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Monotherapy with meropenem versus combination therapy with ceftazidime plus amikacin as empirical therapy for neutropenic fever in children with malignancy

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Fifty-four pediatric cancer patients with a total of 100 febrile neutropenic episodes treated at China Medical College Hospital were randomized to receive meropenem or ceftazidime plus amikacin from January 2001 to April 2002. The characteristics of 76 assessable febrile episodes (39 with meropenem and 37 with ceftazidime plus amikacin) were compared between the 2 groups. The success rate with unmodified therapy was not significantly different between the meropenem group (72%) and the ceftazidime-plus-amikacin group (57%). The incidence of side effects was similar between the 2 groups and these side effects were reversible. Microbiologically documented infection, clinically documented infection, and unexplained fever accounted for 35%, 37%, and 28% of episodes, respectively. The clinical response rates in subgroups of documented infection and unexplained fever did not significantly differ between the 2 treatment groups. Meropenem was significantly more effective than ceftazidime plus amikacin in children at high risks of developing severe infection who had profound neutropenia (absolute neutrophil count [ANC] <100 /mm^3), prolonged neutropenia (ANC <500 /mm^3 lasting for >10 days), or clinically deteriorating shock (p=0.045). As an empirical treatment, meropenem seems to be as effective and safe as ceftazidime plus amikacin for febrile episodes in children with cancer and neutropenia. Meropenem is more effective for pediatric cancer patients at the high risk of severe infection.

Key words: Ceftazidime/amikacin, meropenem, neutropenic fever

Neutropenic patients with malignancy are at a risk of developing life-threatening infections [1]. Broad-spectrum antibiotics should be administered promptly if these patients become febrile. Combination regimens of ceftazidime and amikacin have been the standard treatment modality for infections in neutropenic cancer patients because of their synergism for gram-negative bacteria and reduction of resistance emergence during therapy [2,3]. However there are disadvantages associated with this combination therapy, such as nephrotoxicity and ototoxicity from aminoglycosides as well as limited activity against gram-positive bacteria and anaerobes [4].

Meropenem exhibits a more broad-spectrum antimicrobial activity over the combination regimens of ceftazidime and amikacin and seems to be free of the adverse effects associated with amikacin [5]. The purpose of this prospective randomized study was to compare the efficacy and tolerability of meropenem with those of ceftazidime plus amikacin in the empirical treatment of febrile children with cancer and neutropenia.

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Patients and Methods

This study was designed based on clinical trials proposed by the Immunocompromised Host Society [6]. Pediatric patients aged 3 months to 18 years with cancer who were receiving chemotherapy for underlying malignancy were enrolled in the trial. Patients were considered eligible for participation if they had granulocytopenia (an absolute neutrophil count [ANC] <500 cell /mm^3 or a count <1000 cell /mm^3 with an expected decrease to <500 cell /mm^3 within 48 h), fever (a single oral temperature of ≥38.3°C or a temperature of ≥38°C over at least 1 h), and a presumed infection (ie exclusion of febrile episodes associated with drugs or blood products administration) [1,7,8]. Patients were excluded if they had received any parenteral antibiotics within 72 h or any investigational drugs within 30 days preceding randomization, had a known allergy history

to any of the protocol antibiotics, or had serum creatinine or transaminase levels higher than 2 fold of the normal upper limit [8]. These enrolled patients were first divided into hematological malignancy (including leukemia and lymphoma) and solid tumor. Then the patients in each malignancy group were randomized to receive either meropenem (40 mg/kg/dose, max 1 g/dose, q8h) or ceftazidime (50 mg/kg/dose, max 2 g/dose, q8h) plus amikacin (5 mg/kg/dose, max 0.25 g/dose, q8h).

A total of 100 febrile episodes in 54 neutropenic children treated at China Medical College Hospital, Taichung from January 2001 to April 2002 were enrolled in the trial. There were 24 episodes (13 episodes in the meropenem group and 11 episodes in the ceftazidime/amikacin group) which were excluded for the following reasons: previous antibiotics administered within 3 days prior to randomization (3 episodes in the meropenem group and 2 episodes in the ceftazidime/amikacin group), previous investigation drugs given within 30 days prior to the start of the trials (10 and 7) or non-infectious causes (0 and 2). Finally, 76 episodes in a total 51 patients were included in the analysis.

Before the empirical treatment was started, a complete history was taken and a detailed physical examination was made every day. Blood, urine and samples from other infection sites were collected for culture. If a patient had an indwelling venous catheter, one blood culture from each lumen of the catheter and one from another peripheral vein were taken. Blood samples for hematological and biochemical analyses were taken on admission and again every 3 days. Chest x-ray and other imaging studies were performed as clinically indicated. Bacteriological identifications were made by standard techniques and antibiotic disc sensitivity tests were also performed.

