研究項目： 非血縁者間末梢血幹細胞移植法の臨床試験体制確立に関する研究
資料

【資料　1】

UR-PBSCTの将来

UR-PBSCTの臨床試験に関する私見

UR-PBSCTにおける臨床試験について

1. GVHD予防法を筆頭に、移植前処置法など適切な移植方法がわからない状態で、これらの移植方法を統一した多施設共同臨床試験の実施は難しい。
2. 経験の豊富なUR-BMTと経験の少ないUR-PBSCTを適切に比較するためには、UR-PBSCTについてもある程度の臨床経験と移植方法の至適化が必要である。

UR-PBSCTにおける臨床試験について

1. したがってUR-PBSCTの多施設共同臨床試験を行うのであれば、単群でGVHD予防法などの至適化を目指した臨床試験を計画すべきである。
2. しかし、様々な因子を調整しなければならない現状で、画一的な用量設定試験の実施は困難であり、おそらくLearning curveによる移植成績の改善を妨げる。
3. かといって、各施設の最良にゆだねた診療のretrospective studyには限界がある。(必要な情報を収集できない。)

UR-PBSCTにおける臨床試験について

1. そこで、移植前に前処置、GVHD予防法などの移植方法について、いくつかの選択肢を設定して担当医の裁量で選択できるようにして、その選択理由とともに登録する方式によって、より精度の高い解析ができるような臨床試験を実施する。

患者側の希望
□PBSCTのみ（理由：　　）
□BMT/PBSCTいずれでも可
ドナー側の希望
□PBSCTのみ（理由：　　）
□BMT/PBSCTいずれでも可

移植前処置
□CY-TBI
□BU-CY
□FLU-MEL　□FLU-MEL-TBI (　Gy)
□FLU-BU　□FLU-BU-TBI (　Gy)
□FLU-CY　□FLU-CY-TBI (　GY)
□その他（　　）

前処置選択理由
□施設の標準前処置
□高齢のため
□臓器障害(　　障害)のため

GVHD予防法 (予防として投与を予定しているものをすべて選択)
☐CSA ☐TAC ☐MTX
☐MMF ☐PSL

CSA、TACを用いる場合、その投与方法、開始用量、目標血中濃度
開始用量 _____mg/kg
☐持続静注 (目標血中濃度 ng/ml)
☐1日2回点滴静注 (目標血中濃度 ng/ml ☐トラフ・☐投与__時間後)
☐1日1回点滴静注 (目標血中濃度 ng/ml ☐トラフ・☐投与__時間後)

MTXを用いる場合、その投与日と投与量
☐15 mg/m^2 (day 1) + 10 mg/m^2 (day 3,6,11)
☐10 mg/m^2 (day 1) + 7 mg/m^2 (day 3,6,11)
☐15 mg/m^2 (day 1) + 10 mg/m^2 (day 3,6)
☐10 mg/m^2 (day 1) + 7 mg/m^2 (day 3,6)
☐その他 (__mg/m^2 (day ___) + (__mg/m^2 (day ___)

MMFを用いる場合、その投与日と投与量
☐ (_____mg/m^2 (day ___～___)

CSAの減量開始予定日(GVHDの発症がない場合)
移植後 _____日
CSAの投与終了予定日(GVHDの発症がない場合)
移植後 _____日

今後、明らかにしていきたいこと

1. 前方視的情報収集
↓
2. UR-PBSCTの移植方法の至適化
↓
3. UR-BMTとの比較 (RCT?)
生存率のみならず、QOL、医療費についても。

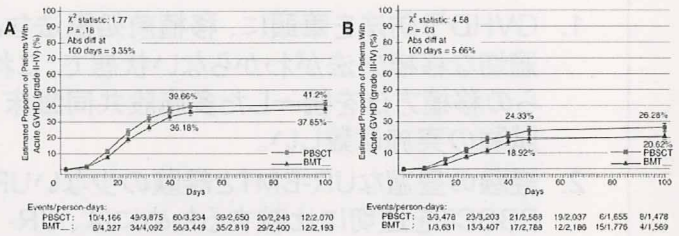
血縁者間PBSCTvsBMT

	Event/Patients PBSCT	BMT	Statistics (O – E)	Var.	OR and 95% CI (PBSCT : BMT)	Odds Redn. (SD)
Survival	207/544	234/563	−13.5	99.6		13% (9); 2P = .2
Disease-free survival	223/544	270/564	−24.0	109.9		20% (9); 2P = .02
Relapse	96/542	132/558	−18.5	53.5		29% (12); 2P = .01
Relapse mortality	53/544	79/563	−13.2	31.5		34% (15); 2P = .02
Nonrelapse mortality	154/544	155/563	−0.4	71.8		1% (12); 2P = 1.0
aGVHD (II-IV)	227/520	213/541	12.7	95.3		−14% (11); 2P = .2
cGVHD (extensive)	189/483	122/490	38.8	61.1		−89% (18); 2P < .0001
Neutrophil engraftment	516/530	528/555	−98.4	83.2		69% (6); 2P < .0001
Platelet engraftment	471/532	476/554	−86.7	131.5		48% (6); 2P < .0001

0.1 1.0 10.0
PBSCT Better BMT Better

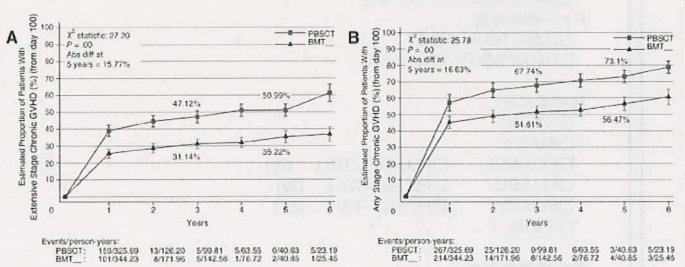
J Clin Oncol 23:5074-5087.

