Regular manuscript

A comparison of oral mucositis in allogeneic hematopoietic stem cell transplantation between conventional and reduced-intensity regimens

Haruhiko Kashiwazaki[1], Takae Matsushita[1], Junichi Sugita[2], Akio Shigematsu[2], Kumiko Kasashi[3], Yutaka Yamazaki[4], Takashi Kanehira[5], Takeshi Kondo[2], Tomoyuki Endo[2], Junji Tanaka[2], Satoshi Hashino[2], Mitsufumi Nishio[2], Masahiro Imamura[2], Yoshimasa Kitagawa[4] and Nobuo Inoue[1]

[1] Gerodontology, Division of Oral Health Science, Hokkaido University Graduate School of Dental Medicine, Kita-13 Nishi-7, Kita-ku, Sapporo, 060-8586, Japan.

[2] Stem Cell Transplantation Center, Hokkaido University Hospital, Kita-14 Nishi-5, Kita-ku, Sapporo, 060-8648, Japan

[3] Division of Pharmacy, Hokkaido University Hospital, Kita-14 Nishi-5, Kita-ku, Sapporo, 060-8648, Japan

[4] Oral Diagnosis and Oral Medicine, Division of Oral Pathobiological Science, Hokkaido University Graduate School of Dental Medicine, Kita-13 Nishi-7, Kita-ku, Sapporo, 060-8586,

Japan.

[5] Preventive Dentistry, Division of Oral Health Science, Hokkaido University Graduate School of Dental Medicine, Kita-13 Nishi-7, Kita-ku, Sapporo, 060-8586, Japan.

Running title: A comparison of oral mucositis between CST and RIST

Address correspondence to Haruhiko Kashiwazaki

Gerodontology, Division of Oral Health Science, Hokkaido University Graduate School of Dental Medicine. Kita-13 Nishi-7, Kita-ku, Sapporo, Hokkaido, 060-8586, Japan.

Telephone; 81-11-706-4321, FAX; 81-11-706-4582

E-mail; kashi@den.hokudai.ac.jp

Abstract

Goals of work Severe oral mucositis developed in allogeneic hematopoietic stem cell transplantation (HSCT) accompanies intolerable pain and risk for systemic bacteremia infection. Conventional stem cell transplantation (CST) and reduced-intensity regimens for allogeneic HSCT (RIST) may differently affect the occurrence and severity of oral mucositis. Here, we comparatively examined oral mucositis in patients undergoing CST and that in RIST patients to search for measures to alleviate oral mucositis.

Patients and methods We retrospectively analyzed the data of 130 consecutive patients undergoing HSCT (conventional, 60; RIST, 70). Oral mucositis was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0. We also investigated risk factors for severe oral mucositis in each regimen.

Main results The incidence of oral mucositis was not significantly different between RIST and CST patients. Use of opioid analgesics to control pain due to oral mucositis was significantly less in patients undergoing RIST compared with those receiving CST. The risk factors for severe oral mucositis, determined by univariate and multivariate analyses, were “younger age (< 40) ” in CST, and “longer duration of neutropenia (≥ 14 days) ” in RIST .

Conclusions Although the incidences of oral mucositis were almost the same, the need for opioid analgesics and the risk factors for severe oral mucositis differed between CST and RIST patients.

Keywords: Hematopoietic stem cell transplantation, Oral mucositis, Reduced-intensity regimens

Introduction

Oral mucositis is one of the most common complications associated with allogeneic hematopoietic stem cell transplantation (HSCT). It was seen in 60-90 % of patients who had received stem cell transplantation [1, 2, 3]. The oral mucositis in HSCT accompanies so severe pain that it can lead to anorexia and dehydration, and a large population of patients with severe oral mucositis require total parenteral nutrition and opioid analgesics [4]. Severe oral mucositis is also associated with worse clinical and economic outcomes, especially systemic bacteremia infection [5].

Recently, reduced-intensity conditioning regimens for allogeneic HSCT (RIST) have been developed for patients who are considered unsuitable for conventional stem cell transplantation

(CST) because of advanced age or medical contraindications [6, 7]. The conditioning regimens typically include a purine analog, such as fludarabine (FLU), an alkylating agent, or low-dose total body irradiation (TBI). We need to consider the differences between CST and RIST protocols in the effects on oral mucositis, because such a variety of RIST protocols have been developed and their toxicity profiles can make differences in the degree of immunosuppression or myeloablation [2, 3, 8, 9, 10].

