＜ 研究成果（論文発表）の刊行に関する一覧 ＞

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★資料提供：「造血幹細胞移植患者の長期フォローアップに関する実態調査」
国立国際医療センター　萩原 將太郎

＜ 学会発表（国内・海外）に関する一覧 ＞

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演者（研究者にｱﾝﾀﾞｰﾗｲﾝ）	演　題　名	学会･ｼﾝﾎﾟｼﾞｳﾑ名等	発表年
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Impact of T Cell Chimerism on Clinical Outcome in 117 Patients Who Underwent Allogeneic Stem Cell Transplantation with a Busulfan-Containing Reduced-Intensity Conditioning Regimen

Bungo Saito, Takahiro Fukuda, Hiroki Yokoyama, Saiko Kurosawa, Toshihiro Takahashi, Shigeo Fuji, Noriko Takahashi, Kinuko Tajima, Sung-Won Kim, Shin-ichiro Mori, Ryuji Tanosaki, Yoichi Takaue, Yuji Heike

Within the concept of reduced-intensity stem cell transplantation (RIST) there is a wide range of different regimens used, and little information is available on the clinical impact of chimerism status in patients conditioned with a busulfan-containing regimen. Therefore, we retrospectively reviewed lineage-specific chimerism and the subsequent clinical outcome in 117 patients (median age, 55 years; range: 29-68) who underwent busulfan-containing RIST. The conditioning regimen consisted of busulfan (oral 8 mg/kg or i.v. 6.4 mg/kg) and fludarabine (180 mg/m^2, n = 64) or cladribine (0.66 mg/kg, n = 53), with or without 2-4 Gy total-body irridiation (TBI) (n = 26) or antihuman T-lymphocyte immunoglobulin (ATG; 5-10 mg/kg; n = 31). Chimerism was evaluated with peripheral blood samples taken on days 30, 60, and 90 after transplantation by polymerase chain reaction (PCR)-based amplification of polymorphic short tandem repeat regions. The median follow-up of surviving patients was 1039 days (153-2535). The percent donor-chimerism was significantly higher in granulocyte than T cell fraction throughout the entire course, and the median (mean) values were, respectively, 100% (96%) versus 95% (83%), 100% (98%) versus 100% (89%), and 100% (98%) versus 100% (91%) at days 30, 60, and 90 after RIST. In a multivariate analysis, having received <2 types of chemotherapy regimens before RIST was the only factor that was significantly associated with low donor T cell chimerism (<60%) at day 30 (hazard ratio [HR]: 6.1; 95% confidence interval [CI], 2.1-18.4; $P < .01$). The median percentage of donor T cell chimerism at day 30 was 9% (0%-63%) in 5 patients who experienced graft failure, which was significantly lower than that (97%; 15%-100%) in the rest of the patients ($P < .01$). No correlation was found between the kinetics of T cell chimerism and the occurrence of acute or chronic GVHD (aGVHD, cGVHD). The stem cell source and the addition of TBI or ATG were not associated with the degree of T cell chimerism, overall survival (OS) or event-free survival (EFS). In a Cox proportional hazard model, low donor T cell chimerism of <60% at day 30 was associated with both poor OS (HR: 2.2; 95% CI, 1.1-4.5; $P = .02$) and EFS (HR: 2.0; 95% CI, 1.1-3.8; $P = .02$). In conclusion, we found that 43% of the patients retained mixed donor T cell chimerism (<90% donor) at day 30, whereas 92% achieved complete chimerism in granulocyte fraction. Low donor T cell chimerism of <60% at day 30 may predict a poor outcome, and a prospective study to examine the value of early intervention based on chimerism data is warranted.

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KEY WORDS: Reduced-intensity stem cell transplantation, Chimerism, Busulfan

From the Hematopoietic Stem Cell Transplantation Division, National Cancer Center Hospital, Tokyo, Japan

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Correspondence and reprint requests: Takahiro Fukuda, MD, PhD, Hematopoietic Stem Cell Transplantation Division, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan (e-mail: tafukuda@ncc.go.jp).

