n (%)				
	BMI < 18 kg/m^2	18 ≤ BMI <25 kg/m^2	25 ≤ BMI < 30 kg/m^2	30 kg/m^2 ≤ BMI	
	(n = 295)	(n = 2906)	(n = 565)	(n = 61)	*P* value
Renal dysfunction					
No	273 (93)	2706 (93)	528 (93)	54 (89)	.90
Yes	7 (2)	90 (3)	19 (3)	2 (3)	
Heart dysfunction					
No	260 (88)	2601 (90)	519 (92)	54 (89)	.32
Yes	20 (7)	195 (7)	28 (5)	2 (3)	
Pulmonary dysfunction					
No	267 (91)	2709 (93)	528 (93)	56 (92)	.27
Yes	13 (4)	87 (3)	19 (3)	0 (0)	

*Disease stage: Standard risk stage included CR1 in acute leukemia, first chronic phase in CML, and CR1 in lymphoma. Others were classified as high-risk stage.

included more young patients, patients receiving high TNCs per body weight, patients with acute leukemia, and male patients with a female donor.

Clinical Outcomes

The incidence of grade II-IV acute GVHD was 42% in the low-BMI group, 45% in the normal-BMI group, 48% in the overweight group, and 58% in the obesity group (Figure 1A). Thus, increased BMI was significantly associated with a higher incidence of grade II-IV acute GVHD (P = .03 by the log-rank trend test). Other factors associated with a higher incidence of grade II-IV acute GVHD were HLA allele disparity, GVHD prophylaxis with CSP (vs with TAC), and donor age ≥ 40 years. Multivariate analysis showed that pretransplantation BMI tended to be associated with an increased risk of grade II-IV acute GVHD (P = .07, log-rank trend test) (Table 2). The incidence of grade III-IV acute GVHD was 17% in the low-BMI group, 17% in the normal-BMI group, 19% in the overweight group, and 25% in the obesity group (Figure 1B). An increase in BMI tended to be associated with a higher incidence of grade III-IV acute GVHD, but this trend was not significant (P = .087, log-rank trend test). Multivariate analysis showed no association between pretransplantation BMI and the incidence of grade III-IV acute GVHD (P = .19, log-rank trend test) (Table 3).

Nonrelapse mortality was 29% in the low-BMI group, 31% in the normal-BMI group, 32% in the overweight group, and 40% in the obesity group at 1 year after BMT (P = .19, log-rank trend test) (Figure 2A). Overall survival was 61% in the low-BMI group, 58% in the normal-BMI group, 59% in the overweight group, and 53% in the obesity group at 1 year after BMT (P = .98, log-rank trend test) (Figure 2B). Progression-free survival was 54%, 52%, 56%, and 47% (P = .72, log-rank trend test), and the relapse rate was 24%, 24%, 18%, 21%, respectively, in the 4 groups at 1 year after BMT (P = .04 by log-rank trend test) (Figure 2C and D). The incidence of systemic infectious diseases, including bacterial, fungal, and viral infections, was 39%, 43%, 46%, and 59%, respectively, in the 4 groups (Figure 3). Obesity was significantly associated with increased incidence of infectious disease compared with normal