血縁者間PBSCTvsBMT



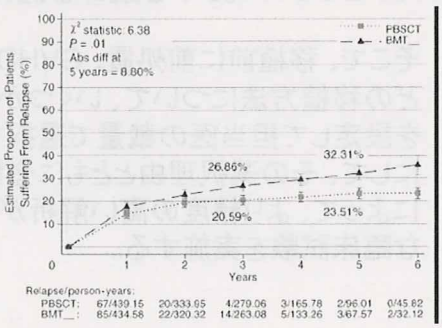
J Clin Oncol 23:5074-5087.

血縁者間PBSCTvsBMT



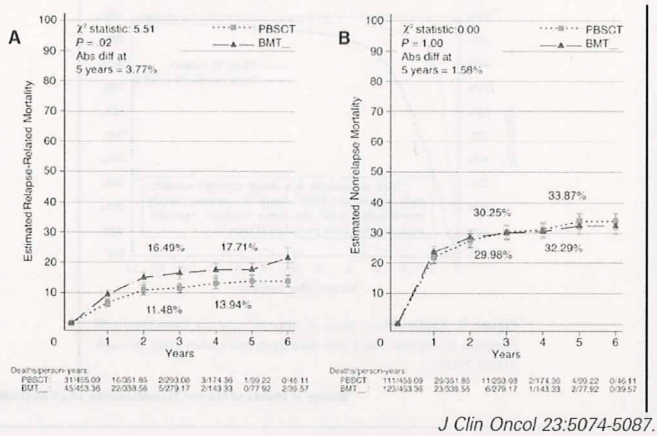
J Clin Oncol 23:5074-5087.

血縁者間PBSCTvsBMT



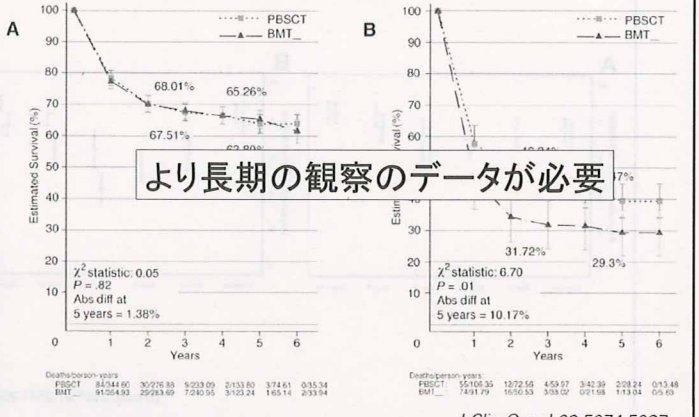
J Clin Oncol 23:5074-5087.

血縁者間PBSCTvsBMT



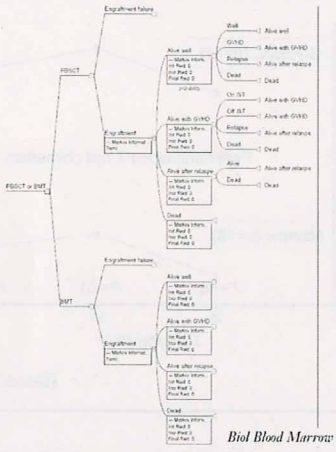
J Clin Oncol 23:5074-5087.

血縁者間PBSCTvsBMT



J Clin Oncol 23:5074-5087.

血縁者間PBSCTvsBMT 決断分析



Biol Blood Marrow Transplant 15: 1415-1421 (2009)

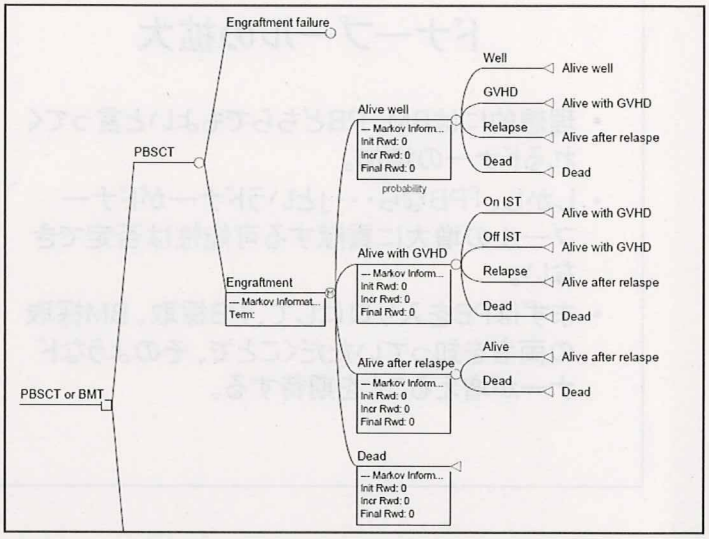
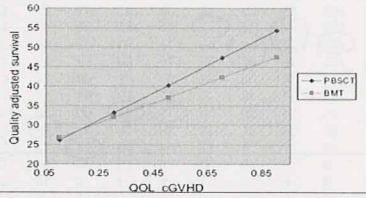


