expression profiles. *Proc Natl Acad Sci U S A.* 2005;102(43):15545-15550.

32. Ivanova NB, Dimos JT, Schaniel C, Hackney JA, Moore KA, Lemischka IR. A stem cell molecular signature. *Science.* 2002;298(5593):601-604.
33. Krivtsov AV, Twomey D, Feng Z, et al. Transformation from committed progenitor to leukaemia stem cell initiated by MLL-AF9. *Nature.* 2006; 442(7104):818-822.
34. Li C, Hung Wong W. Model-based analysis of oligonucleotide arrays: model validation, design issues and standard error application. *Genome Biol.* 2001;2(8):RESEARCH0032.
35. Hess JL, Bittner CB, Zeisig DT, et al. c-Myb is an essential downstream target for homeobox-mediated transformation of hematopoietic cells. *Blood.* 2006;108(1):297-304.
36. Kroon E, Krosl J, Thorsteinsdottir U, Baban S, Buchberg AM, Sauvageau G. Hoxa9 transforms primary bone marrow cells through specific collaboration with Meis1a but not Pbx1b. *EMBO J.* 1998;17(13):3714-3725.
37. Lavau C, Szilvassy SJ, Slany R, Cleary ML. Immortalization and leukemic transformation of a myelomonocytic precursor by retrovirally transduced HRX-ENL. *EMBO J.* 1997;16(14):4226-4237.
38. Ayton PM, Chen EH, Cleary ML. Binding to nonmethylated CpG DNA is essential for target recognition, transactivation, and myeloid transformation by an MLL oncoprotein. *Mol Cell Biol.* 2004; 24(23):10470-10478.
39. Yokoyama A, Somervaille TC, Smith KS, Rozenblatt-Rosen O, Meyerson M, Cleary ML. The menin tumor suppressor protein is an essential oncogenic cofactor for MLL-associated leukemogenesis. *Cell.* 2005;123(2):207-218.
40. Cozzio A, Passegue E, Ayton PM, Karsunky H, Cleary ML, Weissman IL. Similar MLL-associated leukemias arising from self-renewing stem cells and short-lived myeloid progenitors. *Genes Dev.* 2003;17(24):3029-3035.
41. Georgantas RW III, Tanadve V, Malehorn M, et al. Microarray and serial analysis of gene-expression analyses identify known and novel transcripts overexpressed in hematopoietic stem cells. *Cancer Res.* 2004;64(13):4434-4441.
42. Alcalay M, Tiacci E, Bergomas R, et al. Acute myeloid leukemia bearing cytoplasmic nucleophosmin (NPMc+ AML) shows a distinct gene expression profile characterized by up-regulation of genes involved in stem-cell maintenance. *Blood.* 2005;106(3):899-902.
43. Sood R, Talwar-Trikha A, Chakrabarti SR, Nucifora G. MDS1/EVI1 enhances TGF-beta1 signaling and strengthens its growth-inhibitory effect but the leukemia-associated fusion protein AML1/MDS1/EVI1, product of the t(3;21), abrogates growth-inhibition in response to TGF-beta1. *Leukemia.* 1999;13(3):348-357.
44. Kustikova O, Fehse B, Modlich U, et al. Clonal dominance of hematopoietic stem cells triggered by retroviral gene marking. *Science.* 2005; 308(5725):1171-1174.
45. Sato T, Goyama S, Nitta E, et al. Evi-1 promotes para-aortic splanchnopleural hematopoiesis through up-regulation of GATA-2 and repression of TGF-b signaling. *Cancer Sci.* 2008;99(7):1407-1413.
46. Chen W, Kumar AR, Hudson WA, et al. Malignant transformation initiated by Mll-AF9: gene dosage and critical target cells. *Cancer Cell.* 2008;13(5): 432-440.
47. Yagi H, Deguchi K, Aono A, Tani Y, Kishimoto T, Komori T. Growth disturbance in fetal liver hematopoiesis of Mll-mutant mice. *Blood.* 1998;92(1): 108-117.
48. Ernst P, Fisher JK, Avery W, Wade S, Foy D, Korsmeyer SJ. Definitive hematopoiesis requires the mixed-lineage leukemia gene. *Dev Cell.* 2004;6(3):437-443.
49. Gröschel S, Lugthart S, Schlenk R, et al. High EVI1 expression predicts outcome in younger adult patients with acute myeloid leukemia and is associated with distinct cytogenetic abnormalities. *J Clin Oncol.* 2010;28(12):2101-2107.
50. Yokoyama A, Lin M, Naresh A, Kitabayashi I, Cleary ML. A higher-order complex containing AF4 and ENL family proteins with P-TEFb facilitates oncogenic and physiologic MLL-dependent transcription. *Cancer Cell.* 2010;17(2):198-212.

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Comparison of Allogeneic Hematopoietic Cell Transplantation and Chemotherapy in Elderly Patients with Non-M3 Acute Myelogenous Leukemia in First Complete Remission

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The benefits of allogeneic hematopoietic cell transplantation (allo-HCT) for patients with acute myelogenous leukemia (AML) in first complete remission (CR1) have mostly been evaluated in younger patients. Although favorable outcomes of allo-HCT over chemotherapy have been reported with the use of reduced-intensity conditioning (RIC) regimens in elderly patients with AML in CR1, information is still limited, especially on the effects of cytogenetic risks and donor sources. We collected data from AML patients aged 50 to 70 years who achieved CR1, and compared the outcome in 152 patients who underwent allo-HCT in CR1 (HCT group) to that in 884 patients who were treated with chemotherapy (CTx group). The cumulative incidence of relapse in the HCT group was significantly lower than that in the CTx group (22% versus 62%). Both overall survival (OS) and relapse-free survival (RFS) were significantly improved in the HCT group (OS: 62% versus 51%, $P = .012$), not only in the whole population, but also in the intermediate-risk group. Among patients who had a suitable related donor, the outcomes in the HCT group were significantly better than those in the CTx group. The introduction of appropriate treatment strategies that include allo-HCT may improve the outcome in elderly patients with AML in CR1.

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KEY WORDS: Acute myelogenous leukemia, Elderly patients, Allogeneic hematopoietic cell transplantation, First complete remission

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INTRODUCTION

The biologic characteristics of acute myelogenous leukemia (AML) change as the patient becomes older, because such patients are more often associated with unfavorable profiles such as antecedent hematologic disorder (AHD), expression of P-glycoprotein in blasts, and unfavorable-risk cytogenetic abnormalities [1-4]. In addition, elderly patients are more likely to have a worse performance status and an increased risk of comorbidities, which makes it difficult for them to undergo aggressive therapies [5,6]. Consequently, the reported probability of achieving a first complete remission (CR1) is lower than that in younger patients. In most previous studies, the duration of remission has been reported to be 6 to 8 months, with a 3-year survival rate of <20% [7-10].

Although allogeneic hematopoietic cell transplantation (allo-HCT) is an effective strategy for decreasing the risk of relapse in younger patients, an increase in the risk of treatment-related toxicity is inevitable. Although >50% of the reported AML patients are 50

years of age or older, most previous studies have investigated treatment strategies that include allo-HCT in related younger donor/patient pairs by allocating treatment options based on donor availability. Over the past decade, several studies showed that allo-HCT with reduced-intensity conditioning (RIC) is acceptably safe and effective in elderly patients [11-18]. Allo-HCT with RIC has also been reported to be superior to conventional chemotherapy in elderly AML patients in CR1, particularly when they have a matched related donor [19,20]. However, most of these studies included small numbers of patients, and there is still limited information available on the effects of risk factors of AML, differences in donor sources, and conditioning regimens. To address these critical questions, we performed a nationwide retrospective survey.

PATIENTS AND METHODS

Data Source

The study protocol was approved by the institutional review board at the National Cancer Center Hospital. The targeted population was adult patients who were diagnosed with AML between 1999 and 2006, aged 50 to 70 years, and who had achieved CR1 after 1 or 2 courses of induction chemotherapy. The diagnosis of AML was determined by the WHO classification and included myelodysplastic syndrome with 20% or more bone marrow (BM) blasts. CR was evaluated according to standard criteria for hematologic CR, which was defined as a normocellular BM aspirate containing 5% or less blasts with normal maturation. The presence of minimal residual disease was not molecularly examined in this study. Among them, patients with acute biphenotypic leukemia who were treated with chemotherapy for acute lymphoblastic leukemia, those who had extramedullary AML without BM invasion or extramedullary lesion that did not totally disappear after remission induction chemotherapy, those with acute promyelocytic leukemia, and those who received autologous HCT in CR1 were excluded from the analysis. Information about the disease risks at diagnosis, clinical course, HLA typing and donor availability during CR1, conditioning regimen, and donor source of allo-HCT were collected. Related donors included an HLA-matched or 1-antigen (Ag)-mismatched related donor. A haploidentical related donor who had 2 or more Ag mismatches was considered as an alternative donor. Unrelated donors included volunteer BM donors with 0 or 1-Ag mismatches and unrelated cord blood with three or less-Ag mismatches. As HLA typing for unrelated BM donors was predominantly performed by matches at serum levels in this era, detailed information on allele-level matches was not completely available.

Statistical Analysis

Data were retrospectively reviewed and analyzed as of December 2009. Background differences between the 2 groups was examined with the chi-square test for categoric variables, and with *t*-test for metric variables. The primary endpoints of the study were relapse-free survival (RFS) and overall survival (OS) from when CR1 was achieved. The unadjusted probabilities of RFS and OS were estimated using the Kaplan-Meier product limit method according to the treatment group, and 95% confidence intervals (CIs) were calculated using the Greenwood formula. To compare RFS and OS between the treatment groups, the log-rank test was used. We performed landmark analyses by excluding patients who died or relapsed within 60 days from CR1 for those who were treated with chemotherapy alone. Cumulative incidences were estimated for relapse and nonrelapse mortality (NRM) to take into account competing risks. The Pepe and Mori's test was used to evaluate the differences between groups. RFS, OS, incidences of relapse, and NRM were estimated as probabilities at 3 years from CR1. Associations between treatment groups and outcome were evaluated using Cox proportional hazard regression models. In addition to whether allo-HCT in CR1 was performed or not, the following factors were considered as covariates: cytogenetic classification according to the Southwest Oncology Group (SWOG), FAB classification, the number of courses of chemotherapy required to achieve CR1, initial white blood cell (WBC) count, and dysplasia at diagnosis. We considered 2-sided *P*-values of $<.05$ to be statistically significant. Statistical analyses were performed with the SPSS software package and SAS version 9.1.3 (SAS, Cary, NC, USA).