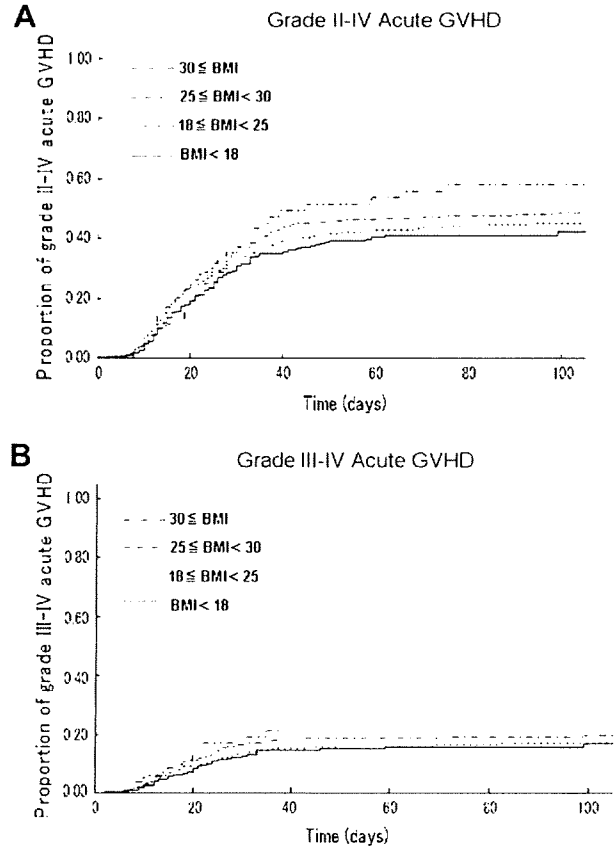

Figure 1. Probability of grade II-IV acute GVHD (A) and grade III-IV acute GVHD (B).

Table 2. Univariate and Multivariate Analyses of Risk Factors for Grade II-IV Acute GVHD

	Univariate Analysis			Multivariate Analysis		
Covariates	HR	95% CI	*P* value	HR	95% CI	*P* value
Recipient BMI						
18 ≤ BMI < 25 kg/m^2	1.00		.026*	1.00		.066*
BMI < 18 kg/m^2	0.91	0.75 to 1.10		1.06	0.85 to 1.31	
25 ≤ BMI < 30 kg/m^2	1.11	0.97 to 1.27		1.19	0.93 to 1.52	
30 ≤ BMI kg/m^2	1.28	0.89 to 1.85		1.29	0.82 to 2.03	
Recipient age, years						
<30	1.00		.85*			
30 ≤ age < 50	1.00	0.88 to 1.13				
≥ 50	0.99	0.86 to 1.14				
Donor age, years						
< 40	1.00		< .0001	1.00		< .0001
≥ 40	1.30	1.17 to 1.45		1.28	1.13 to 1.44	
Sex, donor/recipient						
Match	1.00		.053	1.00		.20
Male/female	1.12	0.98 to 1.27		1.09	0.95 to 1.26	
Female/male	1.15	1.01 to 1.32		1.12	0.97 to 1.30	
TNC (× 10^{-8}/kg)						
TNC <3.0	1.00		.76*			
3.0 ≤ TNC < 5.0	1.03	0.88 to 1.20				
5.0 ≤ TNC	0.99	0.85 to 1.16				
Diagnosis						
Acute	1.00		.28			
Chronic	1.08	0.93 to 1.24				
MDS/MPD	1.01	0.87 to 1.16				
ML	1.17	1.01 to 1.35				
MM	0.92	0.62 to 1.36				
Blood type disparity						
M	1.00		.15	1.00		.49
IA	1.19	0.92 to 1.55		1.14	0.85 to 1.52	
MA	1.03	0.90 to 1.16		1.02	0.89 to 1.17	
MI	1.14	1.00 to 1.29		1.11	0.96 to 1.27	
HLA disparity						
HLA allele match	1.00		< .0001	1.00		< .0001
HLA 1 allele mismatch	1.30	1.16 to 1.47		1.36	1.21 to 1.54	
HLA 2 allele mismatch	1.49	1.18 to 1.88		1.51	1.19 to 1.93	
HLA 3 allele mismatch	2.23	1.16 to 4.30		2.23	1.15 to 4.31	
Conditioning regimen:						
TBI for conditioning						
No	1.00		.67			
Yes	0.98	0.87 to 1.10				
Intensity of conditioning:						
Conventional	1.00		.42			
Reduced-intensity	0.95	0.84 to 1.08				
ATG for conditioning						
No	1.00		.58			
Yes	0.94	0.75 to 1.17				
GVHD prophylaxis						
CSP-based	1.00		.025	1.00		.0003
TAC-based	0.89	0.80 to 0.98		0.80	0.71 to 0.89	
Others	1.21	0.84 to 1.75		0.99	0.66 to 1.49	
Comorbidity						
Liver dysfunction						
No	1.00		.52			
Yes	0.95	0.82 to 1.11				
Renal dysfunction						
No	1.00		.84			
Yes	1.03	0.77 to 1.38				
Heart dysfunction						
No	1.00		.58			
Yes	0.94	0.77 to 1.16				
Lung dysfunction						
No	1.00		.15	1.00		.09
Yes	1.22	0.93 to 1.60		1.29	0.96 to 1.74	

*The log-rank trend test was used for calculating *P* values.