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Original Article

A Comparative Analysis of Meropenem and Doripenem in Febrile Patients with Hematologic Malignancies: a Single-Center Retrospective Study

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SUMMARY: Many patients with hematologic malignancies show immunosuppression and/or neutropenia, and are at a high risk of developing a serious infection that would require empiric therapy with broad-spectrum antibiotics. However, a thorough comparison of the efficacies of different carbapenems has not been carried out. To compare the efficacies of meropenem (MEPM) and doripenem (DRPM) in febrile patients with hematologic neoplasms, we retrospectively reviewed data of 149 consecutive febrile patients with acute myeloid leukemia, acute lymphoblastic leukemia, or myelodysplastic syndrome (MDS) who were treated empirically with MEPM or DRPM. The duration from the start of carbapenem administration to decline of fever was not significantly different between the MEPM and DRPM groups (median, 3 versus 4 days; $P = 0.79$). Multivariate analysis showed that a diagnosis of MDS and the use of liposomal amphotericin-B or voriconazole are statistically significant risk factors for sustained fever. In conclusion, MEPM and DRPM showed similar efficacies in febrile patients with acute leukemia and MDS.

INTRODUCTION

Serious bacterial infections are relatively common in patients with hematologic malignancies because of immunosuppression due to both cytotoxic therapy and/or the hematologic disorder itself. Febrile patients with hematologic malignancies, especially patients with febrile neutropenia, can rapidly become severely ill, and empirical therapies with broad-spectrum antibiotics are needed. The Infectious Diseases Society of America (IDSA) guidelines for the use of antibiotics in neutropenia patients with cancer (1) recommend monotherapy with an antipseudomonal β-lactam agent, such as cefepime, carbapenem, or piperacillin/tazobactam, as the first-line empirical therapy. In patients with persistent fever receiving third/fourth-generation cephalosporin, the recommendations often include a switch to a carbapenem and addition of an anti-methicillin-resistant staphylococcal drug and/or an anti-fungal drug, even when the cause of fever is unclear.

However, we know little about which carbapenem should be used for treatment of patients with hematologic malignancies. In this study, we retrospectively reviewed outcomes of carbapenem administration to compare the efficacies of meropenem (MEPM) and doripenem (DRPM) in febrile patients with hematologic malignancies.

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MATERIALS AND METHODS

Patients: We retrospectively reviewed 149 consecutive patients ($\geq$16 years of age) with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), or myelodysplastic syndrome (MDS) who were hospitalized at The University of Tokyo Hospital, Tokyo, Japan, and were administered MEPM or DRPM between March 2009 and July 2010 for fever. We excluded 25 patients, including those who stopped receiving carbapenems within 4 days, those in which bloodstream or catheter-related methicillin-resistant staphylococcal infections were detected, those with probable/proven fungal infections at the beginning of carbapenem administration, and those who were considered to have paraneoplastic fever. Thus, we included 124 patients in this study. We assumed the presence of paraneoplastic fever when patients had fever that was resistant to carbapenem use for more than 7 days, resistant to antifungal and anti-methicillin-resistant staphylococcal drug use, that had no focal signs or evidence of infection, and that declined soon after chemotherapy.

The following characteristics were recorded: gender, age, disease type (AML, ALL, or MDS), disease status (in complete remission or not), history of stem cell transplantation, type and dosage of carbapenem, days of administration, duration of grade 4 neutropenia, infection site, administration of antifungal drugs other than for prophylactic use (i.e., voriconazole [VRCZ] or liposomal amphotericin-B [L-AMB]), anti-methicillin-resistant staphylococcal drug use, causative organisms, and focus.

This study was conducted in accordance with the Helsinki Declaration and was approved by the Ethics Committee of The University of Tokyo Hospital. All patients provided written informed consent for the

retrospective use of data.