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) with a reduced-intensity conditioning (RIC) regimen has been increasingly used in patients with hematologic diseases who cannot be candidates for conventional HSCT because of age, medical comorbidities, or prior failed myeloablative SCT. Many different RIC regimens are currently in use, but most of them

incorporate fludarabine (Flu) as a background agent in combination with other drugs including cyclophosphamide (Cy) [1], melphalan (Mel) [2], busulfan [2,3], low-dose total body irradiation (TBI) [4], antithymocyte globulin (ATG) [3], and alemtuzumab [5].

RIC regimens have been investigated in the hope of reducing toxicity, whereas their engraftment potential and antileukemia effect rely mainly on the expansion of donor-derived cells and subsequent immune-mediated graft-versus-leukemia (GVL) effects [6,7]. In this setting, lineage-specific chimerism analysis to assess the origin of lymphohematopoietic cells becomes particularly important for identifying patients at risk for graft failure/rejection, graft-versus-host disease (GVHD), and relapse or progressive disease (PD) [4,8,9]. Because the posttransplantation chimerism status is based on a fine balance between the cytotoxicity or immunosuppressive potential of the regimen used and the recipient's reserve immunocompetence, each RIC regimen should be evaluated individually for chimerism kinetics [1,4,10-13].

Compared with a regimen that includes Flu and Me, it has been reported that the combination of Flu and i.v. Bu was associated with improved survival in patients transplanted in remission, which was more frequently associated with mixed chimerism [2]. However, very little information is currently available on the clinical impact of lineage-specific chimerism status in patients who are conditioned with a Bu-containing RIC regimen. Therefore, we examined the correlation between specific patterns of lineage-specific chimerism and subsequent clinical outcomes.

PATIENTS AND METHODS

Patients and Transplantation Procedures

We retrospectively reviewed the medical records of 117 patients who had various hematologic malignancies and underwent allogenic HSCT with Bu-containing RIC at our hospital from January 2000 to December 2006. The reasons for selecting RIC regimens included older patient age, medical comorbidities, and prior failed myeloablative SCT. The patients' characteristics are summarized in Table 1. The median age of the patients was 52 years (range: 29-68 years), and the hematologic malignancy included acute myelogenous leukemia (AML) (n = 23), AML evolving from a myelodysplastic syndrome (MDS) (n = 16), acute lymphoblastic leukemia (ALL) (n = 5), malignant lymphoma (n = 44), MDS (n = 16), chronic myelogenous leukemia (CML) (n = 9), chronic lymphocytic leukemia (CLL) (n = 1), multiple myeloma (MM) (n = 1), and atypical CML (n = 2).

The conditioning regimen consisted of Bu (oral 8 mg/kg or i.v. 6.4 mg/kg) and Flu (180 mg/m^2, n = 64) or cladribine (0.66 mg/kg, n = 53), with or without 2-4 Gy TBI (n = 26) or antihuman T-lymphocyte immunoglobulin (Fresenius Biotech GmbH, Germany) (ATG; 5-10 mg/kg, n = 31).

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 SCT from an unrelated donor, the sustained engraftment rate has been reported to be lower for recipients of bone marrow than for those given granulocyte colony-stimulating factor-mobilized peripheral blood mononuclear cells (G-PBMC) [14]. Therefore, low-dose TBI was also added to the conditioning regimen in 25 of the 32 patients who underwent reduced intensity stem cell transplantation (RIST) from an unrelated bone marrow donor to facilitate engraftment. Recipients of HLA-mismatched grafts tended to receive ATG-containing conditioning regimens (20 of the 27 recipients of HLA-mismatched grafts [74%] versus 11 of the 90 recipients of HLA-matched grafts

Table 1. Association between patients characteristics and donor T-cell chimerism at day 30