RESULTS

Patients

Clinical data for around 1300 patients were collected from 67 institutions. After excluding 45 patients who received autologous HCT in CR1 or other ineligible patients as described in Patients and Methods, 1036 were eligible for this study (Table 1). The median follow-up of the surviving patients was 44 months. As a remission induction therapy, 89% of elderly patients had received cytarabine- and anthracycline (daunorubicin or idarubicin)-based regimens. Low-dose cyatarabine-based regimens were performed in 8% of the elderly patients. Consolidation therapy was continued with cytarabine-based regimens with or without maintenaice therapy at the discretion of physicians.

Donor Availability and Consideration of allo-HCT in CR1

Information on HLA typing during CR1 and the availability of related donors was obtained in 953

Table 1. Patient Characteristics

Characteristics	All Patients n = 1036	Allo-HCT in CR1 n = 152 (%)	No HCT in CR1 n = 884 (%)	*P*
Median age				
years, (range)	60 (50-70)	55 (50-70)	61 (50-70)	<.001
Median time from diagnosis to CR1				
days, (range)	40 (26-283)	48 (26-242)	39 (13-283)	<.001
Disease				
M0, 6, 7	102	24 (16)	78 (9)	<.001
AHD	37	19 (13)	18 (2)	<.001
Cytogenetic risks (SWOG)				<.001
Favorable	164	5 (3)	159 (18)	
Intermediate	589	93 (61)	496 (56)	
Unfavorable	166	27 (18)	139 (16)	
Unknown	99	25 (16)	74 (8)	
Remission induction				0.13
2 courses	199	36 (24)	163 (18)	
WBC (/μL)				<.001
Higher than 20,000	335	28 (18)	307 (35)	
Dysplasia				<.001
Yes	268	74 (49)	194 (22)	

Allo-HCT indicates allogeneic hematopoietic cell transplantation; CR1, first complete remission; AHD, antecedent hematologic disorder; WBC, white blood cell; SWOG, Southwest Oncology Group.

elderly patients. Among these patients, HLA typing was performed in 331 patients in CR1 (35%) and these patients were younger than those who did not have their HLA typed during CR1 (median, 56 years versus 62 years) (Table 2 and Figure 1). Patients who had their HLA typed were associated with more unfavorable features, such as unfavorable FAB types, AHD, a requirement of 2 courses of remission induction therapy, dysplasia at diagnosis, and a lower frequency of favorable-risk AML by the SWOG classification. Related donors (HLA-matched and 1-Ag-mismatched related donors) were found in 134 patients (40%). No significant difference was found in the distribution of age and risk factors between patients who found a related donor and those who did not after HLA typing (Table 2). Among the patients who had a related donor, 76 (57%) actually underwent allo-HCT during CR1. Among the 197 patients who did not find a related donor, 76 (39%) received allo-HCT from an alternative donor in CR1 (Figure 1).

Patients Who Received allo-HCT in CR1

Of the total 1036 patients, 152 underwent allo-HCT in CR1 (15%). Patients who received allo-HCT in CR1 were younger and associated with more unfavorable characteristics than those who did not (Table 1). As shown in Table 3, 49% of the patients

Table 2. Donor Search and Transplantation

		HLA Check in CR1, n = 331				Statistical Differences		
Characteristics	No HLA Check in CR1 N = 622 (%)	Related Donor Available/HCT+[a]* n = 76 (%)	Related Donor Available/HCT−[b] n = 58 (%)	Related Donor not Available/HCT+[c] n =76 (%)	Related Donor not Available/HCT−[d] n =121 (%)	*P**	*P*†	*P*‡
Age, median, years	62	55	55	55	57	<.001	.396	.906
Disease								
M0, 6, 7	47 (8)	17 (22)	5 (9)	7 (9)	13 (11)	0.008	.170	.160
AHD	11 (2)	4 (5)	2 (3)	15 (20)	2 (2)	<.001	186	.450
Cytogenetic risks (SWOG)						<.001	.561	.045
Favorable	118 (19)	4 (5)	12 (21)	1 (1)	19 (16)			
Intermediate	354 (57)	43 (57)	28 (48)	50 (66)	69 (57)			
Unfavorable	92 (15)	13 (17)	9 (16)	14 (18)	17 (14)			
Unknown	48 (8)	16 (21)	9 (16)	11 (14)	14 (12)			
Remission induction						.009	.541	.871
2 courses	103 (17)	19 (25)	14 (24)	17 (22)	29 (24)			
WBC (/μL)						.021	.178	.004
Higher than 20,000	223 (36)	11 (14)	19 (33)	17 (22)	39 (32)			
Dysplasia						<.001	.991	.117
Yes	127 (20)	31 (41)	16 (28)	43 (57)	26 (21)			

CR indicates complete remission; HCT, allogeneic hematopoietic cell transplantation; AHD, antecedent hematologic disorder; WBC, white blood cell; SWOG, Southwest Oncology Group.

*P-value of comparing "No HLA check in CR1" versus "HLA check in CR1."

†P-value of comparing "Related donor available[a+b]" versus "Related donor not available[c+d]".

‡P-value of comparing "HCT+[a]" versus "HCT-[b]" among those who had a related donor.

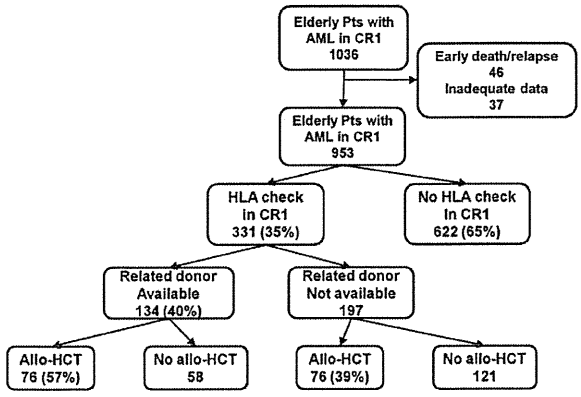

Figure 1. Patient flow. Among 953 patients for whom information was available, HLA typing was performed in 331 patients in CR1 (35%). Related donors were found in 134 patients (40%). Among the patients who had a related donor, 76 (57%) actually underwent allo-HCT in CR1. Among the 197 patients without a related donor, 76 (39%) received allo-HCT from an alternative donor in CR1.

received allo-HCT in CR1 from an HLA-matched or 1-Ag-mismatched related donor. The median interval from CR1 to allo-HCT was 139 days. An RIC regimen was given to 93 patients (61%) with a higher median age of 58 years compared to those who received a myeloablative (MA) regimen, 52 years. Extensive chronic graft-versus-host disease (cGVHD) developed in 61 patients (45%) among 135 who lived and had a follow-up period of longer than 100 days.

Comparison of the Outcomes of allo-HCT versus Chemotherapy in CR1

The outcome in patients who received allo-HCT in CR1 (HCT group) was compared to that in patients who did not receive allo-HCT in CR1 (CTx group). Landmark analyses were performed in all subgroups by excluding 46 patients from the CTx group who relapsed or died within 60 days after achieving CR1. In the CTx group, 183 patients ultimately received salvage allo-HCT after relapse (33% of relapsed patients). The cumulative incidence of relapse in the HCT group was significantly lower than that in the CTx group (22% versus 62% at 3 years from CR1, $P < .001$) (Figure 2). The cumulative incidence of NRM in the HCT group was higher than that in the CTx group (21% versus 3%, $P < .001$). The 3-year RFS in the HCT group was significantly higher than that in the CTx group (56% versus 29%, $P < .001$). Although the difference between the HCT and CTx groups decreased, the 3-year OS in the HCT group was also significantly higher than that in the CTx group (62% versus 51%, $P = .012$). Multivariate analyses for survival showed that performance of allo-HCT, a single course of induction therapy to achieve CR1, lack of dysplasia, WBC below 20,000/μL at diagnosis, and a more favorable cytogenetic risk were significantly associated with better RFS and OS (Table 4). We also used the Cox proportional hazards model with time-dependent variables after taking into account the time from CR1 to allogeneic HCT. By adjusting the influence of waiting time to allogeneic HCT in this analysis, we found that allogeneic HCT in CR1 was also independently associated with better OS.

In a subset analysis according to the cytogenetic risk, patients with intermediate-risk AML showed the similar trends in relapse, NRM, RFS, and OS to the entire patient population (OS: 67% versus 54%, $P = .024$) (Figure 3A). Among patients with unfavorable-risk AML, 27 received allo-HCT in CR1 and 125 did not. In this group of patients, relapse incidence in the HCT group was also substantial (Figure 3B) (41% at 3 years; 95% CI, 21%-61%), which led to OS that did not differ significantly compared to that in the CTx group (OS: 47% versus 35%, $P = .206$).

We also evaluated the outcome in relation to donor availability (Figure 4). Among 134 patients

Table 3. Characteristics of Transplantation in CR1

Characteristics	Allo HCT in CR1 n = 152 (%)	Median Age, Years (Range)	Median Interval from CR1 to HCT, Days (Range)
Total		55 (50-70)	139 (14-981)
Donor			
Matched related	64 (42)	55 (50-70)	121 (14-574)
1-Ag-mismatched related	10 (7)	57 (50-60)	99 (15-436)
Haplo-identical	3 (2)	51 (50-54)	144 (21-147)
Unrelated bone marrow	52 (34)	55 (50-64)	177 (40-981)
Cord blood	23 (15)	55 (50-67)	127 (14-650)
Conditioning			
Myeloablative			
TBI regimen	16 (11)	52 (50-58)	167 (52-436)
Non-TBI regimen	40 (26)	52 (50-59)	141 (14-361)
Reduced-intensity			
Flu/Bu-based	48 (32)	58 (50-70)	147 (15-574)
Flu/Mel-based	29 (19)	58 (50-66)	126 (14-981)
Others	16 (11)	58 (50-69)	99 (23-304)

Allo-HCT indicates allogeneic hematopoietic cell transplantation; CR, complete remission; Ag, antigen; TBI, total body irradiation; Flu, fludarabine; Bu, busulfan; Mel, melphalan.