Therapeutics and clinical assessment: When patients received intravenous chemotherapy, oral fluoroquinolone and an oral antifungal agent (fluconazole or itraconazole) were administered for prophylaxis from the time of chemotherapy initiation to the time of neutrophil recovery. For patients with ALL, sulfamethoxazole-trimethoprim was also added for prophylaxis. When patients became febrile, intravenous antibiotics were started and oral antibiotics were stopped if administered. Although the IDSA guidelines do not recommend switching from the first-line treatment to carbapenems solely on the basis of persistent fever, this is a widely accepted practice in Japan. Prophylactic antifungal agents, such as fluconazole or itraconazole oral solution, were also administered when patients received intravenous chemotherapy. We defined ''pretherapy'' as the antibiotics used just prior to carbapenem administration.

Blood cultures were performed before administering intravenous antibiotics, before changing antibiotics, and on detecting a clinical indication such as persistent fever. Cultures from other sites than blood were also obtained as needed, and imaging tests such as chest X-ray and computed tomography scanning were administered to detect the source of fever.

The typical administered dose was 1 g BID or 1 g TID (according to insurance) in the MEPM group, and 0.5 g TID in the DRPM group. Dosage was adjusted according to renal function.

Vancomycin or teicoplanin was added when Gram-positive coccal infection was suspected, and VRCZ or L-AMB was administered when invasive fungal infections such as those caused by *Aspergillus* spp. were suspected. De-escalation of antibiotics was accomplished based on the susceptibility of the isolated pathogen or patient intolerance.

Decline of fever was defined as a body temperature less than 37.5°C sustained for more than 48 h without scheduled antipyretic medication.

Statistical methods: Categorical variables were compared between the MEPM and DRPM groups by Fisher's exact test, and numerical variables by the *t* test. The incidence of fever decline was calculated using the Kaplan-Meier method, and the log-rank test was applied to evaluate whether the difference was significant.

The impacts of various parameters on the decline of fever were evaluated in univariate analyses with log-rank tests, and in multivariate analyses using the Cox proportional hazards regression model. Factors with *P*-values ≤ 0.1 in the univariate analyses were included in the multivariate analysis for the rate of pyretolysis. The hazard ratio (HR) was estimated with a 95% confidence intervals (CIs) and the respective *P*-values were reported from these analyses. All *P*-values are two-sided, with the type I error rate fixed at 0.05. Statistical analyses were performed with JMP 9 (SAS Institute, Cary, N.C., USA) and R 2.12.0 software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients: Of the 124 subjects, 82 patients were administered MEPM and 42 patients were given DRPM. Their clinical characteristics are shown in Table 1. The MEPM group tended to be younger than the DRPM group (median age, 61 versus 67.5; $P = 0.078$). The proportion of patients who received hematopoietic stem cell transplantation (HSCT) during hospitalization was significantly higher in the DRPM group (1.22% versus 11.9%; $P = 0.031$). The proportion of patients in the MEPM group who were administered DRPM before starting MEPM was significantly lower than the proportion of patients in the DRPM group who were administered MEPM before starting DRPM (8.53% versus 40.4%; $P < 0.0001$). The median administration period was 13 days in the MEPM group and 12.5 days in the DRPM group ($P = 0.91$). The median number of days with grade 4 neutropenia was 13 in the MEPM group and 19.5 in the DRPM group ($P = 0.15$).

Efficacy: The incidence of fever decline was not significantly different between the MEPM and DRPM groups ($P = 0.61$; Fig. 1). The rates of fever decline within 7 days were 67.9% in the MEPM group and 65.0% in the DRPM group, and the rates of fever decline within 14 days were 87.4% in the MEPM group and 82.0% in the DRPM group. The median number of days from the start of carbapenem administration to the decline of fever was 3 in the MEPM group and 4 in the DRPM group.

In order to offset the biased backgrounds of the MEPM and DRPM groups, we conducted sub-analyses with subjects of uniform backgrounds. A subgroup of non-HSCT patients ($n = 104$) showed similar incidences of defervescence between the MEPM and DRPM groups ($P = 0.52$), and a subgroup of febrile neutropenia patients ($n = 101$) also showed similar incidences of fever decline between the groups ($P = 0.30$). Similarly, in patients who had not switched from other carbapenems ($n = 100$) the incidence of pyretolysis was not significantly different between the groups ($P = 0.63$). In the DRPM group ($n = 42$), the incidence of pyretolysis were similar between patients who had switched from MEPM ($n = 17$) and other patients ($P = 0.89$). This tendency was also seen in the MEPM when comparing patients who had switched from DRPM and other patients ($P = 0.59$).