Characteristics	Total (n=117)	T cell chimerism at day 30 <60% (n=18)	T cell chimerism at day 30 ≥60% (n=99)
Patient age, years			
Median (range)	55 (29-68)	57 (35-66)	54 (29-68)
<55	56 (48%)	6 (33%)	50 (51%)
≥55	61 (52%)	12 (67%)	49 (49%)
Diseases type			
Acute leukemia	44 (38%)	5 (28%)	39 (39%)
Lymphoma	46 (39%)	6 (33%)	40 (40%)
MDS/MPD	27 (23%)	7 (39%)	20 (20%)
Disease risk			
High	91 (78%)	15 (83%)	76 (77%)
Low	26 (22%)	3 (17%)	23 (23%)
No. of prior chemotherapy regimens			
≥2	77 (66%)	6 (33%)	71 (72%)
<2	40 (34%)	12 (67%)	28 (28%)
Donor			
Unrelated	32 (27%)	2 (11%)	30 (30%)
Related	85 (73%)	16 (89%)	69 (70%)
HLA			
Match	90 (77%)	15 (83%)	75 (76%)
Mismatch	27 (23%)	3 (17%)	24 (24%)
Stem cell source			
G-PBMC	81 (69%)	13 (72%)	68 (69%)
Bone marrow	36 (31%)	5 (28%)	31 (31%)
Conditioning regimen			
2CdA/Bu	24 (21%)	4 (22%)	20 (20%)
2CdA/Bu/ATG	18 (15%)	4 (22%)	14 (14%)
2CdA/Bu/TBI	11 (9%)	1 (6%)	10 (10%)
Flu/Bu	38 (32%)	8 (44%)	30 (30%)
Flu/Bu/ATG	11 (9%)	1 (6%)	10 (10%)
Flu/Bu/ATG/TBI	2 (2%)	0 (0%)	2 (2%)
Flu/Bu/TBI	13 (11%)	0 (0%)	13 (13%)

Acute leukemia (n=44): acute myelogenous leukemia (AML; n=23), AML evolving from a myelodysplastic syndrome (n=16), and acute lymphoblastic leukemia (ALL; n=5); Lymphoma (n=46): malignant lymphoma (44), chronic lymphocytic leukemia (CLL; n=1) and multiple myeloma (MM; n=1); MDS/MPD (n=27): MDS n=16 and MPD including chronic myelogenous leukemia (n=9) and atypical CML (n=2); G-PBMC indicates granulocyte colony-stimulating factor-mobilized peripheral blood mononuclear cells; 2CdA, cladribine; Bu, busulfan; Flu, fludarabine; ATG, antihuman T-lymphocyte immunoglobulin; TBI, total-body irradiation.

[12%]). Prophylaxis for GVHD consisted of cyclosporin (CsA) alone (n = 55), Cyclosporin with short-term methotrexate (sMTX) (n = 38), tacrolimus alone (n = 13), or tacrolimus with sMTX (n = 11).

In 81 of the 117 patients, the source of stem cells was G-PBMC from a related donor, which contained a mean of 3.3×10^6 $CD34^+$ cells/kg (range: $1.5\text{-}7.0 \times 10^6$ $CD34^+$ cells/kg) and 8.7×10^7 $CD3^+$ cells/kg (range: $6.4\text{-}86.1 \times 10^7$ $CD3^+$ cells/kg). The other 36 patients received related (n = 4) or unrelated (n = 32) bone marrow, which contained a mean of 2.9×10^8 total nucleated cells (TNC)/kg (range: $0.97\text{-}6.53 \times 10^8$ TNC/kg).

A total of 9 patients received donor lymphocyte infusion (DLI), mainly after day 90, and all of them received DLI for relapse of disease. There was no patient who received DLI for low donor T cell chimerism.

Informed consent was obtained according to the Declaration of Helsinki.

Definitions

Graft failure was defined as (1) failure of absolute neutrophil count (ANC) to surpass 500 /mm^3 at day 30 after HSCT or (2) decrease in ANC <100 /mm^3 at 3 determinations after the initial engraftment or (3) absence of donor T cells (<5%) before relapse, disease progression, second HSCT, or death. The diagnosis and clinical grading of acute and chronic GVHD (aGVHD, cGVHD) were performed according to established criteria [15-17]. Complete remission (CR) was defined as according to the International Workshop Criteria in AML [18] and lymphoma [19] patients. Low disease risk was defined as AML or ALL in first CR, MDS-refractory anemia, and CML in first chronic phase. All other diagnoses were classified as high risk.