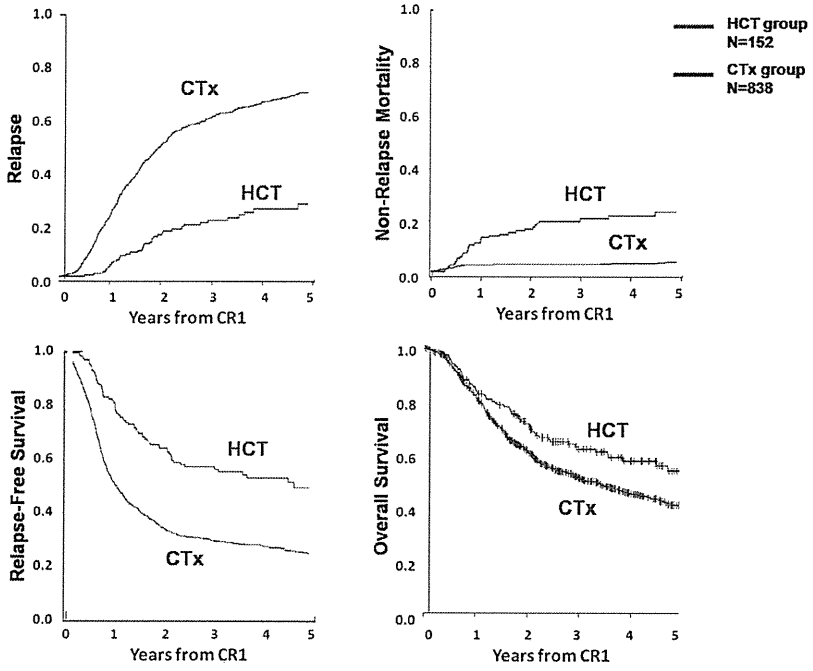

Figure 2. Outcomes according to treatment in CR1 (total elderly patients). Relapse (upper left), nonrelapse mortality (upper right), relapse-free survival (bottom left), and overall survival (OS) (bottom right) of patients who underwent allogeneic hematopoietic cell transplantation in CR1 and those who did not are shown. Forty-six patients who died or relapsed within 60 days from CR1 were excluded as described in the Statistical Analysis. OS was significantly improved in the HCT group ($P = .012$).

who had a related donor, 76 underwent allo-HCT in CR1. The incidence of NRM among the patients who received allo-HCT from a related donor was 14%, which was significantly lower compared to that observed in the whole HCT group. On the other hand, patients who found a related donor but did not undergo allo-HCT in CR1 had a substantial incidence of relapse (80%; 95% CI, 70%-90%). These results led to significant differences in RFS and OS between the HCT and CTx groups (RFS: 64% versus 11%, $P < .001$, OS: 66% versus 43%, $P = .001$) (Figure 4A). These results did not change when 622 patients who did not have their HLA typed (those who were not known to have a suitable related donor) were included in the CTx group (66% versus 54%, $P = .011$) (Appendix 1-A) or when landmark was extended to 5 months from CR1 for the patients in the CTx group who had a related donor (66% versus 54%, $P = .068$) (Appendix 1-B). We also performed the same comparison limited to intermediate-risk AML patients who had a related donor, and found significant differences between the HCT and CTx groups (RFS: 78% versus

Table 4. Multivariate Analysis

	RFS		OS	
Variables	HR (95% CI)	P	HR (95% CI)	P
Allo HCT in CR1 (versus Yes)				
No	2.58 (1.97-3.37)	<.001	1.81 (1.35-2.42)	<.001
Cytogenetic Risk (versus Favorable)				
Intermediate	1.14 (0.90-1.44)	.283	1.10 (0.84-1.45)	.487
Unfavorable	1.70 (1.28-2.24)	<.001	1.89 (1.37-2.59)	<.001
Unknown	1.62 (1.18-2.23)	.003	1.34 (0.92-1.95)	.132
FAB (versus M1, 2, 4, 5)				
M0, 6, 7	1.25 (1.00-1.57)	.052	1.38 (1.07-1.77)	.014
Remission Induction (versus 1 course)				
2 courses	1.52 (1.26-1.84)	<.001	1.61 (1.31-1.99)	<.001
Dysplasia (versus No)				
Yes	1.21 (0.98-1.48)	.075	1.29 (1.02-1.63)	.033
WBC (versus 20,000 or lower)				
Higher than 20,000	1.29 (1.09-1.54)	.004	1.24 (1.01-1.51)	.038

HR indicates hazard ratio; RFS, relapse-free survival; CI, confidence interval; OS, overall survival; allo-HCT, allogeneic hematopoietic cell transplantation; CR, complete remission; WBC, white blood cell count.

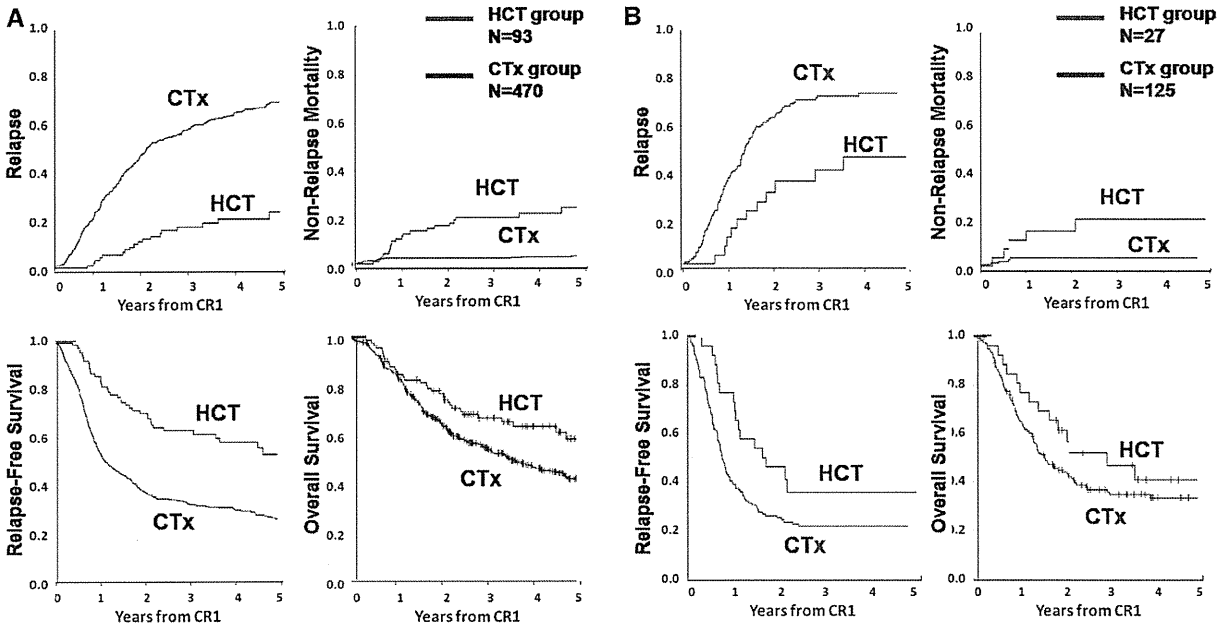

Figure 3. Outcomes according to treatment in CR1 (cytogenetic risks). Relapse (upper left), nonrelapse mortality (upper right), relapse-free survival (bottom left), and overall survival (OS) (bottom right) of patients who underwent allogeneic hematopoietic cell transplantation in CR1 and those who did not are shown among (A) intermediate-risk AML and (B) unfavorable-risk AML. (A) OS was significantly improved in the HCT group among patients with intermediate-risk AML. (B) Relapse incidence was high even after HCT, and OS in the HCT group did not significantly differ from that in the CTx group.

13%, $P < .001$, OS: 78% versus 63%, $P = .048$) (Appendix 1-C).

Among 197 patients who did not have a related donor, 76 underwent allo-HCT from an alternative donor in CR1. Alternative donors included 51 unrelated BM, 22 unrelated CB, and 3 haploidentical related donors. Patients who received allo-HCT in CR1 from an alternative donor had a higher incidence of NRM than those who received allo-HCT from a related donor (28% versus 14% at 3 years, $P = .029$). Additionally, incidence of relapse in allo-HCT from an alternative donor was not reduced compared to that in a related donor transplant setting (22% versus 22%, $P = .743$). Consequently, if we compare the outcomes of the HCT and CTx groups among patients who did not have a related donor, OS did not significantly differ between the two groups (57% versus 47%, $P = .388$) (Figure 4B).

As shown in Table 3, 39% of the patients in the HCT group received an MA regimen. Except for the younger age in those who received an MA regimen, there was no difference in the disease risk between the MA and RIC groups. Additionally, the OS did not significantly differ between the two groups (3-year OS from CR1: 63% versus 61%, $P = .571$) (Appendix 2-A). We also found that OS was not significantly different according to the application of total body irradiation (TBI) (TBI regimen versus non-TBI: 67% versus 61%, $P = .932$) (Appendix 2-B) or among different RIC regimens (fludarabine + busulfan-based, 56%; fludarabine + melphalan-based, 67%; others, 68%, $P = .862$) (Appendix 2-C).

DISCUSSION

We performed retrospective analyses with a 60-day landmark to compare allo-HCT and CTx in 1036 patients aged 50 to 70 years with non-M3 AML in CR1. The results of this study revealed that, overall, elderly patients with AML who received allo-HCT in CR1 had improved outcomes compared to those who were treated with conventional chemotherapy alone. Based on cytogenetic subgroup analyses, patients with intermediate-risk AML had a significantly better OS when they received allo-HCT in CR1. On the other hand, patients with unfavorable-risk AML had a higher risk of relapse even after allo-HCT in CR1, which diminished the benefit of allo-HCT. We also observed that patients who had a related donor had a significantly improved outcome when they received allo-HCT in CR1.

