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Panipenem Versus Cefepime as Empirical Monotherapy in Adult Cancer Patients with Febrile Neutropenia: A Prospective Randomized Trial

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Objective: To compare the efficacy and safety of panipenem/betamipron with cefepime as empirical monotherapy for adult cancer patients with febrile neutropenia, a randomized, open-label, comparative trial was performed.
Methods: All enrolled patients were randomly assigned to receive either panipenem or cefepime. All febrile episodes were classified as microbiologically defined infection (MDI), clinically defined infection (CDI) or unexplained fever (UF). Clinical responses to antibiotic therapy were defined as success, initial response but regimen modified or failure.
Results: A total of 116 patients were enrolled: 55 patients in the panipenem group and 61 patients in the cefepime group. Demographic and clinical characteristics were similar in the two groups ($P > 0.05$). In the final evaluation, the success rate for the panipenem group (89.1%) was similar to that of the cefepime group (91.8%) (non-inferiority, $P = 0.002$, 95% confidence interval: −13.48%, 10.35%). Of the 18 bacterial isolates, nine (50%) were gram-positive and nine (50%) were gram-negative. The prevalence of adverse events in the panipenem group (23.6%) were similar to those in the cefepime group (23.0%) ($P = 0.93$). All of the adverse events were well tolerated and transient.
Conclusions: Although larger studies are necessary, panipenem appeared to be as effective and safe as cefepime for empirical monotherapy in the treatment of adult cancer patients with febrile neutropenia.

Key words: febrile neutropenia − monotherapy − panipenem

INTRODUCTION

Because the progression of infection in neutropenic patients can be rapid, and because such patients with early bacterial infections cannot be reliably distinguished from non-infected patients at presentation, empirical antibiotic therapy should be administered promptly to all neutropenic patients at the onset of fever (1). Monotherapy using a broad-spectrum β-lactam agent is as effective as and safer than the combination of a β-lactam agent and an aminoglycoside (2). Current guidelines recommend the empirical use of a single β-lactam agent, such as cefepime, ceftazidime, imipenem or meropenem, with or without vancomycin (1).

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Panipenem is a parenteral carbapenem, which has been exclusively used in Japan since the 1990s. It has a broad spectrum and potent bactericidal activity against aerobic, anaerobic, gram-positive and gram-negative organisms including non-fermenter and extended-spectrum β-lactamase producers as well as other carbapenems (3–6). Panipenem also showed better *in vitro* activity against *S. pneumoniae* and caused a lower frequency of seizures than imipenem (7–9).

Carbapenems have been preferred as empirical monotherapy for patients with febrile neutropenia, but no study for panipenem has yet been performed. We performed a prospective, randomized, open-label, comparative trial to compare the efficacy and safety of panipenem and cefepime as empirical monotherapy in adult patients with febrile neutropenia.

PATIENTS AND METHODS

Study Population

This prospective, randomized, open-label, comparative trial was conducted from April 2004 to June 2005 at Samsung Medical Center, a 1250-bed, tertiary teaching hospital in Korea. All adult patients who were over 18 years of age and who received chemotherapy for malignancy or underwent hematopoietic stem cell transplantation were screened for enrollment. Of these, any patients who fulfilled all of the following criteria for clinical and laboratory diagnosis of febrile neutropenia were eligible to participate in this study. Febrile neutropenia was defined as follows: (i) a single oral temperature of $\geq$38.3°C or a temperature of $\geq$38°C for $\geq$1 h, and (ii) an absolute neutrophil count (ANC) of $<$500 cells/μl, or a count of $<$1000 cells/μl with a predicted decrease to 500 cells/μl.

Patients were excluded from this study if they met any of the following criteria: history of hypersensitivity reactions and severe adverse events to carbapenem, cephalosporin or glycopeptide; prior use of systemic antibiotic(s) within 72 h before enrollment; pregnancy or lactation; known aplastic anemia, myelodysplastic syndrome, leukemia, central nerve system infection, infective endocarditis, HIV infection; severe renal dysfunction (serum creatinine $>$ 2.5 mg/dl, on hemodialysis or peritoneal dialysis), severe hepatic dysfunction (serum transaminase $>$ 3 times the upper limit of normal or total bilirubin $>$ 3.5 mg/dl); presence of sustained hypotension (systolic blood pressure $<$90 mmHg or diastolic blood pressure $<$60 mmHg for 2 h despite adequate fluid replacement, or need for sympathomimetic agents to maintain blood pressure); suspected infections caused by microorganisms not susceptible to the study drugs; or previous enrollment in this trial.