Chimerism Analysis

We assessed donor-recipient chimerism by the polymerase chain reaction (PCR)-based amplification of a polymorphic short tandem repeat region. Chimerism was evaluated using peripheral blood samples on days 30, 60, and 90 after transplantation. Samples were separated using Ficoll-hypaque into mononuclear cells and a precipitate that included red blood cells and granulocytes. Mononuclear cells were further separated into CD3-positive and -negative fractions with immunomagnetic beads (CD3 Magnetic Particles-DM, BD Pharmingen, San Diego, CA). Granulocytes were collected by lysing red blood cells in the precipitate. Briefly, DNA was extracted from selected cells using QIAamp DNA Mini Kit (QIAGEN, Hilden, Germany). Multiplex PCR was performed using primer sets (AmpFISTR Identifiler Kit, Applied Biosystems, Foster City, CA). Five-color fluorescence detection was performed on an ABI 3100-Avant Genetic Analyzer (Applied Biosystems). For each STR allele, the area under the curve for the corresponding signal was automatically processed using GeneScan 3.7 software (Applied Biosystems). The percentage of donor cells was calculated as (area signal donor)/(area signal donor + area signal recipient). The range of the error of chimerism was regarded as 5% at our laboratory (Heike et al., unpublished data).

Statistical Analysis

The chi-square test, Fisher's exact test, and Pearson correlation coefficients were used to evaluate the association of percent donor chimerism with various clinical factors such as patient age at the time of RIST (with 55 years as a cutoff), disease type (acute leukemia, MDS/myeloproliferative disease [MPD], lymphoma), disease risk (high, low), stem cell source (G-PBMC, bone marrow), serologic HLA matching (match, mismatch), and conditioning with TBI (yes, no) or ATG (yes, no).

Overall survival (OS) was defined as the time between stem cell infusion to death from any cause. Event-free survival (EFS) was defined as the time from stem cell infusion to graft failure, PD, or nonrelapse mortality (NRM), whichever occurred earlier. OS and EFS were estimated by the Kaplan-Meier method [20]. The log-rank test and the generalized Wilcoxon test were used to compare the probabilities of survival after HSCT over time across patient subgroups. Multiple Cox regression models were used for multivariate risk factor analysis for OS and EFS. Clinical factors evaluated in the OS and EFS analyses were donor T cell chimerism at day 30 (with 60% as a cutoff), patient age at the time of RIST, disease type, disease risk, stem cell source, HLA matching, and conditioning. Logistic regression models were used for multivariate risk factor analysis for low donor T cell chimerism (<60%) at day 30. Clinical factors evaluated for the risk of low donor T cell chimerism at day 30 were number of prior chemotherapy regimens (≥2, <2) and donor type in addition to the variables mentioned above. We considered 2-sided *P*-values of <.05 to be statistically significant. Statistical analyses were performed with SAS version 8.2 (SAS Inc., Cary, NC).

RESULTS

Kinetics of Chimerism

Whereas 43% of the patients retained mixed donor chimerism (<90% donor) in the T cell fraction, 92% achieved complete chimerism (≥90%) in the granulocyte fraction at day 30 after RIST (Figure 1). In the peripheral blood mononuclear cell (PBMC) fraction, 72% of the patients achieved complete chimerism

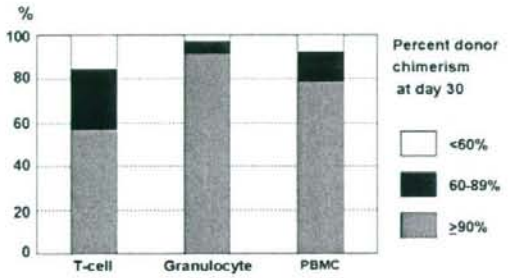

Figure 1. Distribution of chimerism status at day 30 after RIST.

(≥90%). The percent donor-chimerism was significantly higher in granulocyte than T cell fraction throughout the entire course, and the median (mean) values were, respectively, 100% (96%) versus 95% (83%), 100% (98%) versus 100 % (89%), and 100% (98%) versus 100% (91%) at days 30, 60, and 90, respectively after RIST (Figure 2).

In univariate and multivariate analyses (Table 2), having received <2 types of chemotherapy regimens before RIST was the only factor that was significantly associated with low donor T cell chimerism (<60%) at day 30 (hazard ratio [HR]: 6.1; 95% confidence interval [CI], 2.1-18.4; $P < .01$). Non-TBI regimens and related donor also tended to be associated with lower donor T cell chimerism.