Our results that allo-HCT in CR1 provided an improved OS agree with previously reported comparisons of allo-HCT versus chemotherapy in elderly patients with AML in CR1. Mohty et al. [20] performed a retrospective comparison of "donor" versus "no donor" based on their consistent policy of considering allo-HCT with RIC in CR1 when a patient with high-risk AML had an HLA-matched sibling. They reported superior survival rates not only in the "transplant group" compared to the "no transplant group," but also in the "donor group" compared to the "no donor group." Furthermore, Estey et al. [19] reported the first prospective

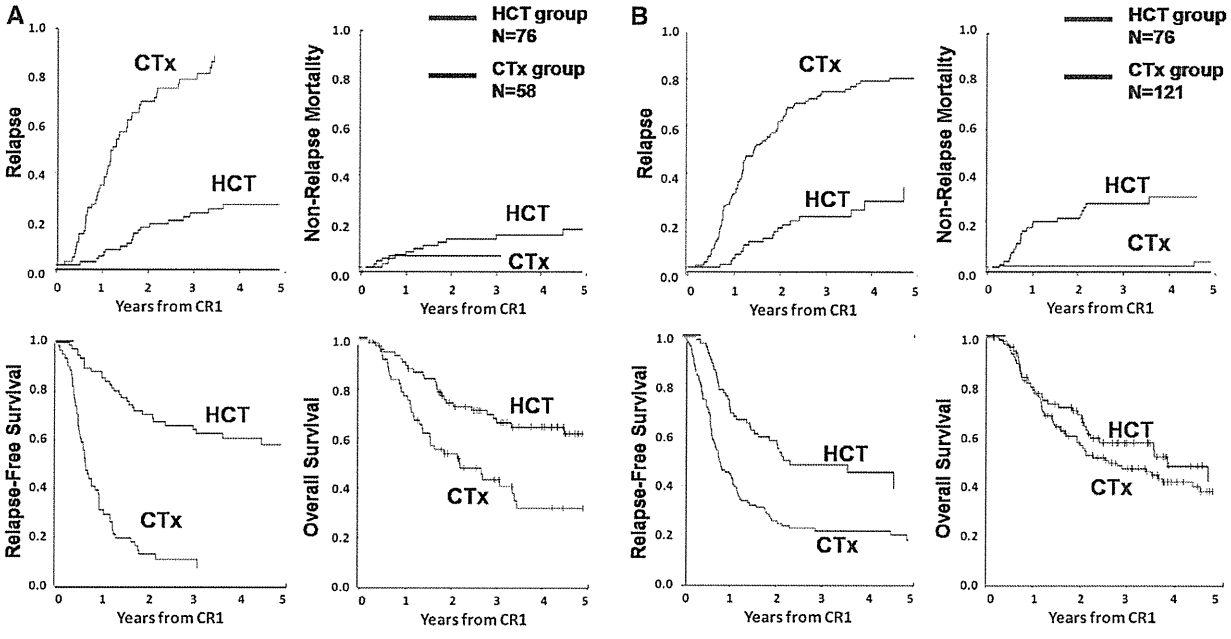

Figure 4. Outcomes according to treatment in CR1 (donor availability). Relapse (upper left), nonrelapse mortality (NRM) (upper right), relapse-free survival (bottom left), and overall survival (OS) (bottom right) of patients who underwent allogeneic hematopoietic cell transplantation in CR1 and those who did not are shown among (A) patients who had a suitable related donor and (B) patients who did not have a suitable related donor. (A) NRM was reduced in related donor transplant and survival probabilities were significantly improved in the HCT group. (B) OS in alternative donor transplant did not significantly differ from that in the CTx group.

observation of allo-HCT with RIC versus chemotherapy in elderly patients. Although the proportions of patients who were referred for transplantation (54%) and those who actually underwent allo-HCT in CR1 (14%) were relatively small, they presented an encouraging outcome that supported the benefit of allo-HCT.

In elderly patients with intermediate-risk AML, we also found improved OS when they received allo-HCT in CR1. This finding is consistent with the result indicated by a meta-analysis by Koreth et al. [21], although their report mostly included prospective studies that targeted younger patients. No previous studies have reported the effects of cytogenetic risks in the transplant setting for elderly patients. In the intermediate-risk group, we found a 60% relapse incidence at 3 years from CR1 when the patients were treated with chemotherapy alone. We also revealed that the incidence of relapse was reduced by 40% with the use of allo-HCT in CR1 without a significant increase in NRM compared to younger patients, which led to a significant improvement of OS.

Our current study did not show a significant benefit of allo-HCT among patients with unfavorable-risk AML. Although fewer patients were analyzed in this subgroup, which may have led to the unlikelihood of yielding a statistical significance, this result may also be explained by the fact that elderly patients tend to be given less-aggressive chemotherapy before allo-HCT because of concerns about toxicity [7,9]. Because no other realistic option can offer a chance of cure for patients with unfavorable-risk AML, many physicians would consider that allo-HCT is optimal for these patients. However, we clearly need to seek novel strategies to reduce the risk of relapse, for example, by reducing the tumor burden before allo-HCT with more intensified chemotherapy or conditioning regimen, or by prevention of recurrence after allo-HCT by vaccination strategy [22-27]. The role of new drugs such as clofarabine or hypomethylating agents should also be estimated for elderly patients with poor-risk AML who are vulnerable to intensive treatments [28,29].

We observed a markedly reduced incidence of NRM after transplantation from a related donor, which improved the outcome of patients who received allo-HCT in CR1 from a related donor. Among 134 patients who had a suitable related donor, 40% did not undergo allo-HCT during CR1. Unfortunately, the exact reason was not available from our retrospectively collected database. Possible reasons include disease relapse before the anticipated timing for allo-HCT, or failure to receive appropriate therapy because of being too ill. However, an analysis with a landmark extended to 5 months still proved that OS in the HCT group was significantly better compared to that in the CTx group among those who had a related donor.

In contrast to the favorable outcome in the setting of allo-HCT from a related donor, the outcome of allo-HCT from an alternative donor in CR1 was not significantly superior to that of chemotherapy alone. In addition to the significantly higher NRM after alternative

donor transplant, the incidence of relapse was not reduced in the alternative donor transplant compared to that in related donor transplant despite our expectation that a graft-versus-leukemia (GVL) effect would be more potent after allo-HCT from alternative donors. Several reports have indicated that the outcomes of allo-HCT from HLA allele-matched unrelated donors are comparable to those from related donors [14,27]. One possible explanation for this disparity is that patients who received allo-HCT from an alternative donor in our database were significantly more likely to have high-risk AML than those who received allo-HCT from a related donor. Second, HLA typing was predominantly performed serologically in the period of our study. About a third of the patient/donor pairs who are considered to be matched unrelated pairs by a serologic examination have been reported to have an allele-mismatch [30]. In addition, voluntary unrelated donors consisted only of BM donors because peripheral blood harvest is not yet allowed in our country, and unrelated CB accounted for one-third of the alternative donors in our study. Although allo-HCT from an alternative donor was not shown to have a benefit in elderly patients in our study, we may expect a better outcome with a smooth access to an allele-matched unrelated donor.

Whereas prior reports that have compared allo-HCT and chemotherapy in elderly patients targeted only allo-HCT with RIC [19,20], one-third of the HCT group patients in our study received an MA conditioning regimen. However, except for patient age, there were no significant differences in the disease risks between the MA and RIC groups, and OS was similar between the two groups. As has been previously pointed out, there were no significant differences in OS among different RIC regimens [31].

Because our database consists of retrospectively collected clinical data, this cohort of patients may have several inherent selection biases. Although we performed a landmark analysis to eliminate the biases by the patients who did not have a chance to receive allo-HCT in CR1 because of earlier relapse or comorbidity, patients in the HCT group may still have had favorable features that enabled them to successfully reach the point of allo-HCT in CR1. Furthermore, our database did not provide detailed information on consolidation chemotherapy after achievement of CR1 or the reasons why patients did not undergo allo-HCT such as the presence of comorbid conditions. Although the number of the elderly patients who received autologous HCT in CR1 was small, the exclusion of these patients may have made the non-HCT group have even more inherent selection bias, Nevertheless, the results drawn from our database, which includes 850 patients in the CTx group and 150 patients in the HCT group, may allow us to suggest optimal strategies for elderly patients with AML especially stratified by cytogenetic subgroups.

In conclusion, our study indicated that elderly patients with AML who underwent allo-HCT in CR1 had improved outcomes compared to those who were treated with conventional chemotherapy alone, and also revealed that intermediate-risk AML patients had an improved OS when they underwent allo-HCT in CR1. Because OS was better in elderly patients when they have a matched related donor and successfully undergo allo-HCT in CR1, they should be encouraged to seek the opportunity of allo-HCT in CR1 by performing HLA typing and donor search in the early period after achievement of CR1. Novel strategies to reduce the risk of relapse and better access to allele-matched unrelated donors should further improve the prognosis of elderly patients with AML.

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AUTHORSHIP STATEMENT

Contribution: S.K. designed the study, prepared the data file, performed the analysis, interpreted data, and wrote the manuscript; T.Yamaguchi was primarily responsible for designing the study, data analysis and interpretation of the data; N. Uchida., S.M., K.U., M.W., T. Yamashita., H.K., J. Tomiyama., Y. Nawa., S.Y., J. Takeuchi., K.Y., F.S., N. Uoshima., T. Yano., Y. Nannya, and Y.M. obtained the patients' data and interpreted data; I.M. reviewed the cytogenetic reports and interpreted data; Y.T. interpreted data and helped to write the paper; T.F. was primarily responsible for the entire paper as an accurate and verifiable report.