Table 1. Probability Estimates with Data Sources

Probability	Data Source	Estimate (PBSCT)	Adjusted for Month Cycle Length (PBSCT)	Estimate (BMT)	Adjusted for Month Cycle Length (BMT)	Range for Sensitivity Analyses
Engraftment failure	Meta-analysis	0.03	0.03	0.05	0.05	0.01-0.08
aGVHD	Meta-analysis	0.412	0.137	0.379	0.126	0.12-0.8
Death from aGVHD	Meta-analysis	RRI*earlyTRM	RRI*earlyTRM	RRI*earlyTRM	RRI*earlyTRM	RRI: 1-5
Relapse, year 1	Meta-analysis	0.153	0.01275	0.156	0.013	0-0.3
Relapse, year 2	Meta-analysis	0.06	0.005	0.069	0.0058	0.03-0.12
Relapse, year 3	Meta-analysis	0.0143	0.0012	0.053	0.0044	0.005-0.08
Treatment success aGVHD	Literature	0.4	0.067	0.4	0.067	0.25-0.75
cGVHD through year 1	Meta-analysis	0.59	0.098	0.45	0.075	0.05-0.7
cGVHD beyond	Meta-analysis	0.09	0.0075	0.08	0.0067	0.05-0.15
cGVHD complications through year 1	Meta-analysis	0.4	0.067	0.25	0.042	0.1-0.5
cGVHD complications beyond	Meta-analysis	0.05	0.0042	0.04	0.0033	0.03-0.06
Transplant complications	Literature	0.125	0.01	0.125	0.01	0.05-0.2
Treatment success cGVHD	Literature	0.3	0.0083	0.3	0.0083	0-0.7
Taper IST	Stewart et al. [32]	0.20	0.0056	0.4	0.011	0.05-0.5
Death from relapse, early	Meta-analysis	0.07	0.0058	0.1	0.0083	0.05-0.3
Death from relapse, late	Meta-analysis	0.045	0.00375	0.065	0.0054	0.04-0.08
Early TRM	Meta-analysis	0.125	0.01	0.125	0.01	0.05-0.2
Late TRM	Meta-analysis	0.02	0.0017	0.02	0.0017	0-0.1
Quality of life	Literature	estimates (see Methods)†		†estimates (see methods)		0-1.0
aGVHD complications	Meta-analysis	0.26	0.087	0.20	0.067	0.09-0.39
Death from cGVHD	Meta-analysis	RRI*lateTRM	RRI*lateTRM	RRI*lateTRM	RRI*lateTRM	RRI: 1-5
Age, years	Base case	35		35		18-65
ASR mortality	Literature	‡U.S. standard ASR mortality		‡U.S. standard ASR mortality		

aGVHD indicates acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; TRM, treatment-related mortality; IST, immunosuppressive therapy; RRI, relative risk increase; ASR, age/sex/race.

血縁者間PBSCTvsBMT 決断分析



同様の手法でcost-effectivenessについても評価可能。

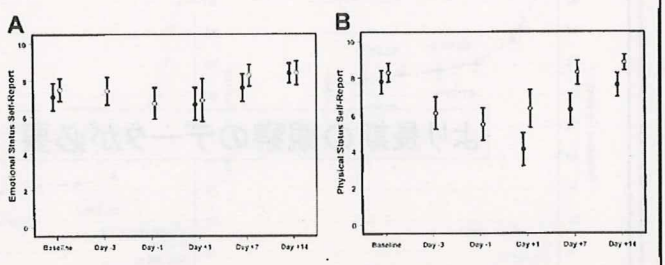
Table 2. Survival Outcomes for PBSCT versus BMT

	PBSCT	BMT
Overall life expectancy, months	61	54
QALE	56	49

PBSCT indicates peripheral blood stem cell transplantation; BMT, blood marrow transplantation; QALE, quality-adjusted life expectancy.

Biol Blood Marrow Transplant 15: 1415-1421 (2009)

ドナーのQOL (Seattle RCT)



(Blood. 2001;97:2541-2548)

ドナーのQOL (NMDP)

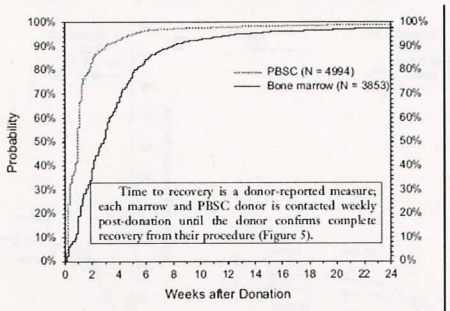


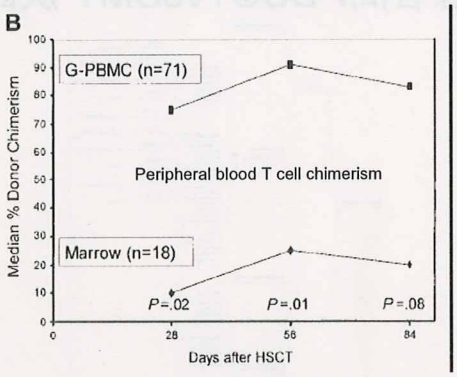
Figure 5. Kaplan-Meier plots of time to recovery from stem cell donation (first donations performed from November 2001 through March 2006).

Biology of Blood and Marrow Transplantation 14:29-36 (2008)

ドナープールの拡大

- 理想的にはBM、PBどちらでもよいと言ってくれるドナーの増加。
- しかし、「PBなら・・・」というドナーがドナープールの増大に貢献する可能性は否定できない。
- まずはPBを入り口にして、PB採取、BM採取の両者を知っていただくことで、そのようなドナーが増えることを期待する。

RICT,NST from UR-donor



(Blood. 2003;102:2021-2030)

平成20年度 全国調査報告書

9.3.3c. 非血縁者からの移植・骨髄 UR-BMT

年齢 Age	'91～'96	'97	'98	'99	'00	'01	'02	'03	'04	'05	'06	'07	合計 Total
0～4	67	27	31	14	10	29	34	26	26	26	39	26	385
5～9	90	31	41	38	43	55	46	36	46	37	38	26	527
10～14	108	35	28	42	35	47	41	39	42	43	37	30	527
15～19	135	57	54	72	72	65	65	48	45	44	43	46	746
20～24	159	57	62	65	71	55	53	40	32	35	45	42	716
25～29	105	46	62	62	70	50	62	56	42	57	49	53	714
30～34	110	36	50	64	59	82	69	61	62	67	59	51	770
35～39	95	32	43	59	67	79	68	57	75	71	74	71	791
40～44	88	34	30	50	79	84	60	50	68	66	81	67	757
45～49	40	28	37	45	70	76	71	85	59	95	81	91	778
50～54	9	7	8	17	54	59	74	72	78	87	87	103	655
55～59	0	0	0	6	9	19	27	50	71	91	110	127	510
60～64	0	0	0	1	0	4	3	16	30	59	46	61	220
65～69	0	0	0	0	0	1	2	5	8	14	12	16	58
70～74	0	0	0	0	0	1	0	0	0	1	2	0	4
75～79	0	0	0	0	0	0	0	0	0	0	0	0	0
80～84	0	0	0	0	0	0	0	0	0	0	0	0	0
85～89	0	0	0	0	0	0	0	0	0	0	0	0	0
90～95	0	0	0	0	0	0	0	0	0	0	0	0	0
不明	0	0	0	0	0	0	0	0	0	0	0	0	0
合計 Total	1,006	390	446	535	669	706	675	641	684	793	803	810	8,158