This study protocol was approved by the Institutional Review Board (IRB) at our hospital. Informed consent was obtained from all patients or their legal representative before enrollment. All enrolled patients were evaluated with regard to clinical, radiographic and microbiological findings.

Clinical and Microbiological Evaluation

A complete history and physical examination were obtained at the baseline evaluation. Laboratory tests included complete blood cell counts, chemistry profiles, coagulation profiles and urinalysis. Paired blood cultures were drawn from each central line and a peripheral vein. Cultures were obtained from all sites suspected to be infected. A chest radiograph was also performed at the baseline evaluation.

A follow-up evaluation was performed for clinical and microbiological responses to antibiotic therapy at initial 72 h of therapy, the end of therapy and 7–14 days after the end of therapy. Complete blood cell counts were evaluated daily until ANC was $>$500 cells/μl. If the previous culture was positive, a follow-up culture was done.

All febrile episodes were subdivided into three categories as follows: microbiologically defined infection (MDI), clinically defined infection (CDI) or unexplained fever (UF). MDI was diagnosed when the infecting organism(s) could be isolated. Febrile episodes that could be attributed to a clinical site of infection were classified as CDI. UF was diagnosed when clinical, microbiological or radiographic evaluation failed to attribute the patient's fever to any infected site or microbial organism.

Antibiotic Treatment

All enrolled patients were randomly assigned to receive panipenem/betamipron (Carbenin®, Hanmi Pharm. Co. Ltd, Seoul, Korea; 0.5/0.5 g intravenously every 8 h) or cefepime (Maxipime®, Boryung Co. Ltd., Seoul, Korea; 2.0 g intravenously every 12 h). Randomization was performed automatically on the exclusive web site located at our hospital. All of empirical antibiotic therapy was initiated within 3 h after enrollment. In addition, vancomycin (Vancomycin®, CJ. Co., Ltd., Seoul, Korea; 1.0 g intravenously every 12 h) was given to patients who presented with prior colonization with a methicillin-resistant *Staphylococcus aureus*, obvious catheter-related infection, or a positive blood culture for gram-positive organisms. The dosages and intervals of antibiotic medications were adjusted according to renal function or serum antibiotic concentration. If the ANC was higher than 100/μl and the oral temperature was $<$38.0°C at 72 h in the group of low-risk patients with unexplained fever, the empirical parenteral antibiotic(s) was changed to oral ciprofloxacin (Cytopcin®, CJ. Co., Ltd., Seoul, Korea; 750 mg every 12 h). Switch therapy to oral ciprofloxacin at 72 h following intravenous broad-spectrum antibiotics, which was one of the recommended regimens by IDSA guideline in 1997 (10), has been the standard therapy in our hospital since our previous study showed that switch therapy to oral ciprofloxacin was effective and safe in low-risk febrile patients with neutropenia during cancer chemotherapy (11). The dosage of ciprofloxacin (750 mg every 12 h) was based on the study of the oral therapy for low-risk febrile neutropenic patients (12). Other therapeutic interventions

were performed according to IDSA guidelines established in 2002 (1).

Definitions

Previously published guidelines for the evaluation of new antibiotic agents for the treatment of febrile episodes in patients with neutropenia were used as the basis for defining the endpoint assessment of therapeutic outcomes (13).

At 7–14 days after the end of therapy, all enrolled patients were clinically evaluated as follows: clinical success, when clinical symptoms and signs of infection improved or vanished without any modification of the initial empirical antibiotics, except change to oral antibiotics; initial response but regimen modified, initial success but with the need to add treatment for viral, fungal or parasitic infections; clinical failure, when clinical symptoms and signs were aggravated, initial empirical antibiotic therapy was modified in order to eradicate the primary infection or the patient died; unable to be determined, when clinical responses were not defined as clinical success or failure.

The microbiological responses were evaluated according to the following criteria: microbiological eradication, when the causative organism(s) was not isolated from the follow-up cultures; microbiological persistence, when the causative organism(s) was persistently isolated from the follow-up cultures; microbiological recurrence, when the causative organism(s) was grown and isolated again from the follow-up culture; microbiological super-infection, when the causative organism(s) was not grown but another pathogen was newly isolated from the follow-up culture; unable to determine, when a microbiological response could not to be evaluated.

Safety Evaluation

Safety of the test article was evaluated in all enrolled patients. When adverse event(s) appeared, the symptoms and signs, their duration and severity, the existence of serious adverse events, the causal relationship and the outcomes were evaluated. Serious adverse events were defined as cases where a patient died or had life threatening side effects, cases with extended hospitalization or rehospitalization was required, cases with permanent disability resulting from treatment and cases where a new cancer was generated. When any of these serious adverse reactions occurred, it was immediately reported to the principle investigator and IRB.