REFERENCES

1. Appelbaum FR. What is the impact of hematopoietic cell transplantation (HCT) for older adults with acute myeloid leukemia (AML)? *Best Pract Res Clin Haematol.* 2008;21:667-675.
2. Frohling S, Schlenk RF, Kayser S, et al. Cytogenetics and age are major determinants of outcome in intensively treated acute myeloid leukemia patients older than 60 years: results from AMLSG trial AML HD98-B. *Blood.* 2006;108:3280-3288.
3. Gardin C, Turlure P, Fagot T, et al. Postremission treatment of elderly patients with acute myeloid leukemia in first complete remission after intensive induction chemotherapy: results of the multicenter randomized Acute Leukemia French Association (ALFA) 9803 trial. *Blood.* 2007;109:5129-5135.
4. van der Holt B, Breems DA, Berna Beverloo H, et al. Various distinctive cytogenetic abnormalities in patients with acute myeloid leukaemia aged 60 years and older express adverse prognostic

value: results from a prospective clinical trial. *Br J Haematol.* 2007;136:96-105.
5. Appelbaum FR, Gundacker H, Head DR, et al. Age and acute myeloid leukemia. *Blood.* 2006;107:3481-3485.
6. Atallah E, Cortes J, O'Brien S, et al. Establishment of baseline toxicity expectations with standard frontline chemotherapy in acute myelogenous leukemia. *Blood.* 2007;110:3547-3551.
7. Grimwade D, Walker H, Harrison G, et al. The predictive value of hierarchical cytogenetic classification in older adults with acute myeloid leukemia (AML): analysis of 1065 patients entered into the United Kingdom Medical Research Council AML11 trial. *Blood.* 2001;98:1312-1320.
8. Klepin HD, Balducci L. Acute myelogenous leukemia in older adults. *Oncologist.* 2009;14:222-232.
9. Rowe JM. Optimal induction and post-remission therapy for AML in first remission. *Hematology Am Soc Hematol Educ Program.* 2009;396-405.
10. Rowe JM, Neuberg D, Friedenberg W, et al. A phase 3 study of three induction regimens and of priming with GM-CSF in older adults with acute myeloid leukemia: a trial by the Eastern Cooperative Oncology Group. *Blood.* 2004;103:479-485.
11. Giralt S, Estey E, Albitar M, et al. Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: harnessing graft-versus-leukemia without myeloablative therapy. *Blood.* 1997;89:4531-4536.
12. Bertz H, Potthoff K, Finke J. Allogeneic stem-cell transplantation from related and unrelated donors in older patients with myeloid leukemia. *J Clin Oncol.* 2003;21:1480-1484.
13. de Lima M, Anagnostopoulos A, Munsell M, et al. Nonablative versus reduced-intensity conditioning regimens in the treatment of acute myeloid leukemia and high-risk myelodysplastic syndrome: dose is relevant for long-term disease control after allogeneic hematopoietic stem cell transplantation. *Blood.* 2004;104: 865-872.
14. Hegenbart U, Niederwieser D, Sandmaier BM, et al. Treatment for acute myelogenous leukemia by low-dose, total-body, irradiation-based conditioning and hematopoietic cell transplantation from related and unrelated donors. *J Clin Oncol.* 2006;24:444-453.
15. Sayer HG, Kroger M, Beyer J, et al. Reduced intensity conditioning for allogeneic hematopoietic stem cell transplantation in patients with acute myeloid leukemia: disease status by marrow blasts is the strongest prognostic factor. *Bone Marrow Transplant.* 2003;31:1089-1095.
16. Shimoni A, Hardan I, Shem-Tov N, et al. Allogeneic hematopoietic stem-cell transplantation in AML and MDS using myeloablative versus reduced-intensity conditioning: the role of dose intensity. *Leukemia.* 2006;20:322-328.
17. Wong R, Giralt SA, Martin T, et al. Reduced-intensity conditioning for unrelated donor hematopoietic stem cell transplantation as treatment for myeloid malignancies in patients older than 55 years. *Blood.* 2003;102:3052-3059.
18. McClune BL, Weisdorf DJ, Pedersen TL, et al. Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. *J Clin Oncol.* 2010; 28:1878-1887.
19. Estey E, de Lima M, Tibes R, et al. Prospective feasibility analysis of reduced-intensity conditioning (RIC) regimens for hematopoietic stem cell transplantation (HSCT) in elderly patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS). *Blood.* 2007;109: 1395-1400.
20. Mohty M, de Lavallade H, Ladaique P, et al. The role of reduced intensity conditioning allogeneic stem cell transplantation in patients with acute myeloid leukemia: a donor vs no donor comparison. *Leukemia.* 2005;19:916-920.
21. Koreth J, Schlenk R, Kopecky KJ, et al. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials. *JAMA.* 2009;301:2349-2361.
22. Lancet JE, Giralt S. Therapy for older AML patients: the role of novel agents and allogeneic stem cell transplant. *J Natl Comp Cancer Netwk.* 2008;6:1017-1025.
23. Lowenberg B, Ossenkoppele GJ, van Putten W, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med.* 2009;361:1235-1248.
24. Lubbert M, Bertz H, Ruter B, et al. Non-intensive treatment with low-dose 5-aza-2'-deoxycytidine (DAC) prior to allogeneic blood SCT of older MDS/AML patients. *Bone Marrow Transplant.* 2009;44:585-588.
25. Pagel JM, Appelbaum FR, Eary JF, et al. 131I-anti-CD45 antibody plus busulfan and cyclophosphamide before allogeneic hematopoietic cell transplantation for treatment of acute myeloid leukemia in first remission. *Blood.* 2006;107:2184-2191.
26. Pagel JM, Gooley TA, Rajendran J, et al. Allogeneic hematopoietic cell transplantation after conditioning with 131I-anti-CD45 antibody plus fludarabine and low-dose total body irradiation for elderly patients with advanced acute myeloid leukemia or high-risk myelodysplastic syndrome. *Blood.* 2009;114:5444-5453.
27. Storb R. Reduced-intensity conditioning transplantation in myeloid malignancies. *Curr Opin Oncol.* 2009;21(Suppl 1):S3-S5.
28. Cashen AF, Schiller GJ, O'Donnell MR, DiPersio JF. Multicenter, phase II study of decitabine for the first-line treatment of older patients with acute myeloid leukemia. *J Clin Oncol.* 2010;28:556-561.
29. Kantarjian HM, Erba HP, Claxton D, et al. Phase II study of clofarabine monotherapy in previously untreated older adults with acute myeloid leukemia and unfavorable prognostic factors. *J Clin Oncol.* 2010;28:549-555.
30. Lee SJ, Klein J, Haagenson M, et al. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. *Blood.* 2007;110:4576-4583.
31. Giralt S, Logan B, Rizzo D, et al. Reduced-intensity conditioning for unrelated donor progenitor cell transplantation: long-term follow-up of the first 285 reported to the national marrow donor program. *Biol Blood Marrow Transplant.* 2007;13:844-852.

APPENDIX: PARTICIPATING CENTERS

National Cancer Center Hospital (Tokyo), Toranomon Hospital (Tokyo), Saiseikai Maebashi Hospital (Gunma), NTT Kanto Medical Center (Tokyo), Fujita Health University (Aichi), Metropolitan Komagome Hospital (Tokyo), Kanagawa Cancer Center (Kanagawa), Metropolitan Bokutoh Hospital (Tokyo), Ehime Prefectural Central Hospital (Ehime), Jikei University (Tokyo), Nihon University (Tokyo), Kurume University (Fukuoka), St. Marianna University Yokohama Seibu Hospital (Kanagawa), Matsushita Memorial Hospital (Osaka), Tokyo Medical Center (Tokyo), University of Tokyo (Tokyo), Sasebo City General Hospital (Nagasaki), Nagasaki University (Nagasaki), Tsukuba University (Ibaraki), Jichi Medical University (Tochigi), Gunma University (Gunma), Teikyo University (Tokyo), Shimane Prefectural Central Hospital (Shimane), Rinku General Medical Center (Osaka), Oakayama Medical Center (Okayama), Miyagi Prefectural Cancer Center (Miyagi), Yokohama City University (Kanagawa), Dokkyo Medical University (Tochigi), Kobe University (Hyogo), Yokohama City University Medical Center (Kanagawa), National Defense Medical College Hospital (Saitama), Sapporo Medical University (Hokkaido), Osaka City University (Osaka), Fukuoka University Hospital (Fukuoka), Saga