The clinical response was evaluated at 72 h after the start of treatment and at the end of the trial. The initial regimen was left unchanged before 72 h unless a resistant pathogen was detected during this period or the condition of the patient was progressively deteriorated [9]. Antibiotic therapy was continued until the patient was afebrile for at least 5 days.

Febrile episodes were classified as microbiologically documented infection, clinically documented infection or unexplained fever. Unexplained fever was defined as fever without clinical signs of infection and without isolation of any organism. If fever was associated with clinical evidence of infection, including image findings, but without isolation of any causative pathogen, it was classified as clinically documented infection. A febrile episode was classified as a microbiologically documented infection when a pathogen was isolated from blood samples or infection sites [7].

Therapy was considered to be a success if all signs and symptoms of infections resolved and if causative microorganisms were eradicated without change of the initial antimicrobial therapy. When treatment with the initial regimens was successful but a second febrile episode arose later which required either modification of the protocol treatment or addition of another antimicrobial agent, the trial was defined as initial success with further infection. The trial was considered to be a failure if (1) bacteremia persisted, (2) the documented pathogen was resistant to the allocated regimen, (3) no response was seen after at least 72 h of empiric therapy, (4) shock, multiple organ failure or death occurred [8,10].

Nephrotoxicity was defined as an increase in serum creatinine levels of 50% greater than the baseline value or at greater than 1.5 mg/dL. Hepatotoxicity was defined as an increase in transaminase, bilirubin, and alkaline phosphatase 1.5 times above the baseline and normal range values [8].

We defined patients as being at high risk of developing serious infections when one or more of following features was present: profound neutropenia (ANC <100 /mm^3), prolonged neutropenia (ANC <500 /mm^3 lasting for more than 10 days) or clinically deteriorating shock [10-12].

The age and duration of neutropenia were compared between the 2 groups by independent t test. Other demographic data, clinical response, side effects and findings of intent-to-treat analysis were compared between the 2 groups using chi-square test. A p value of less than 0.05 was considered statistically significant.

Results

The basic data of the included patients in the 2 groups was similar (Table 1). Details of the clinical response in the 2 groups are summarized in Table 2. There was no significant difference in the success rate with unmodified therapy until the course ended between the meropenem group (72%) and the ceftazidime/amikacin group (57%) (p=0.38). The median duration for defervescence was 2 days in successfully treated patients in both groups. Initial success with recurrent infection occurred in three patients.

Persistent fever was the most common cause of failure in the ceftazidime plus amikacin group (8/14). However, persistent fever and resistant pathogens were equally important causes of failure in the meropenem group (4/10 and 4/10). The resistant microorganisms

Table 1. Demographic characteristics of patients

	Meropenem n = 39 (%)	Ceftazidime + amikacin n = 37 (%)
Age, median (range), years	4.2 (0.7-16.3)	3.6 (0.6-12.4)
Sex, female/male	18/21	13/24
Underlying disease		
Leukemia/lymphoma	18/4	19/3
Solid tumor	17	15
Duration of neutropenia, median (range), days	6 (1-37)	6 (3-30)
Granulocytes at entry, /mm^3		
<100	22 (56)	22 (59)
100-499	10 (26)	10 (27)
500-1000	6 (15)	4 (11)
>1000	1 (3)	1 (3)
G-CSF use	37 (95)	33 (89)
Central venous catheter *in situ*	37 (95)	31 (84)
Shock at onset	2 (5)	1 (3)

Abbreviation: G-CSF = granulocyte colony stimulating factor

in the meropenem group were coagulase-negative staphylococci (CoNS) (bacteremia, n = 3) and probable *Candida* (liver/spleen abscess, n = 1) and in the ceftazidime/amikacin group were CoNS (bacteremia, n = 2; Port-A site infection, n = 1), *Enterococcus* sp. (urinary tract infection [UTI], n = 1) and *Candida albicans* (UTI, n = 1).

There were no prominent differences in the incidence of side effects between the two regimen groups. No protocol antibiotic was withdrawn because of severe side effects and all of these side effects were reversible.

Microbiologically documented infection, clinically documented infection, and unexplained fever accounted for 35%, 37% and 28% of all episodes, respectively (Table 3). Meropenem achieved a higher successful response rate in each subgroup with clinically or microbiologically documented infection, unexplained fever, prolonged neutropenia, and profound neutropenia, but these differences were not significant. Meropenem was significantly more effective than ceftazidime/amikacin in children with profound neutropenia, prolonged neutropenia or clinically deteriorating shock (75% vs 44%, p=0.045).