Univariate analysis for the rate of fever decline showed that a diagnosis of MDS ($P = 0.021$) correlates with the low rate of pyretolysis, whereas the type of carbapenem was not revealed to be a risk factor (Table 2). Factors with *P*-values ≤ 0.1 in the univariate analyses, i.e., disease status ($P = 0.069$) and the use of VRCZ or L-AMB ($P = 0.092$) were included in the multivariate analysis; the type of carbapenem was also included. Multivariate analysis showed that a diagnosis of MDS (HR, 0.35; 95% CI, 0.12–0.98; $P = 0.046$) and the use of VRCZ or L-AMB (HR, 0.55; 95% CI, 0.32–0.93, $P = 0.027$) were statistically significant risk factors. Type of carbapenem was not revealed to be significant ($P = 0.33$).

Causative organisms and infection sites: The causative organisms were as follows: *Escherichia coli*, 6; *Enterococcus faecium*, 5; *Streptococcus*, 4; coagrase-negative staphylococcus, 3; *Enterobacter cloacae*, 1; *Pseudomonas aeruginosa*, 1; *Corynebacterium*, 1; Gram-positive rod (strain not identified), 1; and unknown, 102.

Infection sites were as follows; pneumonia, 20;

Table 1. Characteristics of patients

		Total (n = 124)	MEPM (n = 82)	DRPM (n = 42)	P value
Average dose/day		—	2.19	1.38	
Median administration days		13.0	13.0	12.5	0.913
Gender	Male	62	43	19	0.569
	Female	62	39	23	
Median age		62	61	67.5	0.0786
Diagnosis	AML	106	68	38	0.249
	ALL	10	9	1	
	MDS	8	5	3	
Disease status	CR	54	38	16	0.590
	Non-CR	52	34	18	
	During induction remission	19	11	8	
SCT history	No	105	70	35	1.00
	Yes	19	12	7	
Antineoplastic therapy	Transplantation	6	1	5	0.0318
	Chemotherapy	108	74	34	
	None	10	7	3	
Febrile neutropenia	Yes	102	65	37	0.225
	No	23	18	5	
Median grade 4 neutropenia days		15.5	13	19.5	0.155
Median intravenous antibiotic line		2	2	2	—
Pretherapy	4th generation cephalosporine	76	57	19	0.0009
	PIPC/TAZ	6	4	2	
	MEPM	17	—	17	
	DRPM	7	7	—	
	New quinolone	11	10	1	
	No antibiotics	7	5	2	
Use of anti-MRSA drug	Yes	60	37	23	0.346
	No	64	45	19	
Use of VRCZ or L-AMB	Yes	25	19	6	0.344
	No	99	63	36	

MEPM, meropenem; DRPM, doripenem; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; CR, complete remission; SCT, stem cell transplantation; PIPC/TAZ, piperacillin/tazobactam; MRSA, methicillin-resistant *Staphylococcus aureus*; VRCZ, voriconazole; L-AMB, liposomal amphotericin-B.

bloodstream or catheter-related bloodstream infection, 15; gingivitis, 4; urinary tract infection, 3; enterocolitis, 2; cholecystitis, 2; peritonitis, 1; and unknown, 77 (Table 3).

DISCUSSION

We retrospectively compared the efficacies of MEPM and DRPM in patients with hematologic malignancies. Previous clinical and non-clinical studies that compared DRPM and other carbapenems revealed no inferiority of DRPM (2–4). Lucasti et al., in a prospective randomized study of patients with complicated intra-abdominal infections, reported that clinical cure rates were 78.9% in patients receiving MEPM, and 77.9% in patients receiving DRPM, after 5–14 days of administration (2). Although it is difficult to make a simple comparison between their study and ours, their clinical cure rates and our rates of fever decline are not very different, suggesting that carbapenem therapy achieves relatively favorable efficacy even in febrile patients with hematologic malignancies. However, past clinical studies targeted at relatively immunocompetent patients are not applicable to febrile patients with hematologic malignancies who require special care because their diseases themselves induce immunosuppression, and most therapies for hematologic disorders cause severe neutropenia and/or other immunosuppression.