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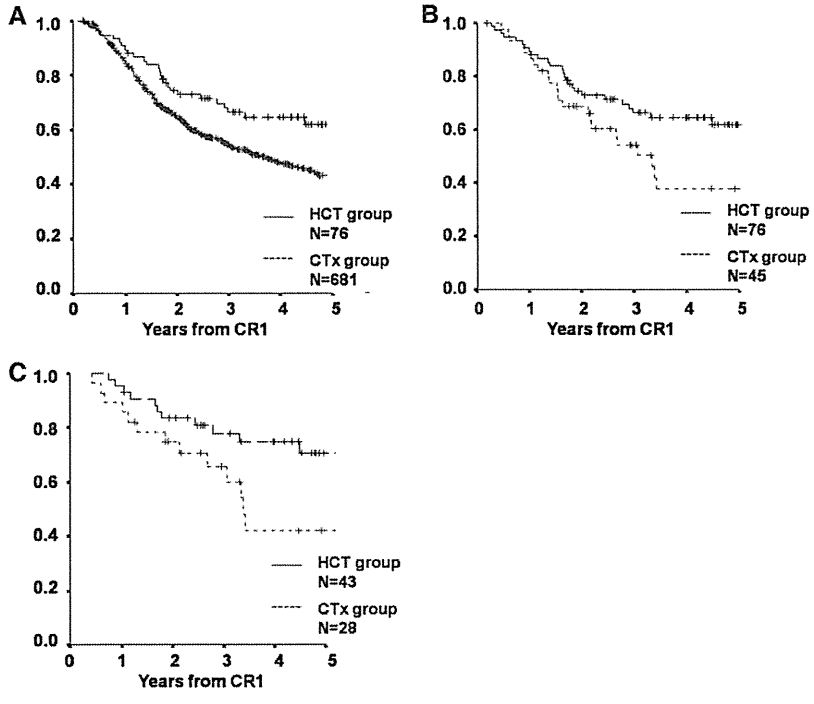
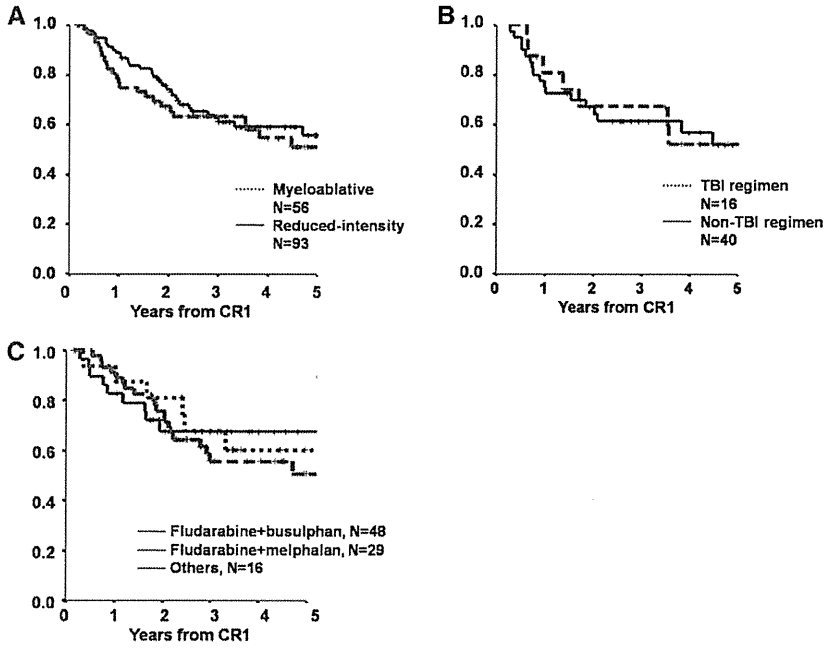


Appendix 1. Overall survival from CR1 are compared between the patients who received allogeneic transplantation in first complete remission and those who did not among the group of patients who had a suitable related donor. (A) Comparison of the two groups when 622 patients who did not have their HLA typed (those who were not known to have a suitable related donor) were included in the chemotherapy group (66% versus 54%, $P = .011$). (B) Comparison of the two groups when landmark was extended to 5 months from CR1 (66% versus 54%, $P = .068$). (C) Comparison of the two groups limited to intermediate-risk AML patients (78% versus 63%, $P = .048$).



Appendix 2. (A) Overall survival (OS) rates from CR1 are compared between myeloablative and reduced-intensity conditioning regimens. There were no significant differences between myeloablative and reduced-intensity conditioning regimens (63% versus 61%, $P = .571$). (B) OS did not differ significantly according to the application of total-body irradiation among patients who received myeloablative regimen (TBI regimen versus non-TBI: 67% versus 61%, $P = .932$). (C) Among patients who received reduced-intensity conditioning regimen, OS from CR1 did not differ significantly among different regimens (fludarabine + busulfan-based, 56%; fludarabine + melphalan-based, 67%; others, 68%, $P = .862$).

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ORIGINAL ARTICLE

Clinical efficacy and safety of biapenem for febrile neutropenia in patients with underlying hematopoietic diseases: a multi-institutional study

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Abstract A multi-institutional study was conducted to assess efficacy and safety of biapenem (BIPM), a carbapenem antibiotic, as an initial-stage therapeutic agent for febrile neutropenia (FN) in patients with hematopoietic diseases. A total of 216 patients from 25 medical institutions were enrolled in this study; of these, 204 were included in the safety analysis and 178 in the efficacy analysis. The combined (excellent and good) response rate was 67.9%, and antipyretic effect (subsidence + tendency to subsidence) was achieved within 3 and 5 days of treatment in 67.3 and 75.9% of patients, respectively. Thus, the clinical responses were gratifying. A response rate of 61.7% (37/60) was observed even in high-risk FN patients in whom neutrophil counts prior to and at 72 h after the start of BIPM were $\leq$100/μl. BIPM is considered to be a highly promising drug, with prompt onset of clinical benefit, as an initial-stage therapeutic agent for the treatment of FN in patients with hematopoietic diseases.

For the Study Group for Infectious Disease involved in hematopoietic diseases.

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Keywords Biapenem · Febrile neutropenia · Hematopoietic diseases

Introduction

Neutropenia associated with intensive chemotherapy, radiation therapy, or hematopoietic stem cell transplantation for acute leukemia and other hematopoietic diseases or solid cancers is often accompanied by discomforting fever and precipitates serious exacerbation in several instances. The disease state associated with neutropenia has come to be referred to by the term febrile neutropenia (FN). Guidelines for treating FN were first issued in 1990, primarily by the Infectious Diseases Society of America (IDSA) [1], and have been revised on two occasions [2, 3]. In Japan, a guideline for treating FN was first published in 1998 by Masaoka and colleagues [4]. FN was also listed in the Japanese national health insurance reimbursement list in 2004. The guideline for FN recommends early-stage treatment with broad-spectrum antimicrobial agents. Cefepime and carbapenems are often administered for empirical treatment of FN in Japan. Biapenem (BIPM) is a carbapenem antibiotic endowed with broad-spectrum antibacterial activity and a quick bactericidal effect and is remarkably stable against renal dehydropeptidase-1 (DHP-1) [5]. It was launched into the market in March 2002. Treatment with BIPM has been shown to yield high response rates of 86.4–100% in patients with respiratory tract, urinary tract, intraperitoneal, and obstetric/gynecologic infections, with a response rate as high as 91.7% (data at the time of approval) in patients with sepsis, so that "sepsis" was approved as an additional indication for the drug in February 2004. Its widespread use in clinical settings is expected. However, there is still limited information on the usefulness of this drug in managing FN [6, 7], and our multi-institutional study was conducted to assess the clinical responses to treatment with BIPM and confirm efficacy and safety in the treatment of FN in patients with hematopoietic diseases.

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Patients and methods

Patients

Patients from the participating institutions who had hematopoietic diseases and developed complicating FN and gave informed consent for participation between June 2006 and September 2007 were enrolled in this study. Definition of FN in patients with hematopoietic diseases (patients meeting the conditions specified below, with the exception of those whose clinical condition was rated as low-risk by the attending physician[1]) were (1) neutropenia: peripheral blood neutrophil count of <1000/μl at the start of the treatment, even if the count appeared likely to decrease to <500/μl; and (2) fever: axillary temperature ≥37.5°C and oral temperature ≥38.0°C in the measurements obtained once.

Exclusion criteria

1. Patients in whom significant effectiveness of the drug against the potential causative organisms cannot be expected
2. Patients with serious cardiac, hepatic, and/or renal dysfunction
3. Patients with a history of hypersensitivity to β-lactam antibiotics
4. Patients with a predisposition to allergies
5. Patients strongly affected by aging and unsuitable for drug evaluation
6. Pregnant and possibly pregnant women and lactating mothers
7. Patients with convulsive disorders, e.g., epilepsy
8. Patients under treatment with valproic acid
9. Other patients judged by the attending physician as being unsuitable for the study

Method of drug administration

Dosage and administration

BIPM (Meiji Seika Kaisha Ltd, Tokyo, Japan) was administered at the dosage of 0.6 or 1.2 g in two divided doses, each given, in principle, by intravenous drip infusion over 2 h or (over 30–60 min. Treatment was initially started at the above dosage and administration schedule and was continued in accordance with the FN guideline (Fig. 1: see the flowchart of treatment in this study).

[1] Patients with fever obviously not attributable to infection were excluded.

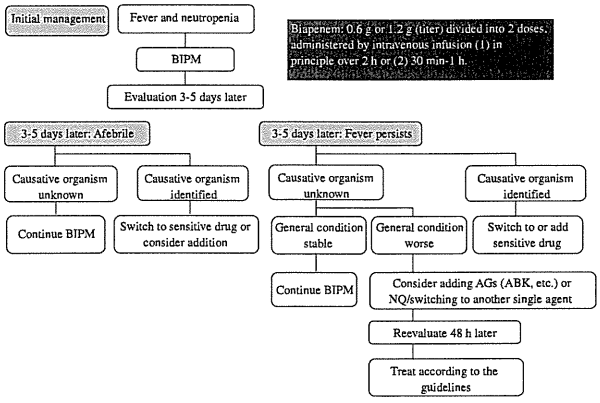

Fig. 1 Summary of treatment algorithm for managing febrile neutropenic (FN) patients. Treatment with biapenem (BIPM) was initially administered at 0.6 or 1.2 g (titer) in two divided doses, each dose given, in principle, by intravenous drip infusion over 2 h or 30–60 min. It usually takes 3–5 days after onset of therapy for a significant improvement in FN to occur. Unless the patient's condition deteriorates rapidly, close follow-up while the same antibiotics are administered is warranted. Defervescence within 3–5 days: When the patient becomes afebrile within 3–5 days of treatment, therapy is continued. If a causative microorganism has been identified, therapy can be adjusted accordingly while a broad-spectrum coverage is maintained. The *panel* suggests that as long as the patient remains in good condition, the initial antibiotic can be continued, regardless of isolated microorganisms. Persistent fever after 3–5 days: If the patient continues to be febrile 3–5 days after treatment with antibiotics begins, he or she should be reevaluated with a thorough physical examination. When cultures of infectious foci or blood yield positive results, and susceptibility of the isolated microorganism is known, specific antimicrobials are added to the ongoing therapy for patients with severe neutropenia. If causes of fever are not identified but the patient is otherwise in a good condition, the same regimen can be continued. If a causative microorganism is unknown, an aminoglycoside should be added, or it can be changed to a broad-spectrum cephalosporin. A 48-h observation period and another reevaluation should follow the change in antimicrobials

Case enrollment procedure

Patient enrollment was performed using the FAX-based centralized enrollment scheme.