Graft Composition and Donor Chimerism

By examining the impact of graft composition of G-PBMC on donor chimerism, we found that increases in TNC and $CD3^+$ T cells contents paralleled the increase in donor T cell chimerism at day 30 ($P < .03$ and $P < .05$, respectively). The same relationship was observed between $CD34^+$ cell contents and granulocyte chimerism ($P = .06$). In patients who received bone marrow, a higher number of TNC infused was associated with a higher level of donor T cell chimerism at day 30 ($P < .01$).

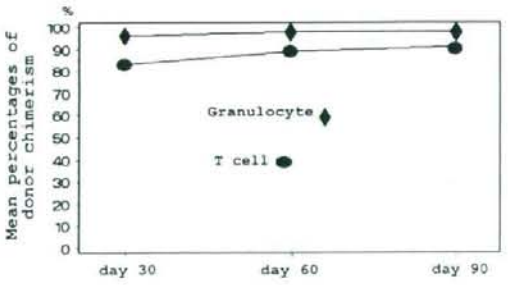

Figure 2. Kinetics of chimerism status after RIST (mean percentages of donor chimerism levels). Percent donor cell chimerism was significantly higher in granulocyte than T cell fraction throughout the entire course, and the mean values were, respectively, 96% versus 83%, 98% versus 89 %, and 98% versus 91% at days 30, 60, and 90 after RIST.

Table 2. Factors affecting low donor T cell chimerism (<60%) at day 30

	Univariate analysis		Multivariate analysis	
Characteristics	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Patient age, years				
<55	1			
≥55	2.04 (0.71 - 5.87)	0.19		
Disease type				
Lymphoma	1			
MDS/MPD	2.33 (0.69 - 7.87)	0.17		
Acute leukemia	0.86 (0.24 - 3.03)	0.81		
Disease risk				
Low	1			
High	1.51 (0.40 - 5.69)	0.54		
No. of prior chemotherapy regimens				
≥2	1		1	
<2	5.07 (1.73-14.83)	<0.01	6.08 (2.01–18.41)	<0.01
Stem cell source				
G-PBMC	1			
Bone marrow	0.84 (0.28 - 2.57)	0.77		
Donor				
Unrelated	1		1	
Related	3.48 (0.75-16.08)	0.11	4.21 (0.86–20.49)	0.08
HLA				
Match	1			
Mismatch	0.63 (0.17 - 2.34)	0.49		
TBI				
No	1		1	
Yes	0.17 (0.02 - 1.38)	0.10	0.13 (0.02–1.05)	0.06
ATG				
No	1			
Yes	1.08 (0.35 - 3.32)	0.89		

Association between Donor T Cell Chimerism at Day 30 and RIST Outcome

Graft failure

The median (mean) percentage of donor T cell chimerism at day 30 was 9% (18%) (0%-63%) in 5 patients who experienced graft failure, which was significantly lower than those in the other patients (97% [86%], 15%-100%, $P < .01$), as shown in Figure 3. Day 30 T cell chimerism below 60% was associated with a significantly increased risk of graft failure (Table 3). Among the 5 patients who experienced graft failure, 4 had achieved complete donor chimerism at day 30 when evaluated in the granulocyte fraction.

Whereas 4 of the 5 patients (80%) who experienced graft failure received HLA-mismatched grafts, 23 of the 112 patients (21%) who did not experience graft failure received HLA-mismatched grafts ($P = .01$). In a multivariate analysis, however, neither day 30 T cell chimerism below 60% nor HLA mismatch was associated with an increased risk of graft failure. Among 18 patients with <60% donor T cell chimerism at day 30, HLA mismatch was significantly associated with an increased risk of grafts failure (3 of 3 who received HLA-mismatched graft versus 1 of 15 who received HLA-matched grafts, $P = .005$). In contrast, HLA mismatch was not associated with an increased risk of graft failure in 99 patients with 60% or more donor T cell chimerism at day 30 (1 of 24