非血縁者間移植数増加の最大の要因

UR-PBSCTの導入によって

- ドナーQOLの改善
- 非血縁ミニ移植の拡大
- 細胞療法への応用(多数の幹細胞、T細胞)
- 緊急時の対応(貯血が不要)

Ⅳ. 平成 21 年度
研究成果の刊行に関する一覧表

発表者氏名	論文タイトル名	発表誌名	巻名	ページ	出版年
Shigematsu A, Yasumoto A, Yamamoto S, Sugita J, Kondo T, Onozawa M, Kahata K, Endo T, Ota S, Sato N, Takahata M, Okada K, Tanaka J, Hashino S, Nishio M, Koike T, Asaka M, Imamura M.	Regimen-related mucosal injury of the gut increased the incidence of CMV disease after allogeneic bone marrow transplantation.	Biol Blood Marrow Transplant.	15	679-685	2009
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Yasuo Mori ,Takatoshi Aoki , Katsuto Takenaka, Takuji Yamauchi, Asataro Yamamoto, Kenjiro Kamezaki, Hiromi Iwasaki, Naoki Harada, Toshihiro Miyamoto, Koji Nagafuji, Takanori Teshima, Koichi Akashi	Successful treatment of refractory advanced nasal NK/T cell lymphoma with unrelated cord blood stem cell transplantation incorporating focal irradiation	The Japanese Society of Hematology	91	107–111	2010
Kamei M, Nannya Y, Torikai H, Kawase T, Taura K, Inamoto Y, Takahashi T, Yazaki M, Morishima S, Tsujimura K, Miyamura K, Ito T, Togari H, Riddell SR, Kodera Y, Morishima Y, Kuzushima K, Ogawa S, Akatsuka Y.	HapMap scanning of novel human minor histocompatibility antigens.	Blood	113	5041-5048	2009
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Kanda Y, Yamashita T, Mori T, Ito T, Tajika K, Mori S, Sakura T, Hara M, Mitani K, Kurokawa M, Akashi K, Harada M.	A randomized controlled trial of plasma real-time PCR and antigenemia assay for monitoring cytomegalovirus infection after unrelated bone marrow transplantation.	Bone Marrow Transplantation		in press	

Ⅴ. 平成 21 年度研究成果の刊行物

ASBMT
American Society for Blood and Marrow Transplantation

Regimen-Related Mucosal Injury of the Gut Increased the Incidence of CMV Disease after Allogeneic Bone Marrow Transplantation

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Cytomegalovirus (CMV) infection is 1 of the major causes of morbidity in patients undergoing allogeneic stem cell transplantation (allo-SCT). The incidences of CMV antigenemia and CMV disease in 43 patients who received allogeneic bone marrow transplantation (BMT) using a reduced-intensity conditioning (RIC) regimen, which mainly consisted of fludarabine (Flu), busulfan (Bu), and total body irradiation (TBI), were compared with those in 68 patients who received a myeloablative conditioning (MAC) regimen, and risk factors for CMV antigenemia and CMV disease were identified. Before engraftment, grade 3-4 mucosal injury because of the conditioning regimen was significantly decreased in RIC patients (stomatitis: $P = .02$; diarrhea: $P < .01$). Rate of engraftment, incidences of acute graft-versus-host disease (aGVHD), and rate of corticosteroid administration were not different in RIC patients and MAC patients. Although the incidences of CMV antigenemia were not significantly different in RIC patients and MAC patients (64.1% versus 57.8%, log rank, $P = .59$), the incidence of CMV disease was significantly decreased in RIC patients (5.4% versus 20.3%, log rank, $P = .04$). CMV seropositivity in the patients ($P < .01$) and corticosteroid administration ($P < .01$) were revealed by multivariate analysis to be significant risk factors for CMV antigenemia. Grade II-IV aGVHD ($P = .02$) and grade 3-4 diarrhea before engraftment ($P = .04$) were revealed to be risk factors for CMV disease. The present study is the first study to show that severe diarrhea before engraftment is a significant risk factor for CMV disease. In summary, risk of CMV disease was significantly decreased in patients without severe mucosal injury of the gut because of the conditioning regimen before engraftment.

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INTRODUCTION

Cytomegalovirus (CMV) infection is 1 of the major causes of morbidity in patients undergoing allogeneic stem cell transplantation (allo-SCT). Preemptive antiviral therapy has been shown to reduce the risk of CMV disease [1-3]. Major risk factors for CMV infection are serologic status of the donor and recipient, graft-versus-host disease (GVHD), corticosteroid administration, and T cell depletion [1,2,4-13]. Recently, reduced-intensity conditioning (RIC) regimens have been developed for patients who had been considered ineligible for SCT using a myeloablative conditioning (MAC) regimen because of advanced age or medical contraindications [14,15]. Although many studies have shown that infection before engraftment was reduced in patients undergoing RIC because of a shorter neutropenic period and less severe mucositis [16-19], risks of CMV infection have not been substantially reduced after RIC-SCT [1,7,8,10-12]. Again, we need to consider the difference in CMV infection depending on the RIC regimen because various RIC protocols have been developed and the toxicity profile might vary from 1 protocol to another because of variability in the degree of

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immunosuppression or myeloablation [8,10,11,14,15]. We should also consider the difference in CMV infection depending on the stem cell source [8,20].

The present study was a retrospective analysis to compare the incidence of CMV infection in 43 consecutive patients who received bone marrow transplantation (BMT) using an RIC regimen, which mainly consisted of fludarabine (Flu), busulfan (Bu), and total body irradiation (TBI) (Flu/Bu/TBI) in our institution with that in 68 patients who received MAC-BMT during the same period. The risk factors for CMV antigenemia and development of CMV disease were also investigated.