Therapeutic response rating

Antipyretic effect on days 3 and 5 (criteria)

Subsidence of fever: Patient's temperature consistently remains at ≤37.0°C, and the drop in body temperature is not due to exacerbation of infection.
Tendency of the fever to subside: Patient's temperature is <38.0°C and decreases by 0.5°C or more on day 3 or day 5 compared with the temperature measured prior to the start of the study medication; the drop in temperature is not due to exacerbation of infection.
Persistence of fever: Any condition other than the above.
Unassessable: Difficult to rate the antipyretic effect of the drug because of overlap with the response to drug(s) used for treatment of the underlying disease, adverse reaction(s) eventually leading to discontinuation of the study medication, or death.

Efficacy (antipyretic effect/clinical response) on day 7 (criteria)

Excellent: Fever subsides within 3–5 days of the start of the administration of BIPM, the patient's temperature remaining normal (≤37.0°C) for 2 days or more thereafter, with improvement of symptoms and laboratory findings associated with the infection.
Good: Fever recedes within 3–5 days of the start of BIPM administration, the patient's temperature returning to normal within 7 days while still on the same medication, with improvement of symptoms and laboratory findings associated with the infection.
Poor: Any condition other than the above.
Unassessable: Adverse event(s) reaction(s) eventually leading to discontinuation of BIPM administration or marked influence of concurrently administered medication (for treatment of the underlying disease).

Bacteriological response (criteria)

Eradicated: The causative organism (including suspected causative organisms) has been eradicated or marked symptomatic improvement at the conclusion of the study, resulting in unfeasibility of specimen collection.
Diminution or partial elimination: Causative organism (including suspected causative organisms) has definitely diminished in infection density or a plurality of causative organisms can be demonstrated with evidence of partial elimination.
Persistence: Indefinite, no diminution, or increase in infection density of the causative organisms (including suspected causative organisms).
Microbial substitution: Substituting organism causes inflammation.
Unassessable: No causative organism can be identified or changes in infection density of the causative organism over time remain unclear.

Statistical analysis

Statistical comparisons were performed using Fisher's exact test. P value of <0.05 was considered statistically significant.

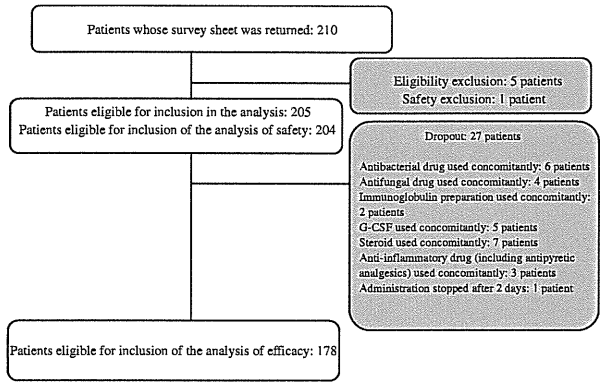

Fig. 2 Safety and efficacy analysis of biapenem (BIPM) carried out based on intention to treat in 178 patients

Results

Distribution of patients

In all, 216 patients from 25 hospitals were enrolled in the study. Survey forms with study data were retrieved from 210 of the 216 patients, of whom 204, excluding six who failed to meet the enrollment criteria, were subjected to the safety analysis. Of these 204 patients, 178 (excluding 26 who had been started on any of other restricted antimicrobial agents, immunoglobulin preparations, granulocyte-colony-stimulating factor (G-CSF) preparations, or corticosteroids on the same day as the start of the study medication) were included for efficacy evaluation (Fig. 2).

The decision as to whether any given patient may be enrolled in the study and whether he or she should be included in the analysis was made by the Case Conference constituted by the members of the Response Evaluation Committee.

Patient background characteristics

Demographic and baseline clinical characteristics of the 178 patients included in the efficacy analysis population are summarized in Table 1. There were 113 male and 65 female patients, ranging broadly in age from 18 to 90 years. The underlying disease was acute myelogenous leukemia in 72 patients and non-Hodgkin's lymphoma in 59 patients, together accounting for 73.5% of all patients (Table 2).

BIPM was administered in doses of 0.3 g b.i.d. in 85 patients and 0.6 g b.i.d. in 83 patients, of whom only 33 received the 2-h intravenous infusions as advocated, taking into consideration the pharmacokinetics/pharmacodynamics (PK-PD) of the drug. Table 3 shows the numbers of patients classified by dosage and administration schedule. Mean duration of BIPM administration was 10.1 days (Table 3).

Table 1 Patient background

Background factors	Number of patients: 178	Composition rate (%)
Stage		
Initial	121	68.0
Recurrence	55	30.9
Unknown	2	1.1
Gender		
Male	113	63.5
Female	65	36.5
Age	18–90 (median 54.4) years	
Body weight	34–100 kg (median 58.5 kg)	
PS		
0	81	45.5
1	64	36.0
2	21	11.8
3	10	5.6
4	1	0.6
Unknown	1	0.6

PS Performance status

Table 2 Patient background (underlying diseases)

Underlying diseases	No. of patients: 178	Composition rate (%)
Acute myelogenous leukemia	72	40.4
Acute lymphoblastic leukemia	14	7.9
Chronic myelocytic leukemia	3	1.8
Myelodysplastic syndrome	9	5.1
Non-Hodgkin's lymphoma	59	33.1
Hodgkin's lymphoma	2	1.1
Multiple myeloma	1	0.6
Aplastic anemia	1	0.6
Other	8	0.4

Clinical response

Clinical responses were evaluated in 162 of the 178 patients; 16 of the 178 were judged to be unassessable in terms of clinical response. The therapeutic response during the first 7 days of treatment with BIPM was excellent in 71 (43.8%), good in 39 (24.1%), and poor in 52 (32.1%); hence a response rate (percentage of combined excellent and good responders) of 67.9% (Fig. 3).

In patients obtaining relief from fever within 3–5 days of the start of BIPM administration, subsidence of fever was achieved in 61 and the fever tended to subside in 48 within 3 days of start of the study medication (67.3%). Subsidence of fever was achieved in 86 patients and fever showed a tendency toward subsidence in 37 patients within 5 days (75.9%) (Table 4).

Table 3 Dosage method and duration of administration

Item	No. of patients	Composition rate (%)
Dosage		
0.3 × 2	85	47.8
0.6 × 2	83	46.6
Other	10	5.6
IV drip time		
120 min	33	18.5
30–60 min	138	77.5
Unknown	7	3.9
No. of days administered	Mean: 10.1 (minimum 2; maximum 30)	

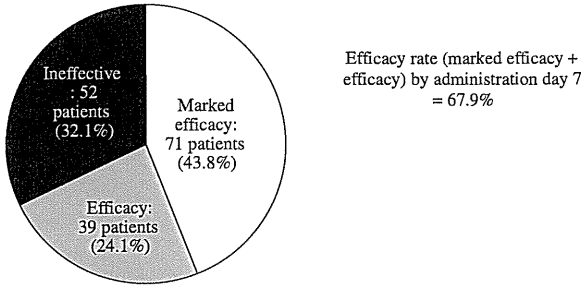

Fig. 3 Clinical efficacy shown in the *circle*. Clinical responses were evaluated in 162 of the 178 patients included in the efficacy analysis population; 16 of the 178 were judged to be unassessable in terms of the clinical response

As for clinical responses classified by the underlying hematopoietic disease, the response rate was 65.2% in patients with acute myeloid leukemia, 62.7% in patients with non-Hodgkin's lymphoma, 61.5% in patients with acute lymphocytic leukemia, and 66.7% in patients with myelodysplastic syndrome (MDS). There was no significant difference in response rates among disease categories (Table 5).

Clinical response by the neutrophil count

Data were analyzed with patient stratification according to neutrophil count, which is considered one of the background factors, in particular, exerting influence on clinical response to treatment. For FN patients whose baseline (i.e., before the start of BIPM administration) neutrophil counts were ≤100/μl and whose neutrophil counts at 72 h after the start of the study medication were still ≤100/μl (reflective of a severely myelosuppressed status) the response rate was 61.7% (37/60). In patients with a baseline neutrophil count of ≤100/μl in whom neutrophil count at 72 h after the start of the study medication was 101–500 or ≥501/μl, response rates were 83.3 (5/6) and 85.7% (6/7), respectively. The response rate tended to increase with progressive recovery of neutrophil count (Table 6).

Table 4 Antipyretic effect

Defervescence rate	No. (%)
Within 3 days	
Subsidence of fever + tendency toward subsidence of fever[a]	109 (67.3)
Subsidence of fever	61 (37.7)
Within 5 days	
Subsidence of fever + tendency toward subsidence of fever	123 (75.9)
Subsidence of fever	86 (53.1)

[a] Tabulation of 162 patients after excluding 16 who were incapable of being evaluated

Clinical response by dosage and administration

Response rates of patients treated with BIPM at 0.3 g b.i.d. and 0.6 g b.i.d. were 64.0 and 73.1%, respectively. Furthermore, in patients administered BIPM by 2-h intravenous infusions in consideration of the PK-PD of the drug, the response rate was 62.5%, which was not significantly different from that in patients administered the drug over the usual duration of intravenous infusion (30–60 min) (Table 7). Stratification of response rates by dose level and infusion time revealed that the response rate in patients administered BIPM at 0.6 g b.i.d. by a 2-h intravenous infusion, although few, was as high as 83.3% (5/6) (Table 8).

Bacteriological response

As regards bacteriological responses, pathogenic organisms were isolated by blood culture from 24 patients (30 isolates), including methicillin-sensitive *Staphylococcus epidermidis* (MSSE) (six patients), methicillin resistant coagulase-negative staphylococci (MRCNS) including methicillin-resistant *S. epidermidis* (MRSE) (5 patients), methicillin-resistant *S. aureus* (MRSA) (three patients), and methicillin-sensitive *S. aureus* (MSSA) (two patients) in gram-positive bacteria, and *Escherichia coli* (four patients) in gram-negative bacteria. The bacteriological responses classified by the genus/species of the isolated organisms are presented in Table 9. The relationship between bacteriological responses and clinical responses in 24 patients with isolated pathogenic organisms is shown in Table 10. Of the 24 patients, 13 were responders (marked efficacy + efficacy) and 11 were nonresponders; from five nonresponders, the resistant bacteria, such as MRSA and MRSE, were isolated.