The most frequent clinically documented infection was respiratory tract infection (n = 16) and its complications (n = 4) (Table 4). Among patients with bacteremia, gram-positive cocci were responsible for the infection in 6 patients and gram-negative bacilli in 5 patients. CoNS were the most frequently isolated bacteria (n = 5) from these 11 patients (Table 5). Urinary tract infections were caused predominantly by *Enterobacteriaceae*, especially *E. coli*.

Five patients died during the trial. One patient in

Table 2. Clinical response at the end of therapy in all episodes

	Meropenem n = 39 (%)	Ceftazidime + amikacin n = 37 (%)
Success	28 (72)	21 (57)
Defervescence, median (range)	2 (1-5)	2 (1-7)
Initial success with new infection	1 (3)	2 (5)
Failure	10 (25)	14 (38)
Reasons for first modification		
Persistent fever	4	8
Resistant pathogen	4	5
Development of shock	2	1
Side effects		
Skin rash	0	0
Nausea/vomiting	3 (8)	2 (5)
Diarrhea	3 (8)	5 (13)
Liver impairment	6 (15)	6 (16)
Renal impairment	0	0

Table 3. Intent-to-treat analysis of all included episodes

	Meropenem n = 39 (%)	Ceftazidime + amikacin n = 37 (%)	*p*
Unexplained fever	11 (28)	10 (27)	
Success	6	5	0.84
Failure	5	5	
Microbiological infection	13 (33)	14 (38)	
Success	9	7	0.31
Failure	4	7	
Clinical infection	15 (39)	13 (35)	
Success	13	9	0.26
Failure	2	4	
Profound neutropenia[a]			
Success	15	11	0.30
Failure	8	11	
Prolonged neutropenia[b]			
Success	4	2	0.30
Failure	4	6	
High-risk subgroup[c]			
Success	18	11	0.045
Failure	7	14	

[a]Profound neutropenia was defined as absolute neutrophil count (ANC) decreased to less than 100 /mm^3

[b]Prolonged neutropenia was defined as the duration of neutropenia (ANC <500 /mm^3) lasting for more than 10 days.

[c]High-risk subgroup was defined as the patient's condition under profound neutropenia, prolonged neutropenia or clinical shock.

the meropenem group died of fulminant septic shock at 48 h after admission. Another patient in the meropenem group suffered from all relapse and related infections, and died 3 months after the start of therapy. Three in the ceftazidime/amikacin group died of refractory infections with progressive multiorgan failure within 1 month after admission.

Discussion

The difference in the treatment success rate without modification between the meropenem group and the ceftazidime/amikacin group was not significant in this study. Our trial found higher success rates for these two individual regimens than in previous studies [7-9,13], which might have been due to postponement of the time to the first modification if fever tended to subside [10]. The longest duration until defervescence for successfully treated patients was 5 days in meropenem group and 7 days in the ceftazidime/amikacin group. As an empirical therapy, meropenem was as effective as ceftazidime plus amikacin in all assessable episodes.

Table 4. Infection diagnosis in 28 clinically documented episodes

Infection diagnosis	No. of cases (%)
Upper respiratory tract infection	9 (12)
AOM, mastoiditis, sinusitis	4 (5)
Lower respiratory tract infection	7 (9)
Acute gastroenteritis	3 (4)
Typhilitis	2 (3)
Liver/spleen abscess	1 (1)
Skin and soft tissue infection	2 (3)

Abbreviation: AOM = acute otitis media

Febrile neutropenic patients with malignancy are not equally predisposed to severe infection partly because underlying malignancy, chemotherapy and comorbidity factors are different for each patient [14]. Management should be based on prediction of the degree of risk in these patients. Induction or relapse, toxic appearance, profound neutropenia and prolonged neutropenia are considered to be high-risk factors [11, 12,14]. The neutrophil count and duration of neutropenia quantitatively reflects the infection rate of these patients after intensive chemotherapy in induction and relapse. Our results indicated that meropenem was significantly more effective than ceftazidime/amikacin in children with profound neutropenia, prolonged neutropenia or clinically deteriorating shock. These findings suggest that meropenem is more optimal in the treatment of pediatric cancer patients at the high risk of severe infection.

The incidence of unexplained fever in this study was less than in previous studies [7-10,13,15,16]. This may be because most of the enrolled patients in previous studies were adults [8-10,13,15], and clinical judgments for unexplained fever were strictly made in this trial. Neutropenic children, like normal children, are vulnerable to common viruses [14]. These common

Table 5. Isolated microorganisms from 27 eligible episodes including 4 polymicrobial infections and 23 monomicrobial infections

	Bacteremia	UTI	Other infections
Gram-negative bacilli			
Escherichia coli	1	6	0
Klebsiella pneumoniae	1	2	0
Klebsiella oxytoca	1	1	0
Enterobacteria cloacae	1	0	0
Proteus mirabilis	1	3	0
Morganella morganii	0	1	0
Pseudomonas aeruginosa	0	1	1[a]
Gram-positive cocci			
OSSA	0	0	1[b]
ORSA	0	0	1[c]
CoNS	5	0	1[b]
Streptococcus pneumoniae	1	0	0
Enterococcus	0	2	0
Fungus			
Candida albicans	0	1	0

Abbreviations: UTI = urinary tract infection; CoNS = coagulase-negative staphylococci; ORSA = oxacillin-resistant *Staphylococcus aureus*; OSSA = oxacillin-susceptible *Staphylococcus aureus*

[a]The patient had osteomyelitis.