PATIENTS AND METHODS

Patients

One hundred eleven consecutive adult patients with advanced hematologic diseases who received allogeneic BMT using RIC regimens (43 patients) or MAC regimens (68 patients), between September 2000 and March 2007, at Hokkaido University Hospital were analyzed for CMV infections. Twenty-eight patients received an RIC regimen because of advanced age (>50 years), and 10 received an RIC regimen because of prior autologous transplantation (5 patients overlapped with the patients of advanced age). A difference in the risk of CMV infection depending on stem cell source has been reported [8,20], and we cannot use peripheral blood stem cells (PBSC) from an unrelated donor (PBSC can be used only from related donors) in Japan. Moreover, it has been reported that cord blood showed differences in the incidences of infections and kinetics of immunologic recovery from other stem cell sources. Therefore, we analyzed only patients who received BMT. Patients who had already received allogeneic SCT were excluded from this study.

Conditioning Regimens

In the RIC group, 38 (88.4%) of the patients received a conditioning regimen of Flu/Bu/TBI, which consisted of Flu at a dose of 30 mg/m^2 once daily administered intravenously (i.v.) on days −7 to −2 (total dose: 180 mg/m^2) and Bu at 1 mg/kg 4 times daily administered orally (p.o.) on days −3 and −2 (total dose: 8 mg/kg) combined with fractionated TBI at 2 Gy twice daily on day −1 (total dose: 4 Gy), and the other 5 patients received Flu plus melphalan (mel; n = 4) or Flu plus cyclophosphamide (Cy) (n = 1). In the MAC group, 10 patients (14.7%) received a conditioning regimen of Cy/TBI, which consisted of Cy at a dose of 60 mg/kg once daily administered i.v. on days −5 and −4 combined with fractionated TBI at 2 Gy twice daily on days −3 to −1 (total dose: 12 Gy), and 44 patients (64.7%) received Cy/TBI plus VP-16 (VP/Cy/TBI), in which VP-16 was added to Cy/TBI at a dose of 15 mg/kg once daily administered i.v. on days −7 and −6 (total dose: 30 mg/kg) [21,22]. The other patients received other regimens of Bu/Cy or Cy/TBI plus cytarabine. GVHD prophylaxis consisted of cyclosporine A (CsA) and a short course of methotrexate (MTX; 15 mg/m^2 on day 1 and 10 mg/m^2 on days 3 and 6) for HLA-matched related donor recipients, and tacrolimus plus a short course of MTX was given for HLA-matched unrelated donor or HLA-mismatched donor (MMD) recipients. The patients received GVHD prophylaxis from day −1 for 3 months, and drug doses were tapered in patients with no active GVHD, the dose of CsA or tacrolimus being adjusted by plasma level.

Supportive Care and Infection Prophylaxis

Levofloxacin (300 mg daily) was administered p.o. for prevention of bacterial infections until engraftment, and antifungals (fluconazole at 400 mg daily p.o., itraconazol capsules at 200 mg daily p.o., or micafungin at 100 mg daily i.v.) were administered for prevention of fungal infections. Oral acyclovir was given on day −7 to day 35 for prevention of herpes simplex virus (HSV) infection. Oral trimethoprim-sulfamethoxazole or pentamidine inhalation was started after engraftment for prevention of Pneumocystis jiroveci infection. Prophylactic intravenous immunoglobulin (10 g) was given biweekly until serum IgG levels reached >400 mg/dL. Prednisolone was administered for patients who developed grade ≥ii acute GVHD (aGVHD) at a dose of 0.5-1.0 mg/kg daily according to a physician's decision. The dose of prednisolone administered was lower than the dose used in other countries because of the lower incidence of critical aGVHD in Japan [23].

CMV Surveillance and Treatment

Pretransplant serum samples from all patients and donors were tested for serologic evidence of past infection with CMV by an enzyme-linked immunosorbent assay or complement fixation test. When a patient and a donor were both negative for CMV, patients received CMV-negative blood products. When a patient or a donor was positive for CMV, the patient was given unscreened blood products. Surveillance blood CMV pp65 antigenemia was monitored once or twice a week between engraftment and day 100 post-SCT [1,10,24]. Patients with persistent CMV infection, GVHD, and/or corticosteroid administration were screened beyond this period at the discretion of the doctor [1,3]. When a patient developed respiratory symptoms or abdominal symptoms suggestive of CMV disease, bronchoalveolar lavage (BAL) or colonoscopy was performed to determine whether the patient had CMV disease. The patients received preemptive ganciclovir (GCV) at a dose of 5 mg/kg twice

daily i.v. from onset day of CMV antigenemia until the second day of 2 consecutive days on which patients were negative for CMV antigenemia with clinical improvement. Patients with aGVHD received maintenance therapy of GCV (5 mg/kg once daily) for 2 weeks. Foscavir was administered for patients who showed rising CMV antigenemia, those who developed CMV disease despite GCV administration, or those who developed serious toxicity because of GCV.

Definitions

CMV antigenemia was considered positive if there was more than 1 pp65+ cell/10^4 neutrophils assessed. CMV pneumonitis was defined as the demonstration of CMV in tissue by culture or histology or in BAL by culture, direct fluorescence antibody stain, or cytology in the presence of new or changing pulmonary infiltrates. However, detection of CMV by culture or by cytology showed low sensitivity, and it was difficult to perform lung biopsy because of complications after SCT. Therefore, CMV pneumonitis was also defined as the demonstration of all of the following factors: detection of CMV by polymerase chain reaction (PCR), respiratory symptoms, presence of new or changing pulmonary infiltrates, and CMV antigenemia. CMV enteritis was diagnosed when gastrointestinal signs or symptoms occurred, and evidence of CMV in the gastrointestinal tract was diagnosed by culture, immunohistochemistry, or in situ hybridization from biopsy specimens [10]. CMV hepatitis was diagnosed when liver dysfunction occurred, and evidence of CMV in liver tissue was diagnosed by culture, immunohistochemistry, or in situ hybridization from biopsy specimens. aGVHD and chronic GVHD (cGVHD) were graded by standard criteria [25,26]. Overall survival (OS) was calculated from the day of SCT until death or last follow-up.