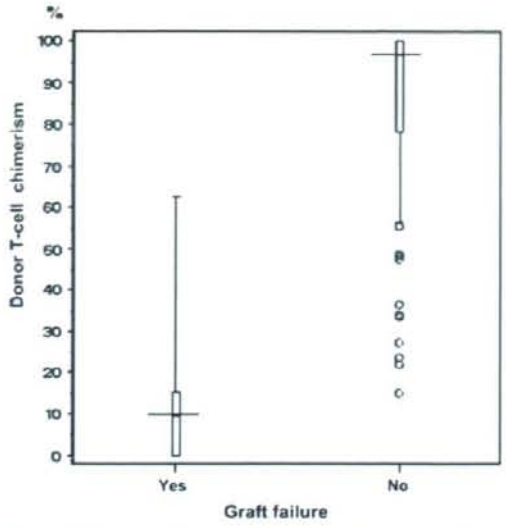

Figure 3. Donor T cell chimerism levels at day 30 in patients with or without subsequent graft failure. Five of the 117 patients (4%) who experienced graft failure had a significantly lower donor T cell chimerism level than the other engrafted patients (n = 112) (donor T cell chimerism, median 9% [range: 0%-63%] versus 97% [range: 15%-100%], respectively) ($p < .01$). Horizontal lines, median; boxes, 25-75 percentile; vertical lines, 10-90 percentile; circles, individual data outside the 10-90 percentile.

who received HLA-mismatched grafts versus 0 of 75 who received HLA-matched grafts, $P = .24$).

GVHD

Grade II-IV aGVHD occurred in 54 patients (46%), and cGVHD occurred in 63 patients (64%). No correlation was found between the kinetics of T cell chimerism and the occurrence of aGVHD or cGVHD, as shown in Table 3.

Table 3. Association between donor T-cell chimerism at day 30 and clinical outcome

Outcome	Total (n=117)	T-cell chimerism at day 30 <60% (n=18)	T-cell chimerism at day 30 ≥60% (n=99)	P
Graft failure				
No	112 (96%)	14 (78%)	98 (99%)	<0.01
Yes	5 (4%)	4 (22%)	1 (1%)	
Acute GVHD				
0-I	64 (55%)	11 (61%)	53 (54%)	
II-IV	53 (45%)	7 (39%)	46 (46%)	0.55
Chronic GVHD*				
No	36 (36%)	7 (50%)	29 (34%)	0.25
Yes	63 (64%)	7 (50%)	56 (66%)	
NRM (at 1 year)	11.0%	11.1%	10.9%	0.26
PD (at 1 year)	27.3%	22.6%	28.1%	0.45
OS (at 1 year)	78.0%	65.7%	80.3%	0.02
EFS (at 1 year)	61.8%	55.6%	62.8%	0.02

GVHD indicates graft-versus-host disease; NRM, non-relapse mortality; PD, relapse or progressive disease; OS, overall survival; EFS, event-free survival;
*Proportion of patients with chronic GVHD was assessed among 99 evaluable patients.

NRM and PD

Nineteen patients experienced NRM, with a 1-year probability of 11% (Table 3). No correlation was found between T cell chimerism at day 30 and the incidence of NRM.

PD was observed in 39 patients, with a 1-year probability of 27% (Table 3). No correlation was found between T cell chimerism at day 30 and the incidence of PD.

Cause of death

Among the 18 patients who had <60% donor T cell chimerism at day 30, 7 (39%) died of PD and 4 (22%) died of NRM, including bacteria sepsis (n = 2), pneumonitis (n = 1), and secondary carcinoma (n = 1). In contrast, among the remaining 99 patients who achieved 60% or more donor T cell chimerism, 21 (21%) died of PD and 15 (15%) died of NRM, including pneumonitis (n = 8), sepsis (n = 3), hemorrhage (n = 1), GVHD (n = 1), cerebral infarction (n = 1), and unknown cause (n = 1).