[b]The patients had Port-A catheter site infection.

[c]The patient had mastoiditis.

viruses are likely to result in mild to life-threatening diseases in immunocompromised children [17]. A survey found that one-fourth of patients with cancer and neutropenic fever had a viral infection after controlling for the possible influence of seasonality [18]. Upper respiratory tract infection (URI) is mostly caused by viruses. The incidence of URI was in this study (12%) more than in previous studies [10,16]. A complete virological work-up was not done for these patients. Therefore, clinically documented infection relatively had a more prominent role in this analysis.

Modification of treatment must be based on microbiological data and clinical evaluation. In this study, three patients had septic shock at admission and their clinical conditions continued to deteriorate. Vancomycin and meropenem were immediately administered to these patients, regardless of which treatment group they were randomized to. Glycopeptides were added to the treatment in 9 children in the meropenem group and 10 children in the ceftazidime/amikacin group. The most frequent reasons for this addition were persistent fever (4 in the meropenem group and 4 in the ceftazidime/amikacin group) and isolation of resistant pathogens (CoNS) (3 and 3). This addition of glycopeptides in neutropenic patients with persistent fever is common in practice, even though there is no direct evidence of its benefit [8]. Among the patients who had persistent fever with unknown origin, defervescence occurred after the addition of glycopeptides in 1 of 3 patients in the meropenem group and in 1 of 5 patients in the ceftazidime/amikacin group; however, defervescence occurred after the modification of meropenem in 3 of 5 patients in the ceftazidime/amikacin group. Therefore, if oxacillin-resistant *Staphylococcus* is highly suspected according to the culture report and clinical assessment, glycopeptides should be added. If gram-positive bacteria infection is not suspected and these patients have persistent fever with unknown origin after ceftazidime/amikacin treatment, switching to meropenem appears to be appropriate.

In this study, most cases of gram-negative bacilli infections were caused by *Enterobacteriaceae*. All of the gram-negative pathogens isolated were susceptible to ceftazidime/amikacin and meropenem *in vitro*. One osteomyelitis patient had persistent fever after administration of ceftazidime and meropenem although isolated *P. aeruginosa* was susceptible to ceftazidime and meropenem in the laboratory report.

The incidence of UTI in this study was higher than in past studies [7-10,13,15,19]. UTI in the study was confirmed by clinical and microbiological findings (positive urine culture $>10^5$/mL). Immunocompromised patients demonstrated an increased susceptibility to UTI by virtue of organism virulence and altered host defect [20,21]. Further structural evaluation was not routinely arranged for these children with UTI episodes. In this study, one boy had grade III vesicoureteral reflux (VUR). One girl with abdominal Burkitts' lymphoma metastasis had 4 recurrent episodes of UTI, but she had

no VUR and had a normal intravenous pyelogram.

During the past decade, gram-positive bacteria have been the most frequently isolated bacteria in many countries. Akova *et al* assumed this phenomenon to be due to early intervention with broad-spectrum antibiotics mainly active against gram-negative bacteria, more intensive chemotherapy causing severe mucositis and widespread use of indwelling catheters [14]. In this study, CoNS were isolated most frequently (n = 6) in cases with documented bacteremia and local infection associated with a central venous catheter, followed by oxacillin-susceptible *S. aureus* (n = 1). CoNS are resistant to meropenem and ceftazidime/amikacin. Among the patients with intravenous catheter-related infections, 5 had a Port-A catheter and 1 had a central venous line. The Port-A catheter was removed in 4 children as a result of local infection and recurrent catheter-related bacteremia.

In this study, a high dose regimen was used for patients with severe infection in order to ensure the regimens' bactericidal effect. This practice increased the incidence of adverse effects in this study compared with the 5% to 15% range reported in past studies [7-10,13,15]. However, it was difficult to rule out whether some of these effects were due to unremitting chemotherapy in the induction stage or modified regimens of antibacterial or antifungal drugs.

As an empirical treatment, meropenem monotherapy is as effective and safe as ceftazidime plus amikacin combination for febrile neutropenic children with cancer. There are no significant differences in adverse effects between these two treatment groups. Meropenem is more effective for pediatric cancer patients at the high risk of severe infection.

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