The rate of fever decline was not significantly different between the MEPM and DRPM groups in our study. It is true that the MEPM group may have an advantage because of the relatively higher proportion of older patients in the DRPM group, the greater number of patients who received HSCT during hospitalization, and the significantly higher proportion of patients in the DRPM group who were initially administered MEPM than that of patients in the MEPM group who were initially administered DRPM. However, in our study, older age and antineoplastic therapy were not risk factors for sustained fever. DRPM/MEPM use before MEPM/

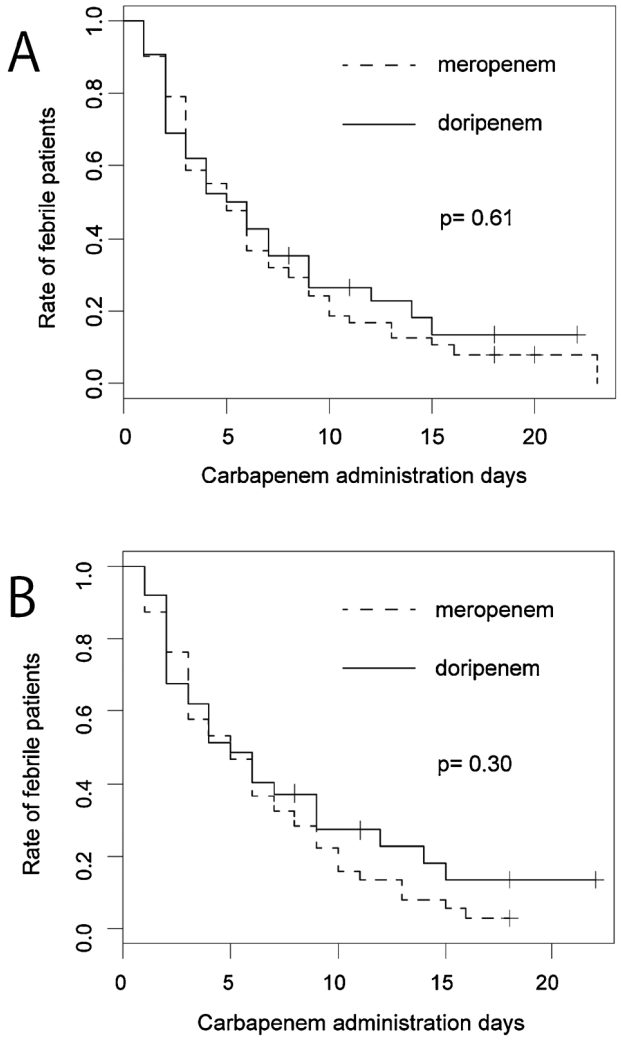

Fig. 1. The rate of defervescence. Kaplan-Meyer estimation for the rate of decline of fever about (A) whole patients (n = 124) and (B) patients with febrile neutropenia (n = 102).

Table 2. Factors associated with decline of fever: univariate and multivariate analysis

Variable	Univariate analysis	Multivariate analysis	
	P value	HR (95% CI)	*P* value
Gender			
Male	0.54		
Female			
Age			
<65	0.21		
≥65			
Carbapenem			
MEPM	0.61	1	
DRPM		0.80 (0.52–1.2)	0.33
Diagnosis			
Acute leukemia	0.021	1	
MDS		0.35 (0.12–0.98)	0.046
Disease status			
CR	0.069	1	
Non-CR		0.67 (0.42–1.0)	0.090
At diagnosis		0.58 (0.32–1.07)	0.082
Febrile neutropenia			
Yes	0.24		
No			
Neutropenia days			
<5	0.13		
≥5			
Anti-MRSA antibiotics			
Yes	0.18		
No			
VRCZ or L-AMB use			
Yes	0.092	0.55 (0.32–0.93)	0.027
No		1	
Intravenous antibiotic line			
≥3	0.72		
<3			
Pretherapy			
4th cefem			
Carbapenem	0.84		
Fluoroquinolone			
Penicillin			
No pretherapy			
Antineoplastic therapy			
SCT	0.14		
Chemotherapy			
None			
Use of prophylactic fluoroquinolone			
Yes	0.32		
No			

Abbreviations are in Table 1.