End Points and Statistical Analysis

The aims of this study were to compare the incidences of CMV antigenemia and the incidences of CMV disease in patients undergoing RIC and MAC regimens and to identify risk factors. Univariate analyses were performed using the chi-square test and Fisher's exact test, as appropriate. The probabilities of CMV antigenemia, CMV disease, OS, and progression-free survival (PFS) were estimated using the Kaplan-Meier method. Effects of the conditioning regimens on survival and CMV infections were studied using the log rank test. Multivariate logistic regression models were used to analyze the influence of selected variables with the forward stepwise method on the risk of CMV antigenemia and CMV disease. All *P*-values were 2-sided, and a *P*-value of .05 was used as the cutoff for statistical significance.

RESULTS

Patient and Transplantation Characteristics

Patient and transplantation characteristics are summarized in Table 1. Median age, GVHD prophylaxis, underlying disease, prior autologous transplantation, and months from diagnosis to transplantation were significantly different between RIC patients and MAC patients. CMV serostatus was not different between RIC patients and MAC patients.

Transplantation Outcomes

Transplantation outcomes are summarized in Table 2. Stomatitis and diarrhea were assessed as regimen-related mucositis, and grade ≥3 stomatitis and grade ≥3 diarrhea were significantly less in RIC patients. Except for 1 patient who died early after engraftment, all patients who achieved engraftment were assessed for aGVHD and CMV infection (RIC: n = 39, MAC: n = 65). Although incidence of aGVHD was not different between the groups, median onset day of aGVHD was significantly delayed in RIC patients (day 33 versus day 20, $P < .01$). The rate of corticosteroid administration and the median dose of corticosteroid for GVHD (1 mg/kg prednisolone) were the same in RIC patients and MAC patients, but the median duration of corticosteroid therapy was longer in RIC patients than in MAC patients with marginal significance (RIC: median 180.5 days [range: 39-975 days], MAC: 85 days [range: 20-404 days], $P = .08$). The median follow-up period was 18.1 months (range: 0.1-83.4 months) for all patients and 30.3 months (range 8.1-83.4 months) for patients alive. The 2-year OS was not different between the groups. There was no difference between causes of death in RIC patients and MAC patients (RIC: disease progression, n = 5; transplantation-related complication, n = 8, versus MAC: disease progression, n = 13; transplantation-related complication, n = 10).

CMV Antigenemia and CMV Disease (Table 2 and Figure 1)

Durations of CMV monitoring in RIC patients and MAC patients were similar. Incidences of CMV antigenemia were not different in RIC patients and MAC patients (RIC: n = 25 [64.1%] versus MAC: n = 37 [57.8%], log rank, $P = .59$), and the median onset day of CMV antigenemia was the same (day 43). Incidence of CMV disease was significantly decreased in RIC patients (RIC: n = 2 [5.4%] versus MAC: n = 13 [20.3%], log rank, $P = .04$, hazard ratio [HR] 0.24, 95% confidence interval [CI] 0.1-1.0). In the RIC group, 69.4% and 0.0% of the CMV-seropositive and CMV-seronegative patients, respectively, developed CMV antigenemia, and no difference was observed between RIC patients and MAC patients.

Table 1. Patients and transplantation characteristics

	RIC (n = 43)	MAC (n = 68)	*P-value*
Age, median (range)	52 (17-66)	34.5 (15-58)	*<.01*
Patient sex, %			
Male	48.8%	63.2%	*.13*
Underlying disease, %			
Acute leukemia	16.3%	54.4%	*<.01*
MDS	27.9%	10.3%	
CML	9.3%	20.6%	
ML/ATL	27.9%	10.3%	
MM	11.6%	0.0%	
Others	7.0%	4.4%	
Prior autologous SCT, %	23.3%	0.0%	*<.01*
Diagnosis to SCT, months; median (range)	22.5 (1.7-240)	8.3 (5.0-276.1)	*<.01*
CR at SCT, %	53.5%	68.7%	*.11*
Donor, %			
MRD	23.3%	30.9%	*.48*
MUD	67.4%	55.9%	
MMD	9.3%	13.2%	
TBI, %	88.4%	91.2%	*.63*
GVHD prophylaxis, %			
CsA+MTX	44.2%	67.6%	*.02*
TK+MTX	53.5%	30.9%	
CMV serostatus, %			
High risk (R+)	93.0%	88.2%	*.71*
Intermediate risk (R−/D+)	4.7%	8.8%	
Low risk (R−/D−)	2.3%	2.9%	

MDS indicates myelodysplastic syndrome; CML, chronic myelogenous leukemia; ML, malignant lymphoma; ATL, adult T cell leukemia/lymphoma; MM, multiple myeloma; SCT, stem cell transplantation; CR, complete remission; MRD, HLA-matched related donor; MUD, HLA-matched unrelated donor; MMD, HLA-mismatched donor; TBI, total body irradiation; GVHD, graft-versus-host disease; CsA, cyclosporine A; MTX, methotrexate; TK, tacrolimus; CMV cytomegalovirus; R, recipient; D, donor. RIC, reduced-intensity conditioning; MAC, myeloablative conditioning.

One (2.7%) of the RIC patients developed CMV enteritis on day 45, and 1 (2.7%) of the RIC patients developed pneumonitis on day 185. In 11 patients who developed both aGVHD and CMV disease, 9 patients (81.8%) developed aGVHD earlier than CMV disease. In MAC patients, 8 (12.5%) of the patients developed enteritis, 4 (6.3%) of the patients developed pneumonitis, and 1 (1.6%) of the patients developed hepatitis on median day of 47 (days 25-71). All cases of enteritis or hepatitis were diagnosed by tissue biopsy and immunohistochemical staining. No case was confirmed by culture. Only 1 patient who received an RIC regimen developed CMV disease beyond day 100. There was no difference in type of CMV disease between RIC patients and MAC patients ($P = .2$ for enteritis, $P = .7$ for pneumonitis). Only 1 patient who developed CMV pneumonitis following the MAC regimen died of CMV infection.

Risk Factors for CMV Antigenemia and CMV Disease (Table 3)

Univariate analysis showed that CMV seropositivity of patients at SCT, any grade of aGVHD, gastrointestinal aGVHD, and corticosteroid administration were risk factors for CMV antigenemia.