Statistical Analysis

The primary end point was a comparison of clinical success rates with initial empirical monotherapy, as assessed 7–14 days after therapy. The purpose of this trial was to determine whether monotherapy with panipenem was as effective as monotherapy with cefepime, using a non-inferiority analysis. Assuming a clinical success rate of 80% for cefepime and accepting α and β error rates of 10% and 15%, respectively, and theoretical confidence interval for acceptance of non-inferiority of 20%, 57 evaluable cases were needed per treatment group. On the basis of an evaluable rate of 90%, it was postulated that 126 cases needed to be studied.

All variables were analysed by SPSS 11.5 (SPSS Inc., Chicago, IL, USA). Continuous variables in each study regimen were analysed by the Student's *t*-test. Categorical variables in each group were compared by means of a chi-square test or Fisher's exact T test. A *P*-value of <0.05 was considered significant.

RESULTS

Patient Characteristics

A total of 116 patients were included in this study: 55 patients (47.4%) in the panipenem group and 61 (52.6%) in the cefepime group. Most patients [$n = 112$ (96.6%)] received monotherapy and only four patients (3.4%; two in the cefepime and two in the panipenem group) received vancomycin in accordance with the protocol for obvious catheter-related infections caused by gram-positive organisms. Because all enrolled patients had normal renal function, there was no need for adjusting dosages and intervals of antibiotic medications. Demographic characteristics of all enrolled patients are shown in Table 1. Of the 116 enrolled, 76 patients (66.0%) had solid tumors and 40 patients (34.0%) had lymphoma and multiple myeloma. There were no differences between the two groups with regard to age, sex, underlying disorders, mean ANC at the time of enrollment and type of febrile episodes ($P > 0.05$). UF (67.2%) was the most common type of febrile episode, followed by CDI (21.6%) and MDI (11.2%). Pneumonia (nine episodes) and pharyngitis (9) were the most frequent sites of infection, followed by catheter-related bloodstream infection (6), gastroenteritis (4) and sinusitis (3).

Isolated Pathogens

A total of 18 bacterial pathogens were isolated from 13 patients, of which five had a mixed infection (Table 2). Seventeen strains were isolated from blood and one from pleural fluid. Of 18 bacterial isolates, nine (50%) were gram-positive and nine (50%) were gram-negative. *Escherichia coli* (four strains) were the most common isolate, followed by methicillin-susceptible *S. aureus* (3). Except for two methicillin-resistant Staphylococci and one *Stenotrophomonas maltophilia*, 15 isolates were susceptible to both panipenem and cefepime.

Clinical Outcomes

Clinical outcomes are summarized in Table 3. Of the 116 enrolled patients, 105 (90.5%) showed clinical success at the final evaluation: 49 (89.1%) in the panipenem group and 56

Table 1. Clinical characteristics of enrolled patients

Characteristics	No. of patients (%)		*P* value
	Panipenem ($n = 55$)	Cefepime ($n = 61$)	
Mean age (Mean ± SD, years)	51.4 ± 13.2	52.8 ± 13.0	0.57
Sex (M/F)	30/25	28/33	0.35
Underlying disorders			0.43
Hematological disorders	21 (38.2)	19 (31.1)	
Multiple myeloma	1	2	
Lymphoma	20	17	
Solid tumor	34 (61.8)	42 (68.9)	
Breast cancer	10	15	
Stomach cancer	6	5	
Lung cancer	5	7	
Others	13	15	
ANC at admission (mean ± SD, cells/μl)	206.8 ± 238.7	170.8 ± 195.4	0.37
Causes of fever			0.51
MDI	8 (14.5)	5 (8.2)	
Primary bacteremia	0	2	
Pneumonia	3	0	
Liver abscess	1	0	
Catheter-related infection	4	2	
Biliary tract infection	0	1	
CDI	9 (16.4)	16 (26.2)	
Pneumonia	2	4	
Pharyngitis	5	4	
Gastroenteritis	1	3	
Skin and soft tissue infection	0	2	
Septic shock	1	0	
Sinusitis	1	2	
UF	38 (74.5)	40 (65.6)	

ANC, absolute neutrophil count; CDI, clinically defined infection; MDI, microbiologically defined infection; UF, unexplained fever.