DRPM administration was also not a risk factor for failure of defervescence (data not shown). Subgroup analyses also showed that the incidence of fever decline was not significantly different according to the type of carbapenem used.

Multivariate analysis detected the use of VRCZ or L-AMB as a risk factor for sustained fever. However, VRCZ or L-AMB administration is considered when fungal infection is suspected or when fever is sustained in spite of the administration of broad-spectrum antibiotics; therefore, it is no surprise that the use of VRCZ or L-AMB correlates with sustained fever.

The prophylactic use of oral fluoroquinolone and antifungal agents (i.e., fluconazole or itraconazole oral solution) during remission induction therapy and consolidation therapy for AML and ALL is relatively common (5). Although a prospective randomized study revealed that prophylactic fluoroquinolone is effective in reducing fever risk (6), there is concern about the risk of producing fluoroquinolone-resistant bacteria. Tanimoto et al. reported that fluoroquinolones enhanced the risk of mutation frequency for carbapenem resistance in *P. aeruginosa* in vitro (7). However, in our study, there was no tendency for prophylactic fluoroquinolone to increase the risk of sustained fever during carbapenem administration.

Tanimoto et al. also reported that carbapenem-resistant mutants in *P. aeruginosa* tended to be selected

Table 3. Infection sites and detected organisms

	Total	MEPM	DRPM
Infection sites			
Pneumonia	20	13	7
Sepsis	15	11	4
Gingivitis	4	2	2
Urinary tract	3	2	1
Enterocolitis	2	2	0
Cholecystitis	2	1	1
Peritonitis	1	1	0
Unknown	77	50	27
Organisms			
Escherichia coli	6	5	1
Enterococcus faecium	5	2	3
Enterobacter cloacae	1	1	0
CNS	3	3	0
Streptococcus	4	2	2
Pseudomonas aeruginosa	1	1	0
Corynebacterium	1	1	0
GPR	1	1	0
Unknown	102	66	36

CNS, coagrase-negative staphylococcus; GPR, Gram-positive rod. Other abbreviations are in Table 1.

by MEPM, but not by DRPM (7). However, in our study, *P. aeruginosa* infection was detected in just 1 patient, and no breakthrough *P. aeruginosa* infection was observed. This may be partially because many patients were administered fourth-generation cephalosporine, which is active against *P. aeruginosa*, before starting a carbapenem. Staphylococci were frequently detected as pathogens in previous studies of febrile patients with hematologic malignancies or neutropenia (8,9); this is not consistent with our data. However, the discrepancy was thought to be due to the fact that vancomycin or teicoplanin was started when Gram-positive cocci were detected in blood culture, and in those cases, carbapenem was rarely administered. Coliform bacteria such as *E. coli* and *E. cloacae* were frequently detected in our study; this is consistent with previous reports (9,10).

It is not clear whether neutropenia really affects the profiles of infectious organisms in hematologic malignancies; previous studies of bloodstream infection in patients with hematologic malignancies showed that there was no significant difference in the range and frequency of bacterial species between patients with or without neutropenia (11,12). Therefore, we conducted both analyses for the entire group of patients as well as for febrile neutropenia patients alone.

Although more than half of the events were fever of unknown origin, pneumonia and sepsis were main sites of infection in our study; this was consistent with previous reports (13,14).

In conclusion, MEPM and DRPM had comparable efficacies for the treatment of febrile patients with acute leukemia and MDS.

Conflict of interest None to declare.

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