Table 2. Transplantation outcomes

	RIC	MAC	*P-Value*
Grade≥3 stomatitis before engraftment	19.0%	41.5%	*0.02*
Grade≥3 diarrhea before engraftment	11.9%	34.4%	*<0.01*
Engraftment	93.0%	95.6%	*0.56*
day, median (range)	16 (7-21)	15 (9-39)	*0.81*
Acute GVHD			
overall	71.8%	78.5%	*0.44*
onset, median (range)	33 (18-127)	20 (8-59)	*<0.01*
grade II-IV	41.0%	52.3%	*0.26*
grade III-IV	17.9%	15.4%	*0.73*
gastrontestinal aGVHD	30.8%	27.7%	*0.70*
Corticosteroid	46.2%	52.3%	*0.54*
CMV Antigenemia	64.1%	57.8%	*0.59*
onset, median (range)	day 43 (16-86)	day 43 (1-137)	
CMV seropositive patient	69.4%	60.7%	*0.39*
CMV seronegative patient	0.0%	25.0%	*0.62*
CMV disease			
overall	5.4%	20.3%	*0.04*
onset, median (range)	day 45,185	day 47 (25-71)	
CMV enteritis	2.7%	12.5%	*0.20*
CMV pneumonitis	2.7%	6.3%	*0.75*
PFS (2 y)	61.0%	58.0%	*0.65*
OS (2 y)	67.5%	65.0%	*0.88*

PFS indicates progression-free survival; OS, overall survivial; GVHD, graft-verses-host-disease; CMV, cytomegalovirus; RIC, reduced-intensity conditioning; MAC, myeloablative conditioning.

CMV seropositivity of the patients and corticosteroid administration remained significant in multivariate analysis.

Analyses of risk factors for CMV disease were also performed. In univariate analysis, MAC regimen,

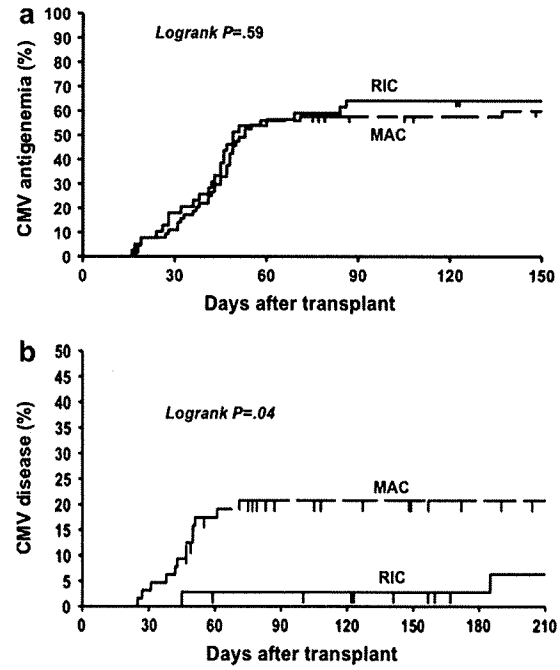

Figure 1. Cumulative incidences of CMV antigenemia (a) and CMV disease (b).

Table 3. Univariate and multivariate analyses of risk factors for CMV antigenemia and CMV disease

Variables	CMV Antigenemia	Univariate P	Multivariate Odds Ratio (95%CI)	Multivariate P	CMV Disease	Univariate P	Multivariate Odds Ratio (95%CI)	Multivariate P
Conditioning regimen								
RIC	64.1%	.52			5.4%	.04		
MAC	57.8%				20.3%			
CMV serostatus (recipient)								
Positive	64.1%	.04	11.8 (2.4-58.0)	<.01	15.6%	.90		
Negative	27.2%				9.1%			
Diarrhea before engraftment (grade)								
-2	59.5%	.85			8.3%	.04	4.1 (1.0-15.6)	.04
3-	61.5%				26.9%			
Acute GVHD, overall								
Yes	67.9%	<.01			13.4%	.74		
No	36.0%				8.3%			
Acute GVHD, grade II-IV								
Yes	72.0%	.02			26.5%	<.01	7.0 (1.4-35.8)	.02
No	49.1%				3.8%			
Acute GVHD, gastrointestinal								
Yes	77.4%	.02			32.1%	<.01		
No	53.4%				8.2%			
Corticosteroid								
Yes	78.4%	<.01	8.3 (3.0-23.2)	<.01	24.0%	.01		
No	42.3%				5.9%			

CI indicates confidence intervea; GVHD, graft-verses-host-disease; CMV, cytomegalovirus; RIC, reduced-intensity conditioning; MAC, myeloablative conditioning.

grade 3-4 diarrhea before engraftment, grade II-IV aGVHD, gastrointestinal aGVHD, and corticosteroid administration were revealed to be significant risk factors for development of CMV disease. Bacterial infection and fungal infections occurred in 28% and 11% of the patients, respectively, and there were no differences in the incidences of CMV antigenemia (bacterial infection, $P = .12$; fungal infection, $P = .91$) and CMV diseases (bacterial infection, $P = .34$; fungal infection, $P = .41$) between patients with bacterial infection or fungal infection and patients without bacterial or fungal infection. Grade 3-4 diarrhea before engraftment and grade II-IV aGVHD remained significant in multivariate analysis. CMV disease did not occur in any of the patients who had grade 3-4 diarrhea before engraftment without grade II-IV aGVHD (Figure 2, Group C). However, in patients who developed grade II-IV aGVHD, the incidence of CMV disease was divided into 2 groups according to the presence of grade 3-4 diarrhea before engraftment (grade II-IV aGVHD+/grade 3-4 diarrhea+ [Group A]: 46.7% versus grade II-IV aGVHD+/grade 3-4 diarrhea− [Group B]: 12.5%, logrank, $P = .01$ HR 4.01 [1.38-18.54]).