The present study was a retrospective analysis to compare oral mucositis in 70 consecutive patients who had received RIST, which mainly consisted of FLU, busulfan (BU) and TBI, with that in 60 patients who had received CST during the same period. We also investigated risk factors for severe oral mucositis in each regimen.

Materials and methods

Patients

We retrospectively analyzed the data of 130 consecutive patients undergoing HSCT between March 2006 and December 2009 at Stem Cell Transplantation Center of Hokkaido University Hospital (M, 67; F, 63; 47.6±15.2 years). CST and RIST were administered to 60 (M, 28; F, 32)

and 70 (M, 39; F, 31) patients, respectively. Characteristics of the patients and transplantation are shown in Table 1.

The Ethical Committee of Hokkaido University Hospital approved this study. Informed consent was obtained from each patient.

Conditioning regimens

Most of the conventional conditioning regimens consisted of TBI (12 Gy in six fractions) plus cyclophosphamide (60 mg/kg once daily i.v. for 2 days, total dose of 120 mg/kg) ± VP-16 (15 mg/kg once daily i.v. for 2 days, total dose of 30 mg/kg) [11, 12], and most of the reduced-intensity conditioning regimens consisted of FLU (30 mg/m^2 once daily i.v. for 6 days, total dose of 180 mg/m^2) plus oral BU (4 mg/kg p.o. in divided doses daily for 2 days, total dose of 8 mg/kg) or intravenous BU (3.2 mg/kg i.v. in divided doses daily for 2 days, total dose of 6.4 mg/kg) plus low-dose TBI (4 Gy in two fractions). Cyclosporine A (CsA, 3 mg/kg) or tacrolimus (FK, 0.03 mg/kg) and short-course methotrexate (MTX) were used for graft-versus-host disease (GVHD) prophylaxis. MTX was given at a dose of 15 mg/m^2 or 10 mg/m^2 on day 1, and 10 mg/m^2 or 7 mg/m^2 on day 3 and day 6.

Assessment of oral mucositis

Oral mucositis was graded as follows according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0[13]:

Grade 1: Erythema of the mucosa

Grade 2: Patchy ulcerations or pseudomembranes

Grade 3: Confluent ulcerations or pseudomembranes, bleeding in response to minor trauma

Grade 4: Tissue necrosis, significant spontaneous bleeding, life-threatening consequences

Grade 5: Death

Grading was done daily by nurses under the instruction of dentists, and the consistency of assessments was double-checked by the dentists during their rounds at least once per week. Severe oral mucositis was defined as grade 3-4.

Assessment of use of opioid analgesics to control pain due to oral mucositis

Use of opioid analgesics to control pain due to oral mucositis was evaluated for all patients, and frequencies of its use were compared among HSCT types.

Oral management

All subjects were referred to dentists, and necessary dental treatment was completed before HSCT. Namely at least two dentists examined the patients' oral health, including oral hygiene and potential causes of infections in the oral region by radiographic survey and by clinical examination of the hard and soft tissues; and dental problems that might cause infection, such as periapical and marginal periodontitis, dental caries, and semi-impacted or impacted teeth, were treated by surgical procedures as much as possible until HSCT. All subjects received instruction regarding self-management of oral hygiene: tooth brushing after every meal and before going to bed, and oral rinsing with normal saline solution every 3 h during the day. Dentists and hygienists weekly performed an oral examination on the patients and monitored their compliance in a clean room.

Statistical analysis

Univariate analyses were performed using the chi-square test and Fisher's exact test, as appropriate. The factors with a P-Value of 0.05 or less in the univariate analyses were included

in the multivariate analysis. Multivariate logistic regression models were used to analyze the influence of selected variables on the risk for severe oral mucositis. For most of the statistical analysis, SPSS 14.0 for Windows (SPSS, Chicago, IL, USA) was used. The P value was set to <0.05 as significant.

Results

Patients and transplantation characteristics

Characteristics of the patients and transplantations are shown in Table 1. Median age, underlying disease, and disease status at transplantation were significantly different between CST and RIST patients. Other parameters such as sex, TBI, GVHD prophylaxis were not different between CST patients and RIST patients.