OS and EFS

Seventy patients (60%) are currently alive at a median follow-up of 1040 days after RIST (range: 153-2535). The 1-year probabilities of OS and EFS among all of the patients were 78% and 62%, respectively. As shown in Figure 4, OS was significantly better in patients who achieved 60% or more donor T cell chimerism at day 30 than in those who did not ($P = .02$). In a Cox proportional hazard model, low T cell donor chimerism (<60%) at day 30 was associated with poor OS (HR: 2.2; 95% CI, 1.1-4.5; $P = .02$) and EFS (HR: 2.0; 95% CI, 1.1-3.8; $P = .02$) adjusted for other significant prognostic factors (Table 4). In addition, high-risk disease and patient age (≥55 years) were associated with an increased risk of poor EFS (HR: 2.4; 95% CI, 1.2-5.0; $P = .02$, HR: 1.8; 95% CI, 1.1-3.0; $P = .03$, respectively) (Table 4).

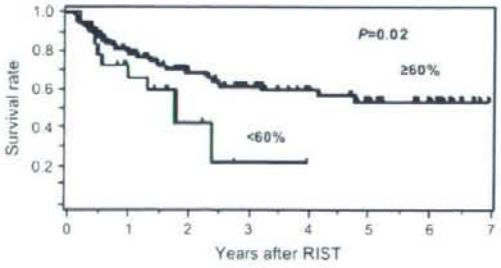

Figure 4. OS stratified according to donor T cell chimerism at day 30. OS was significantly better in patients who achieved 60% or more donor T cell chimerism at day 30 than in those who did not ($P = .02$).

Table 4. Multivariate analysis: factors associated with clinical outcome

Outcome	Variable	Harzard ratio	95% CI	P
OS				
	Donor T-cell chimerism at day 30			
	≥60%	1		
	<60%	2.25	1.13–4.47	0.02
EFS				
	Donor T-cell chimerism at day 30			
	≥60%	1		
	<60%	2.05	1.10–3.81	0.02
	Patients age, years			
	<55	1		
	≥55	1.80	1.07–3.04	0.03
	Disease risk			
	Low	1		
	High	2.44	1.19–5.01	0.02

Clinical factors evaluated in the OS and EFS analyses were donor T-cell chimerism at day 30 (with 60% as a cutoff), patient age at the time of RIST, disease type, disease risk, stem cell source, HLA matching and conditioning.

DISCUSSION

In this retrospective study of RIST with Bu, we showed that 43% of the patients retained mixed donor T cell chimerism (<90%), whereas 92% achieved complete chimerism in the granulocyte fraction, which was consistent with previously published observational studies in RIST [4,10,11,13,21]. Furthermore, we showed that low donor T cell chimerism of <60% at day 30 predicted poor OS and EFS, which suggests that the kinetics of T cell chimerism are important after Bu-containing RIST.

Consistent with other reports, we found that the induction of complete chimerism in T cell fraction after a Bu-containing regimen was rather slow, and granulocyte engraftment was earlier than T cell engraftment compared to patients who received RIC regimens containing a combination of Flu and Mel [10]. When the combination of Cy and Flu was used for RIST conditioning, full donor chimerism was achieved earlier in T cells than in myelogenous cells [1,22]. Interestingly, when alemtuzumab was used in a RIC regimen, 58% retained mixed donor chimerism at day 90 after RIC [13]. This may be because of the fact that alemtuzumab remained in the peripheral circulation long after RIST, which suppressed not only host but also donor lymphocytes. Based on these reports, we suspected that a Cy-containing regimen suppresses host granulocytes less intensely than a Bu-containing regimen, whereas a Mel-containing regimen suppresses host lymphocytes more intensely than a Bu-containing regimen.

The only significant variable associated with a lower level of donor T cell chimerism at day 30 was having received <2 regimens of chemotherapy pretransplant in our results. This result was consistent with previous reports [4,10]. When a patient is treated with RIST, such as our low-dose Bu-containing regimen, prior chemotherapy may facilitate the achievement of higher levels of donor T cell chimerism by decreasing the recipient immunocompetence.

In previous reports there has been some controversy regarding whether there are any differences in the levels of donor T cell chimerism after RIST with or without low-dose TBI [11,13]. In our study with Bu-containing regimens, regimens that included additional low-dose TBI tended to offer higher donor T cell chimerism in a multivariate analysis. However, there was no correlation between ATG-conditioning regimens and donor T cell chimerism at day 30, which was consistent with other regimens [13]. This might be because of the lower dose of ATG (Fresenius, 5-10 mg/kg) in our regimens compared to other studies that utilized the same ATG preparation (Fresenius, 40-90 mg/kg) [23,24]. Alternatively, this might be simply because of the small number of patients who received ATG in our study.