(91.8%) in the cefepime group, demonstrating statistically significant non-inferiority (95% confidence interval: −13.48%, 10.35%, P=0.002). In the panipenem group, six cases (11.1%) showed clinical failure including two deaths due to septic shock and adult respiratory distress syndrome associated with pathologically confirmed adenoviral pneumonia. In the cefepime group, five cases showed clinical failure including one death due to biliary sepsis. In the subgroup analysis categorized by MDI, CDI and UF, the clinical responses were not different between the two groups ($P > 0.05$). The mean duration of fever and neutropenia, drug administration, the number of patients who received colony stimulating factor was also not different between the two groups ($P > 0.05$).

Table 2. Isolated strains from patients ($n = 13$) with microbiologically documented infections (MDIs)

Isolated strains	Number of isolates (%)		
	Panipenem ($n = 10$)	Cefepime ($n = 8$)	Total ($n = 18$)
Gram-positive cocci	6 (60.0)	3 (37.5)	9 (50.0)
MSSA	2	1	3
MRSA	1	0	1
MSCNS	1	0	1
MRCNS	1	1	2
S. viridans	0	1	1
S. pneumoniae	1	0	1
Gram-negative bacilli	4 (40.0)	5 (62.5)	9 (50.0)
E. coli	0	4	4
P. fluorescens/putida	1	0	1
K. oxytica	0	1	1
Stenotrophomonas maltophilia	1	0	1
E. cloacae	1	0	1
K. pneumoniae	1	0	1

MRCNS, methicillin-resistant coagulase negative *Staphylococcus*; MRSA, methicillin-resistant *Staphylococcus aureus*; MSCNS, methicillin-susceptible coagulase negative *Staphylococcus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

Microbiological Outcomes

Among 18 bacterial isolates from 13 cases including five mixed infections, 17 (94.4%) were microbiologically eradicated at the final evaluation (Table 3). In one case (5.6%) of the panipenem group, a panipenem-resistant, cefepime-susceptible *S. maltophilia* was isolated from blood at 72 h after the initiation of panipenem. The bacteremia persisted and fever recurred after the substitution of panipenem with cefepime. After the removal of the tunneled central venous catheter and the addition of trimethoprim-sulfomethoxazole, at 8 days after the enrollment, the follow-up culture became negative and the fever subsided. There was no significant difference in microbiological eradication rates between the two groups ($P = 0.60$).

Safety

Among 116 enrolled patients, a total of 27 adverse events related to the use of the test medications were observed in 25 patients (Table 4): 13 events (23.6%) in the panipenem and 14 (23.0%) in the cefepime group ($P = 0.93$). There were no severe adverse events that required withdrawal from this study. Gastrointestinal dysfucntion (10.9%) such as nausea or vomiting was the most frequent in the panipenem group and liver dysfunction (14.8%) was the most frequent in the cefepime group. Gastrointestinal dysfunction was

Table 3. Clinical and microbiological responses at the final evaluation

Outcomes	Number of patient (%)		*P* value
	Panipenem ($n = 55$)	Cefepime ($n = 61$)	
Overall clinical response			0.60
Success	49 (89.1)	56 (91.8)	
Failure	6 (11.1)	5 (8.2)	
Clinical response in cases with MDI			1.00
Success	5	4	
Failure	3	1	
Clinical response in cases with CDI			1.00
Success	7	13	
Failure	2	3	
Clinical response in cases with UF			1.00
Success	37	39	
Failure	1	1	
Overall microbiological response			1.00
Eradication	9	8	
Persistence	1	0	
Duration of fever (Mean ± SD, days)	2.02 ± 2.17	1.80 ± 1.65	0.55
Duration of neutropenia[a] (mean ± SD, days)	1.98 ± 1.16	2.25 ± 1.51	0.29
Duration of drug administration (mean ± SD, days)	4.24 ± 2.35	4.18 ± 2.14	0.89
CSF administration[b]	48 (87.3)	56 (91.8)	0.42

CSF, colony stimulating factor.
[a]Absolute neutrophil counts $\leq$500 cells/μl
[b]Number of patients who received colony stimulating factor.