Incidences and severity of oral mucositis in CST and RIST

As shown in Table 2, the incidences of oral mucositis (>grade 1) were not significantly different between CST and RIST patients according to the NCI CTCAE; the frequencies were 83.3% (50/60) and 75.7% (53/70), respectively. Severe mucositis (grades 3 and 4) was observed

in 33.3% (20/60) of CST patients, and 32.9% (23/70) of RIST patients, which showed no significant difference. However, a significantly lower percentage of patients undergoing RIST (32.2%) required opioid analgesics to control pain due to oral mucositis compared with those undergoing CST (60.4%) as shown in Fig. 1 ($P = 0.0028$). .

Univariate and multivariate analyses for severe oral mucositis in CST and RIST

To identify risk factors for severe mucositis in CST and RIST, univariate and multivariate analyses were performed in each regimen. The results in CST are summarized in Table 3. The univariate analysis showed that “younger age (< 40) ”, “VP-16 regimen”, and “longer duration of neutropenia (≥ 14 days) ” were significantly associated with a high incidence of severe oral mucositis in CST. Of those, only “younger age (< 40) ” remained significant in multivariate analysis (odds ratio, 5.6; 95%CI, 1.9-16.5; $P<0.05$). With regards to RIST, the results are summarized in Table 4. Only “longer duration of neutropenia (≥ 14 days) ” was significantly associated with sever oral mucositis in RIST in both univariate and multivariate analyses (odds ratio, 12.4; 95%CI, 1.4-109; $P=0.02$).

Discussion

The results of this study are summarized as follows: (1) The incidence of oral mucositis was almost the same between CST and RIST patients; (2) Use of opioid analgesics to control pain due to oral mucositis was significantly less in patients undergoing RIST compared with those receiving CST; (3) Univariate and multivariate analyses revealed that the risk factors for severe oral mucositis were “younger age (< 40) ” in CST, and “longer duration of neutropenia (≥ 14 days) ” in RIST.

While Takahashi et al. reported that the severity of oral mucositis was reduced in RIST patients compared with CST patients [1], no significant difference was observed in the incidence of severe oral mucositis between patients who received CST and those who received RIST in our study. Several studies reported that severe oral mucositis was correlated with TBI [14, 15]. One of the reasons for this “no significant difference” in our study might be associated with the use of TBI in most RIST patients. The patients who received our RIST regimen including TBI tended to have a longer neutropenic period and more mucosal injury than those in patients who received other RIST regimens [16, 17]. Furthermore, both CST and RIST regimens in the present cases used the same doses of MTX on days 1, 3, and 6 as GVHD prophylaxis.

Severe oral mucositis causes intolerable pain, which is often controlled by administration of opioid analgesics. As recent trends in cancer pain control recommend the appropriate use of narcotics to minimize pain, the use of opioid analgesics in RIST patients was significantly less compared with that in CST patients. As RIST tends to dispense with narcotics, their major side effects such as ileus could be also avoided.

In multivariate analysis, “younger age (< 40) ” was significantly associated with severe oral mucositis in CIST patients (odds ratio, 5.6; 95%CI, 1.9-16.5; $P < 0.05$). This confirms the report of Vagliano where severe oral mucositis was observed more in adult patients than in the elderly patients [18]. Sonis reported that young patients, who typically have a higher proliferating fraction of basal cells, are three times more likely to develop mucositis than elderly adults in whom the basal cell proliferation is slow [19]. In RIST patients, “duration of neutropenia (more than 14 days) ” was significantly associated with severe oral mucositis in multivariate analysis (OR = 12.4, 95%CI 1.4-109, P = 0.024). Once patients developed oral mucositis, it continued to worsen during neutropenia. In those patients, it is important to prevent the development of oral mucositis.

Although our analysis has limitations due to its retrospective nature and the small sample size,

our results showed that the need for opioid analgesics and the risk factors for severe oral mucositis differed between CST and RIST patients. Further prospective controlled studies are needed to assess the differences between CST and RIST for better management of oral mucositis in HSCT patients.

Acknowledgements

We thank Ms M Yanome for help in preparing the manuscript.