Adverse reactions

Of the 204 patients included in the safety analysis population, 13 (6.4%) experienced adverse reactions, which

Table 5 Clinical response according to underlying disease

	Marked efficacy	Effective	Ineffective	Unable to evaluate	Total	Efficacy rate (marked efficacy + efficacy)/number of evaluable patients (%)
Acute myelogenous leukemia	24	19	23	6	72	43/66 (65.2)
Acute lymphoblastic leukemia	7	1	5	1	14	8/13 (61.5)
Chronic myelocytic leukemia	3	–	–	–	3	3/3 (100.0)
Myelodysplastic syndrome	3	3	3	–	9	6/9 (66.7)
Non-Hodgkin's lymphoma	22	10	19	8	59	32/51 (62.7)
Hodgkin's lymphoma	1	1	–	–	2	2/2 (100.0)
Multiple myeloma	4	4	1	–	9	8/9 (88.9)
Aplastic anemia	1	–	–	–	1	1/1 (100.0)
Other	6	1	1	1	9	7/8 (87.5)
Total	71	39	52	16	178	110/162 (67.9)

Table 6 Clinical response according to neutrophil count

No. of effective cases/no. of patients[a] (efficacy rate)	Neutrophil count 72 h after administration				Total (%)
	≤100/μl (%)	101–500/μl (%)	≥501/μl (%)	Unknown (%)	
Neutrophil count before administration					
≤100/μl	37/60 (61.7)	5/6 (83.3)	6/7 (85.7)	17/21 (81.0)	65/94 (69.1)
101–500/μl	11/13 (84.6)	12/17 (70.6)	4/4 (100.0)	4/10 (40.0)	31/44 (70.5)
≥501/μl	1/2 (50.0)	2/4 (50.0)	4/5 (80.0)	7/13 (53.8)	14/24 (58.3)
Total	49/75 (65.3)	19/27 (70.3)	14/16 (87.5)	28/44 (63.6)	110/162 (67.9)

[a] Tabulation of 162 patients after excluding 16 who were incapable of being evaluated

included liver-function-related events (13), rash/drug eruption (four), paroxysmal supraventricular tachycardia (one), abdominal pain (one), and fever (one) (Table 11). The incidence of adverse reactions among patients aged ≥65 years and those with depressed renal function are presented in Table 12. There were no deaths that were judged to be causally related to BIPM administration.

Discussion

It is of vital clinical importance to provide appropriate therapy for infections complicating hematopoietic disorders, as infections reportedly rank first among the causes of death in these patients, particularly those with acute leukemias and MDS [8]. FN occurring as a complication in patients with hematopoietic disorders may be associated with serious outcomes, and the patient prognosis can be profoundly affected by appropriate investigation, precise diagnosis, and prompt institution of empirically proven effective antimicrobial agents. BIPM has been demonstrated to have a broad-spectrum antibacterial activity against gram-positive and gram-negative organisms, including *Pseudomonas aeruginosa*, and exerts a rapid bactericidal effect. Satisfactory antimicrobial activity of this antibiotic has been maintained since it was first launched into the market in 2002 [9]. As a unique clinical feature of this drug, it was proved to have an earlier effect than imipenem/cilastatin in a comparative trial, particularly for the treatment of lower respiratory tract infections [10].

This study was conducted in patients treated at the institutions listed in Table 13 with the objective of assessing the efficacy and safety of BIPM in patients with acute myeloid leukemia, non-Hodgkin's lymphoma, or other hematopoietic disorders. Response rate in the efficacy analysis population was 67.9%, being comparable with response rates reported from other studies of drugs belonging to a similar class for similar indications in patients with the same disorders [11–13]. According to the 2004 Guideline for Management of FN, subsequent therapy should be selected on the basis of the response evaluated 3–5 days after the start of initial treatment in initial management. Assessment of therapeutic response in the early stage is a point of great importance, and, in this context, the excellent response rate of 43.8% and the antipyretic rate of 67.3% within 3 days and 75.9% within 5 days of start of

Table 7 Clinical response according to administration and dosage (1)

	No. of patients[a]	Effective	Ineffective	Efficacy rate (%)	Statistical test (Fisher)
Dosage					
No. of patients[a]	162	110	52	67.9	$p = 0.296$
0.3 g × 2	75	48	27	64.0	
0.6 g × 2	78	57	21	73.1	
Other	9	5	4	55.6	
Intravenous infusion time					
No. of patients[a]	162[a]	110	52	67.9	$p = 0.527$
30–60 min infusion	123	85	38	69.1	
2 h infusion	32	20	12	62.5	
Unknown	7	5	2	71.4	

[a] Tabulation of 162 patients after excluding 16 who were incapable of being evaluated

Table 8 Clinical response according to administration and dosage (2)

	No. of patients[a]	Effective	Ineffective	Efficacy rate (%)	Statistical test (Fisher)
0.3 g × 2 group					
No. of patients[a]	75	48	27	64.0	$p = 0.797$
30–60 min IV infusion	46	30	16	65.2	
2-h IV infusion	25	15	10	60.0	
Unknown	4	3	1	75.0	
0.6 g × 2 group					
No. of patients[a]	78	57	21	73.1	$p = 1.000$
30–60 min IV infusion	71	51	20	71.8	
2-h IV infusion	6	5	1	83.3	
Unknown	1	1	–	100.0	

[a] Tabulation of 162 patients after excluding 16 who were incapable of being evaluated

Table 9 Antimicrobial efficacy

	No. isolated	Eradicated	Diminution	Persistence	Substitution	Unknown
MSSE	6	2				4
MRCNS (including MRSE)	5	1		1		3
MRSA	3			1	2	
MSSA	2	1	1			
Streptococcus spp.	3	1				2
Enterococcus spp.	2				1	1
Total gram-positive bacteria	21	5	1	2	3	10
Escherichia coli	4	2			1	1
Enterobacter cloacae	1					1
Serratia marcescens	1	1				
Stenotrophomonas maltophilia	1			1		
Proteus vulgaris group	1					1
Capnocytophaga spp.	1					1
Total[a]	30	8	1	3	4	14

MSSE methicillin-sensitive *Staphylococcus epidermidis*, *MRCNS* methicillin resistant coagulase-negative staphylococci, *MRSE* methicillin-resistant *S. epidermidis*, *MRSA* methicillin-resistant *S. aureus*, *MSSA* methicillin-sensitive *S. aureus*

[a] Total number of isolates, 30 (microbial detection 24 patients)

Table 10 Relationship between bacteriological and clinical responses

	Clinical efficacy ($N = 24$)		
	Marked efficacy ($N = 6$)	Effective ($N = 7$)	Ineffective ($N = 11$)
Bacterial response			
Eradicated	3	2	3
Diminution	1	0	2
Persistence			3
Substitution		1	1
Unknown	2	4	2

Table 11 Breakdown of adverse events

Adverse event	No. of events[a]
Liver-function-related	13
Rash/drug eruption	4
Paroxysmal supraventricular tachycardia	1
Abdominal pain	1
Fever	1
Total	20 events/13 patients (6.4%)

[a] Patients eligible for evaluation of safety: 204

the administration observed in this series following treatment with BIPM are worthy of good appraisal.

Decrease in neutrophil count is a factor of prime importance in the treatment of FN, and it is generally recognized that the risk of development and rate of progression of infections vary with duration of sustained FN, rate and severity of decrease of neutrophil count, and recovery status. In fact, it has been reported that the incidence of infection rises when the neutrophil count is ≤500/μl, and the incidence of a fatally severe infection, including sepsis, is markedly elevated when the neutrophil count is ≤100/μl [14]. The data presented in this report represent remarkably gratifying clinical responses, with a response rate of 61.7% (37/60) even in high-risk FN patients in whom the neutrophil counts prior to and at 72 h after the start of BIPM were ≤100/μl.

In recent years, appropriate use of antimicrobial agents based on the PK-PD theory has been recommended and has become widespread in the treatment of infections in patients with immune deficiency states such as FN, because responses to β-lactam antibiotics, including carbapenems, have been shown to be correlated with the time above the minimum inhibitory concentration (T > MIC%), and such correlation with T > MIC% has also been reported for BIPM [15–19]. In view of this, we adopted a protracted 2-h intravenous infusion schedule to obtain greater T > MIC%. Results revealed no significant difference in the response rate between a cohort administered the drug by 2-h intravenous infusion (62.5% [20/32]) and that administered infusion over the usual 30–60 min [69.1% (85/123)]. However, when response rates were compared by dose and infusion time, a high clinical efficacy with a response rate up to 83.3% (5/6) was observed in patients who were administered BIPM at 0.6 g b.i.d. by 2-h intravenous infusion. Further study is therefore needed to establish the optimal method BIPM administration.

The causative microorganisms often remain unclear in patients with FN. The reported percentage of FN patients with a positive blood culture is ≤10%, whereas clinically overt infections such as stomatitis or pneumonia and fever of unknown etiology are said to account for 10–20 and 70–80% of FN patients, respectively [20, 21]. In our study, causative organisms were isolated from 24 (13.5%) of 178 patients studied, and gram-positive bacteria mainly comprising *S. epidermidis*, including MRSE, and *S aureus*, including MRSA, accounted for 70% of the isolates. These results support a recent report concerning clinical bacterial isolates [22], and the current trend of an increasing rate of isolation of gram-positive organisms as the causative pathogens is considered to be attributable to prolonged use of central venous catheters and prophylactic use of oral

Table 12 Safety evaluation

	No. of patients	Adverse events	Incidence of adverse events (%)	Statistical test (Fisher)
Incidence of adverse reactions in elderly patients				
No. of patients	204	13	6.40	$p = 1.000$
<65 years	138	9	6.50	
≥65 years	66	4	6.10	
Incidence of adverse reactions according to renal function (creatinine clearance) prior to the start of administration				
No. of patients	204	13	6.4	$p = 1.000$
<50 years	12	1	8.3	
50–79 years	31	2	6.5	
≥80 years	115	9	7.8	
Unknown	46	1	2.2	