Table 4. Adverse events of enrolled patients

Types	Number of patient (%)		*P* value
	Panipenem ($n = 55$)	Cefepime ($n = 61$)	
Total	13 (23.6)	14 (23.0)	0.93
Liver dysfunction	4 (7.3)	9 (14.8)	0.29
GI dysfunction	6 (10.9)	1 (1.6)	0.052
Eosinophilia	1 (1.8)	2 (3.3)	1.00
Prolongation of prothrombin time	0	1 (1.6)	1.00
Headache	1 (1.8)	1 (1.6)	1.00
Drug fever	1 (1.8)	0	0.474

GI, gastrointestinal.

more frequent in the panipnem group (10.9%) than in the cefepime group (1.6%) and liver dysfunction was more frequent in the cefepime group (14.8%) than in the panipenem group (7.3%), although both differences were not statistically significant ($P > 0.05$). Using the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3.0), scoring system (14), no Grade 3, 4 of gastrointestinal toxicity with antibiotic treatment occurred. All of these adverse events spontaneously resolved after completion of treatment.

DISCUSSION

Monotherapy with broad-spectrum antibiotic agents has tended to replace the classic combination therapy in empirical treatment of febrile neutropenia (15). Monotherapy with β-lactam agents has been shown to be equally effective compared with conventional β-lactam/aminoglycoside combinations (2,16). Carbapenem demonstrated superiority over ceftazidime monotherapy, with comparable efficacy and safety with cefepime (17–19). Monotherapy with a suitable agent has been associated with a non-significant trend toward better survival, a significant advantage in preventing treatment failures, fewer adverse effects and similar super-infection rates (2). Recently, systematic review and meta-analysis of randomized controlled trials for empirical antibiotic monotherapy, for febrile neutropenia, showed that cefepime is associated with increased mortality, whereas ceftazidime, piperacillin/tazobactam, imipenem/cilastatin and meropenem appear to be suitable agents for monotherapy (20).

Panipenem has good activity against a broad range of aerobic and anaerobic bacteria and has demonstrated efficacy in adults, the elderly and children with various infections (3). Panipenem also proved better *in vitro* activity against *Streptococcus pneumoniae* and had a lower frequency of seizures as a side effect than imipenem (7–9). Like other carbapenems, panipenem has a time-dependent killing activity with minimal to moderate post-antibiotic effects against susceptible organisms. Considering these pharmacokinetic and pharmacodynamic aspects of panipenem, it has been recommended that panipenem (0.5∼1.0 g) be administrated intravenously every 8∼12 h. In this study, panipenem (0.5 g) was administrated intravenously every 8 h for the achievement of maximal therapeutic efficacy. Since panipenem has been approved in Japan, China and Korea, it has been used for the treatment of lower respiratory tract, urinary tract, obstetrical/gynecological and surgical infections (3). This is the first clinical trial to evaluate the efficacy and safety of panipenem monotherapy for adult patients with febrile neutropenia.

The results of this study demonstrated that panipenem monotherapy was as effective and safe as cefepime monotherapy in adult patients with febrile neutropenia. Although the 95% confidence limits (−13.48%, 10.35%) of success rate difference between the two groups were <20%, the sample size was too small and acceptable difference of

non-inferiority was too high. The success rate was higher in this study than reported in other studies because patients with relatively high risks were excluded from this study. The type of underlying malignancy (leukemia, lymphoma or solid tumors) and the duration of neutropenia are two of the major prognostic factors affecting favorable outcomes (21). In this study, 40 (34.5%) patients had hematological malignancies other than leukemia and 76 had solid tumor (65.5%). Most patients were included in this study at 7–14 days after they received anti-cancer chemotherapy.

Gram-positive bacteria now account for 60–70% of microbiologically documented infection in Korea as well as United States, although the distributions of causative organisms depend on countries, regional areas or individual institutions (1,22–25). Among isolated strains in this study, 50% were gram-positive cocci and the remaining 50% were gram-negative bacilli. However, the number of evaluated cases with MDI was too small to represent distributions of causative organisms in our hospital.

A total of 27 (23.3%) adverse events were observed without severe adverse events in this study. Although there were no significant differences in the prevalence of these adverse events between the two groups (Table 4), gastrointestinal dysfunction such as nausea or vomiting was more frequent in the panipenem group than in the cefepime group ($P = 0.052$). Gastrointestinal symptoms have been well established with regard to the use of carbapenems and spontaneously resolved after the completion of panipenem therapy (17). Panipenem should be co-administered with betamipron, an organic anion tubular transport inhibitor with very low toxicity that inhibits the active transport of panipenem in the renal cortex, thereby reducing the nephrotoxic potential of the antimicrobial agent (26,27). However, nephrotoxicity related with the use of panipenem was not observed in this study.

This is the first prospective randomized trial to show that the efficacy and safety of panipenem/betamipron was comparable to cefepime as empirical monotherapy for adult cancer patients with febrile neutropenia, even though there was a limitation regarding the lack of statistical power caused by small enrolled cases.

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Conflict of interest statement

None declared.

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