Financial disclosure: This work was supported in part by Grant-in-Aid for Scientific Research (C) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

References

1. Takahashi K, Soga Y, Murayama Y, Udagawa M, Nishimoto H, Sugiura Y, Maeda Y, Tanimoto M, Takashiba S (2010) Oral mucositis in patients receiving reduced-intensity regimens for allogeneic hematopoietic cell transplantation: comparison with conventional regimen. Support care in cancer; 18: 115-119

2. Vokurka S, Steinerova K, Karas M, Koza V (2009) Characteristics and risk factors of oral mucositis after allogeneic stem cell transplantation with FLU/MEL conditioning regimen in context with BU/CY2. Bone marrow transplant 44: 601-605

3. Langner S, Staber P, Schub N, Gramatzki M, Grothe W, Behre G, et al. (2008) Palifermin reduces Incidence and severity of oral mucositis in allogeneic stem-cell transplant recipients. Bone marrow transplant 42: 275-279

4. Sonis ST, Elting LS, Keefe D, Peterson DE, Schubert M, Hauer-Jensen M, et al. (2004) Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. Cancer 100: 1995-2025

5. Sonis ST, Oster G, Fuchs H, Bellm L, Bradford WZ, Edelsberg J, et al. (2001) Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. Journal of clinical oncology 19: 2201-2005

6. Giralt S, Estey E, Albitar M, et al. (1997) Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: harnessing graft-versus-leukemia without myeloablative therapy. Blood 89: 4531-4536

7. Slavin S, Nagler A, Naparstek E, et al. (1998) Nonmyeloablative stem cell transplantation

and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. Blood 91:756-763

8. Mohty M, Faucher C, Vey N, et al. (2000) High rate of secondary viral and bacterial infections in patients undergoing allogeneic bone marrow mini-transplantation. Bone Marrow Transplant 26:251-255

9. Mohty M, Jacot W, Faucher C, et al. (2003) Infectious complications following allogeneic HLA-identical sibling transplantation with antithymocyte globulin-based reduced intensity preparative regimen. Leukemia 17:2168-2177

10. Toubai T, Tanaka J, Mori A, et al. (2004) Efficacy of etoposide, cyclophosphamide, and total body irradiation in allogeneic bone marrow transplantation for adult patients with hematological malignancies. Clin Transplant 18: 552-557

11. Shigematsu A, Yamamoto S, Sugita J, Kondo T, et al. (2010) Increased risk of bacterial infection after engraftment in patients treated with allogeneic bone marrow transplantation following reduced-intensity conditioning regimen. Transplant Infection Disease, in press

12. Shigematsu A, Kondo T, Yamamoto S, et al. (2008) Excellent outcome of allogeneic

hematopoietic stem cell transplantation using a conditioning regimen with medium-dose VP-16, cyclophosphamide and total-body irradiation for adult patients with acute lymphoblastic leukemia. Biol Blood Marrow Transplant 14: 568-575

13. U.S. National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (CTCAE).

14. Gori E, Arpinati M, Bonifazi F, Errico A, Mega A, Alberani F, et al. (2007) Cryotherapy in the prevention of oral mucositis in patients receiving low-dose methotrexate following myeloablative allogeneic stem cell transplantation: a prospective randomized study of the Gruppo Italiano Trapianto di Midollo Osseo nurses group. Bone marrow transplant 39: 347-352

15. Robien K, Schubert M, Bruemmer B, Lloid M, Potter J, Ulrich C (2004) Predictors of oral mucositis in patients receiving hematopoietic cell transplants for chronic myelogenous leukemia. Journal of Clinical Oncology 22: 1268

16. Junghanss C, Marr KA, Carter RA, et al. (2002) Incidence and outcome of bacterial and fungal infections following nonmyeloablative compared with myeloablative allogeneic hematopoietic stem cell transplantation: a matched control study. Biol Blood Marrow

Transplant 8: 512-525

17. Hori A, Kami M, Kim SW, et al. (2004) Development of early neutropenic fever, with or without bacterial infection, is still a significant complication after reduced-intensity stem cell transplantation. Biol Blood Marrow Transplant 10: 65-72