In previous reports, recipients of G-PBMC after RIST showed higher percentages of donor T cell chimerism than those who received bone marrow [4,25], which was not confirmed in our study. With regard to regimens that include Bu, no previous large-scale study has analyzed the correlation between the type of stem cell source and T cell engraftment. When low-dose Bu is contained in the RIC regimen, the stem cell source may no longer influence the level of T cell chimerism. Alternatively, this may be because of the fact that most of the bone marrow recipients in our study also received an additional 2-4 Gy TBI. There was a trend toward a decreased risk of low donor T cell chimerism in recipients of unrelated grafts, although the difference was not significant. We speculate that a lower probability of low donor T cell chimerism might be because of the addition of low dose TBI for patients who underwent unrelated HSCT.

Patients who received G-PBMC showed an increase in TNC and $CD3^+$ T cells that paralleled an increase in donor T cell chimerism at day 30 after RIST in our study. The same relationship was observed between $CD34^+$ cell contents and granulocyte chimerism. Baron et al. [26] reported that higher numbers of donor T cells and $CD34^+$ progenitor cells in the grafts were associated with higher levels of day 28 donor T cell chimerism. Similarly, Carvallo et al. [22] reported that higher levels of $CD34^+$ progenitor cells in the grafts were associated with higher levels of donor myeloid chimerism early after RIST.

In this study, donor T cell chimerism levels of below 60% early after RIST were significantly associated with an increased risk of graft failure. It has been reported that patients with <50% donor T cell chimerism early after nonmyeloablative HSCT were more likely to have graft failure than those with more than

50% donor T cell chimerism [4]. After Bu-containing RIC, Mattsson et al. [21] reported that 2 of the 8 patients who had >50% recipient T cells on day 28 had graft failure or rejection, whereas this was not seen in any of the 22 patients with <50% recipient T cells. Lower donor natural killer NK-cell chimerism after Bu-containing RIST was associated with an increased risk of graft failure [4,27]. Although significant associations of low donor T cell chimerism and HLA mismatch with graft failure disappeared in our multivariate model, our data suggested that HLA mismatch was an important predictor of graft failure only in patients with <60% donor T cell chimerism at day 30. The current study demonstrated that patients at high risk of graft failure could be identified by chimerism analysis at day 30 in T cell fractions, but not in granulocyte fractions, and that chimerism analysis at day 30 after Bu-containing RIST may allow early interventions aimed at reversing graft failure.

Our results suggest that low donor T cell chimerism of <60% at day 30 may predict a poor outcome, although levels of donor T cell chimerism were not associated with NRM PD. In our study, the levels of donor T cell chimerism were not associated with aGVHD or cGVHD, although some reports have stated that donor T cell chimerism was associated with the risk of GVHD [1,4,13,19,28]. It is still controversial whether or not achievement of complete donor T cell chimerism is needed to improve OS and reduce the relapse risk in patients who undergo RIST. Baron et al. [9] suggested that the assessment of donor chimerism levels helps to identify patients who are at higher risk of relapse after nonmyeloablative HSCT. High donor chimerism levels among immune competent cells including T cells and NK cells might be a surrogate for a high graft-versus-tumor effect, and a fractionated chimerism analysis may be useful for detecting and quantifying minimal residual disease after RIST. In a small case series of Bu-containing RIST, mixed donor chimerism was associated with an increased risk of relapse and a worse prognosis [12,29]. In contrast, among patients who underwent RIST that contained Flu, Bu, and alemtuzumab, those who showed mixed donor chimerism beyond day 100 were associated with an improved OS and a lower incidence of GVHD and NRM, without any effect on the relapse risk [13]. Further studies are needed to determine whether the achievement of complete chimerism after RIST is beneficial with less risk of PD and/or more risk of NRM.

In conclusion, within the limitations of a retrospective study, we found that the percentage of donor chimerism was significantly higher in granulocyte than T cell fraction throughout the entire course after Bu-containing RIST. Low donor T cell chimerism of <60% at day 30 may predict a poor outcome, and a prospective study to examine the value of early intervention based on chimerism data is warranted.

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