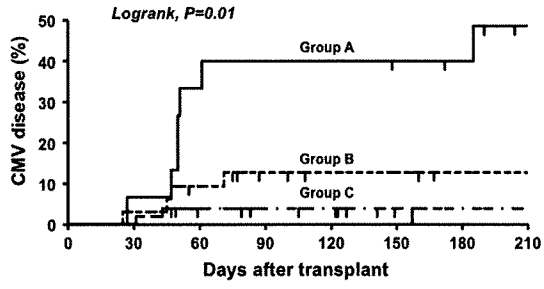

Figure 2. Cumulative incidence of CMV disease according to the combination of 2 risk factors: grade II-IV aGVHD and grade 3-4 diarrhea before engraftment. Group A included patients who had both grade II-IV aGVHD and grade 3-4 diarrhea before engraftment (n = 15). Group B included patients who had grade II-IV aGVHD, but did not develop grade 3-4 diarrhea before engraftment (n = 32). Group C included patients who did not develop grade II-IV aGVHD (n = 52).

DISCUSSION

In this study, we analyzed the incidence and characteristics of CMV infections in patients who received allogeneic BMT after an RIC regimen of Flu/Bu/TBI, and we compared the incidences of CMV antigenemia and CMV disease in RIC patients and MAC patients.

CMV antigenemia developed in 64% of the RIC patients, a higher incidence than the incidence found in other studies (about 40%-50%) [1,8,10,11,13]. It has been reported that the incidence of CMV activation was not reduced in RIC patients [1,7,8,10-12], and reported risk factors for CMV infection in RIC patients include CMV serostatus, HLA-matched unrelated donor, advanced age of donor, grade II-IV aGVHD, corticosteroid administration, Campath-1H and/or antithymocyte globulin (ATG) in the conditioning regimen and BM as a stem cell source [1,2,4-6,8-13,27,28]. In our study, all patients received BM as a stem cell source, and the number of high-risk patients of CMV serostatus in our study was larger than that in other studies, which might explain the higher incidence of CMV antigenemia. Multivariate analysis in this study confirmed CMV serostatus and

corticosteroid administration as significant risk factors for CMV antigenemia.

Although the incidence of CMV antigenemia was not decreased in RIC patients, CMV disease was decreased in RIC patients. The incidence of CMV disease in this study was not increased compared to that in other studies, and it was significantly decreased in RIC patients compared with that in MAC patients. In the present study, grade II-IV aGVHD and grade 3-4 diarrhea before engraftment were revealed by multivariate analysis to be significant risk factors for development of CMV disease. The incidences of grade II-IV aGVHD and the median dose of corticosteroid for GVHD in RIC patients and MAC patients were the same. The median duration of corticosteroid therapy was longer in RIC patients with marginal significance. Therefore, we do not think that the incidence of grade II-IV aGVHD and the intensity and the duration of immunosuppressants mainly contribute to the higher incidence of CMV disease in MAC patients. This is the first study to show an increased risk of CMV disease among patients with severe diarrhea because of the conditioning regimen, which reflected mucosal injury of the gut. Almost all of the CMV diseases that occurred in our patients were CMV enteritis; therefore, diarrhea was determined to be a risk factor for CMV disease. The incidence of CMV antigenemia was not different between patients with grade 3-4 diarrhea and patients without grade 3-4 diarrhea. Also, the incidences of grade II-IV aGVHD and gastrointestinal aGVHD were not different between patients with grade 3-4 diarrhea and patients without grade 3-4 diarrhea (data not shown). These findings suggested that severe diarrhea affected the incidence of CMV disease directly, not via aGVHD. CMV disease occurred in 46.7% of the patients who developed both grade 3-4 diarrhea and grade II-IV aGVHD, but CMV disease occurred in only 12.5% of the patients who developed grade II-IV aGVHD without grade 3-4 diarrhea. CMV disease occurred in only 1 patient who had no grade II-IV aGVHD. These results suggested that immunosuppression in the whole body because of aGVHD (and corticosteroid) was most important for "CMV reactivation," but that mucosal injury of the gut was also necessary for development of "CMV disease." It has been reported that mucosal immunity of the gut is an important defensive system against pathogens including CMV, and that immunoglobulin, macrophages, and T-lymphocytes play a pivotal role in this local immunity. Therefore, impairment of mucosal immunity of the gut because of the conditioning regimen might have influenced the incidence of CMV enteritis in our patients [29-31]. Risk of severe diarrhea before engraftment may be complicated with our MAC regimen, which mainly included VP-16 [22]. We should consider the increased risk for development of CMV disease in patients with severe diarrhea before engraftment and in these patients who develop grade II-IV aGVHD. Although our analysis has limitations because of its retrospective fashion and small sample size, patients who received an RIC regimen showed a lower risk of CMV disease, and mucosal injury of the gut was determined to be a significant risk factor for development of CMV disease. Further studies are needed to confirm these findings.

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Incidence and Risk of Postherpetic Neuralgia after Varicella Zoster Virus Infection in Hematopoietic Cell Transplantation Recipients: Hokkaido Hematology Study Group

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To assess the incidence of and risk factors associated with postherpetic neuralgia (PHN) after hematopoietic cell transplantation (HCT) varicella zoster virus (VZV) infection, we conducted a retrospective chart review of 418 consecutive patients who underwent HCT between April 2005 and March 2007. The male/female ratio was 221/197, median age at HCT was 47 years (range: 0-69 years), and autologous/allogeneic/syngeneic HCT ratio was 154/263/1. Seventy-eight patients developed VZV infection after HCT. Sixty-two patients had localized zoster, 11 patients had disseminated zoster (rash like chicken pox), and 4 patients had visceral zoster. All cases were treated with acyclovir (ACV) or valacyclovir (VACV), and there was no VZV infection-related death. Twenty-seven (35%) of the 78 patients with VZV infection suffered PHN after resolution of VZV infection. Multivariate analysis showed that advanced age is the only risk factor in autologous HCT ($P = .0075$; odds ratio [OR] = 1.14; 95% confidence interval [CI], 0.97-1.33). On the other hand, advanced age ($P = .0097$; OR = 1.06; 95% CI, 1.01-1.12), male gender ($P = .0055$; OR = 12.7; 95% CI, 1.61-100.1), and graft-versus-host disease (GVHD) prophylaxis with a tacrolimus-based regimen ($P = .0092$; OR = 9.56; 95% CI, 1.44-63.3) were associated with increased risk of PHN in allogeneic HCT. This study for the first time clarified the risk of PHN in HCT recipients.

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