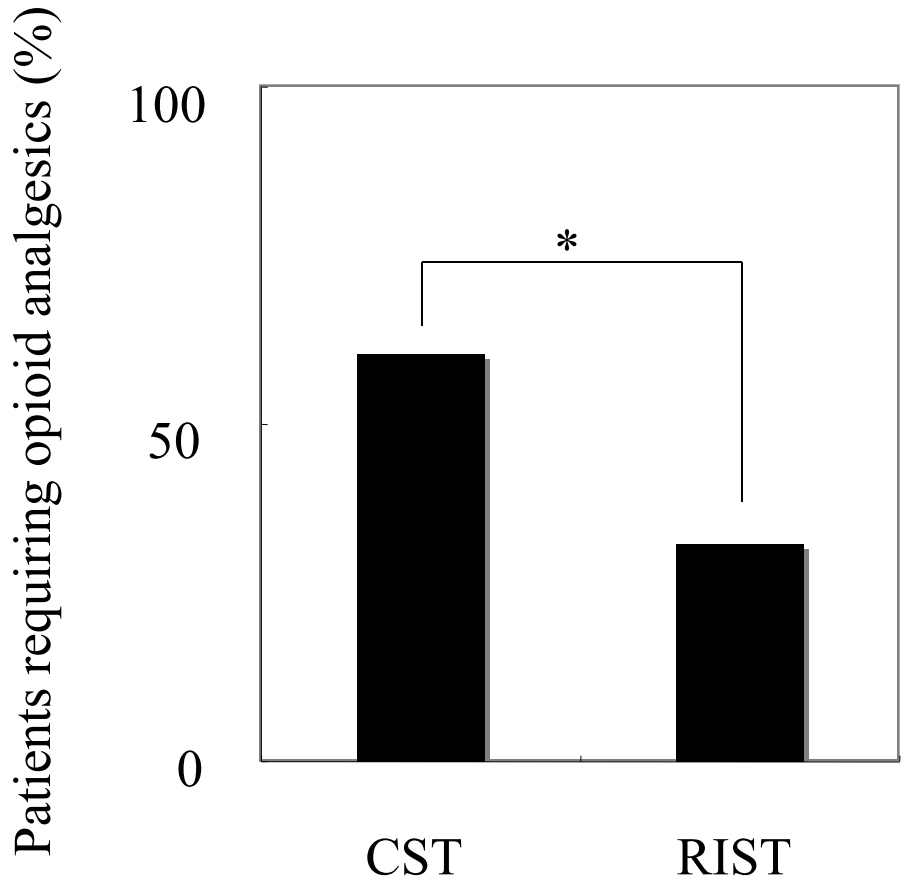
18. Vagliano L, Feraut C, et al. (2010) Incidence and severity of oral mucositis in patients undergoing haematopoietic SCT (HSCT) –results of a multicentre study. Bone marrow transplant : 1-6

19. Sonis ST (1998) Mucositis as a biological process: a new hypothesis for the development of chemotherapy-induced stomatotoxicity. Oral Oncol 34:39–43

Figure legend

Figure 1 Use of opioid analgesics to control pain due to oral mucositis in CST and RIST. Difference in frequencies of patients requiring opioid analgesics between CST and RIST were analyzed by the chi-square test.

Fig.1



* P = 0.0028

Table 1 Patients and transplantation characteristics

		CST (n=60)	%	RIST (n=70)	%	P-value
Age, median (range)		36 (17-54)		55 (17-68)		< 0.01
Patient sex	Male	28	46.70%	39	55.70%	0.3
Underlying disease,	ALL	23	38.30%	3	4.30%	< 0.01
	AML	28	46.70%	22	31.40%	
	MDS	3	5.00%	7	10.00%	
	CML	4	6.60%	2	2.90%	
	ML	1	1.70%	24	34.30%	
	ATLL	1	1.70%	1	1.40%	
	MM	0	0.00%	5	7.10%	
	others	0	0	6	8.60%	
Disease status at transplantatio	CR	41	68.30%	27	38.60%	< 0.01
	non CR	15	25.00%	31	44.30%	
	Chronic phase/stable disease	4	6.70%	12	17.10%	
Conditioning regimen	Fludarabine/ Busulfan	0	0.00%	62	88.60%	-
	Fludarabine/ Melphalan	0	0.00%	5	7.10%	
	CY/ VP-16/ TBI	27	45.00%	0	0.00%	
	CY/ TBI	23	38.30%	0	0.00%	
	Others	10	16.70%	3	4.30%	
Total Body Irradiation		57	95%	64	91.40%	0.6
GVHD prophylaxis	Cyclosporine A+ methotrexate	23	38.30%	27	38.60%	0.9
	Tacrolimus+ methotrexate	37	61.60%	43	61.40%	
Stem cell source	related BM	6	10%	8	11%	0.5
	related PBSC	8	13.30%	5	7.10%	
	unrelated BM	37	61.70%	47	67.20%	
	unrelated CB	9	15.00%	10	14.30%	

Abbreviations: CST, conventional stem cell transplantation; RIST, reduced-intensity stem cell transplantation; ALL, acute lymphoblastic leul AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; CML, chronic myelogenous leukemia; ML, malignant lymphoma; ATLL, adult T-cell leukemia/lymphoma; MM, multiple myeloma; CR, complete remission; CY, cyclophosphamide; VP16, etoposide; TBI, total body irradiation; GVHD, graft-versus-host disease; BM, bone marrow; PBSC, peripheral blood stem cell; CB, cord blood.

Table 2 Incidence of oral mucositis

	Grades of oral mucositis				
	0	1	2	3	4
Total (n=130)	27	30	30	42	1
%	20.80%	23.10%	23.10%	32.30%	0.70%
CST (n=60)	10	15	15	19	1
%	16.70%	25.00%	25.00%	31.70%	1.70%
RIST (n=70)	17	15	15	23	0
%	24.30%	21.40%	21.40%	32.90%	0%

Table 3 Univariate and multivariate analysis for severe mucositis in CST (n=60)

Variables		Severe mucositis				Univariate	Multivariate	
		Yes	%	No	%	P-value	Odds ratio (95%CI)	P-value
Age								
	<40	16	44.40%	20	55.60%	< 0.05	5.6 (1.9-16.5)	< 0.05
	≥40	4	16.70%	20	83.30%			
	<50	19	33.30%	38	66.70%	0.53		
	≥50	1	33.30%	2	66.70%			
Sex								
	Male	8	28.60%	20	71.40%	0.65		
	Female	12	37.50%	20	62.50%			
Disease status at transplantation								
	CR	14	34.10%	27	65.90%	0.93		
	non CR	6	40.00%	9	60.00%			
Conditioning regimen								
	VP/CY/TBI	13	48.10%	14	51.60%	< 0.05		
	non VP/CY/TBI	7	31.20%	26	78.80%			
GVHD prophylaxis								
	CsA+MTX	8	34.80%	15	65.20%	0.93		
	FK+MTX	12	32.40%	25	67.60%			
Dose of MTX								
	15 10 10	12	32.40%	25	67.60%	0.81		
	10 10 10	5	31.20%	11	68.80%			
	10 7 7	1	33.30%	2	66.70%			
Stem cell source								
	related BM	3	50.00%	3	50.00%	0.93		
	related PBSC	2	25.00%	6	75.00%			
	unrelated BM	12	32.40%	25	67.60%			
	unrelated CB	3	33.30%	6	66.70%			
Duration of neutropenia (<500/ml)								
	≥21days	9	45.00%	11	55.00%	0.29		
	<21days	11	27.50%	29	72.50%			
	≥14days	20	39.20%	31	60.80%	< 0.05		
	<14days	0	0%	9	100%			

CI indicates confidence interval; other abbreviations, see Table 1

Table 4 Univariate and multivariate analysis for severe mucositis in RIST (n=70)

Variables		Severe mucositis				Univariate	Multivariate	
		Yes	%	No	%	P-value	Odds ratio (95%CI)	P-value
Age								
	<40	2	28.60%	5	71.40%	0.78		
	≥40	21	33.30%	42	66.70%			
	<50	4	21.10%	15	78.90%	0.32		
	≥50	19	37.30%	32	62.70%			
	<60	17	30.90%	38	69.10%	0.72		
	≥60	6	40.00%	9	60.00%			
Sex								
	Male	10	25.60%	29	74.40%	0.15		
	Female	13	41.90%	18	58.10%			
Disease status at transplantation								
	CR	10	37.00%	17	63.00%	0.7		
	non CR	10	32.30%	21	67.70%			
Conditioning regimen								
	FLU/BU	21	33.90%	41	66.10%	0.88		
	FLU/LPAM	1	20.00%	4	80.00%			
Total Body Irradiation								
	Yes	21	32.80%	43	67.20%	0.67		
	No	2	33.30%	4	66.70%			
GVHD prophylaxis								
	CsA+MTX	7	25.90%	20	74.10%	0.47		
	FK+MTX	16	37.20%	27	62.80%			
Dose of MTX								
	15 10 10	6	17.10%	29	82.90%	0.06		
	10 10 10	13	52.00%	12	48.00%			
	10 7 7	0	0%	2	100%			
Stem cell source								
	related BM	0	0%	8	100%	0.98		
	related PBSC	2	40.00%	3	60.00%			
	unrelated BM	16	34.00%	31	66.00%			
	unrelated CB	5	50.00%	5	50.00%			
Duration of neutropenia (<500/ml)								
	≥21days	11	57.90%	8	42.10%	0.015		
	<21days	12	23.50%	39	76.50%			
	≥14days	21	46.70%	24	53.30%	0.0024	12.4 (1.4-109)	0.024
	<14days	2	8.00%	23	92.00%			