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Ceftazidime versus Imipenem-Cilastatin as Initial Monotherapy for Febrile Neutropenic Patients

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One hundred febrile episodes in 89 neutropenic patients after cytotoxic chemotherapy were randomized to be treated with either ceftazidime or imipenem as initial monotherapy. The clinical characteristics of the two groups of patients were comparable. The response of the fever in patients who received imipenem was significantly better than that in those who received ceftazidime (77 versus 56%, respectively; $P = 0.04$), especially in those with microbiologically documented infection (81 versus 33%, respectively; $P = 0.02$). The in vitro susceptibilities and the clinical responses suggested that, with the possible exception of *Pseudomonas* spp., imipenem was more effective than ceftazidime in treating neutropenic infections caused by both gram-positive and -negative organisms. An additional 23 and 21% of the patients in the ceftazidime and imipenem groups, respectively, responded to the addition of cloxacillin and amikacin following failure of monotherapy. The majority of the treatment failures, relapses, and superinfections were related to resistant infective organisms such as methicillin-resistant *Staphylococcus* spp. and *Pseudomonas* spp. or disseminated fungal infections.

In the management of hematological malignancies, reversible bone marrow depression by cytotoxic chemotherapy inevitablly accompanies the effort to maximize the efficacy of treatment. Prompt administration of empiric broad-spectrum antibiotic therapy to neutropenic patients who become febrile is essential (13, 16). A combination of intravenous antibiotics consisting of an aminoglycoside and an antipseudomonal penicillin or a cephalosporin is often recommended to provide broad-spectrum coverage, to achieve a synergistic effect, and to reduce the likelihood of emergence of resistant organisms (11, 18). However, the antibiotic combinations, especially those containing an aminoglycoside, are potentially toxic (9). Single-agent therapy in the management of neutropenic infections has been encouraged by the availability of new antibiotics with broad spectra of antibacterial activity. As this approach has the potential risk of allowing the emergence of resistant organisms during therapy, its clinical role remains uncertain. New agents, including ceftazidime, imipenem-cilastatin, and ciprofloxacin, have been studied and have been shown to be useful as initial monotherapy for febrile neutropenic patients (1, 2, 5, 9, 10, 14, 17, 19, 21, 22). We report here the results of our prospective randomized study in which we compared the efficacy and safety of ceftazidime and imipenem as initial monotherapy for our febrile neutropenic patients after cytotoxic chemotherapy. For patients who failed to respond to monotherapy, the effectiveness of the subsequent addition of combination antibiotics was assessed.

MATERIALS AND METHODS

Patients with hematological malignancies who were treated in the University Department of Medicine, Queen Mary Hospital, and who became febrile while they were neutropenic were eligible for entry into the study. Febrile episodes were defined by at least two oral temperature readings above 38°C at least 4 h apart within a 24-h period or a single oral temperature above 38.5°C. Neutropenia was defined as an absolute neutrophil count of less than 0.5×10^9/liter. Patients were excluded from the study for any of the following reasons: history of anaphylactic reaction to any β-lactam antibiotics, including imipenem-cilastatin, or nalidixic acid; severe hepatic or renal impairment (serum bilirubin of >50 μmol/liter or serum creatinine of >0.3 mmol/liter); or a history of receiving any antibiotics within the preceding 72 h. Patients were allowed to reenter the study during a second infective episode that complicated a second neutropenic episode, provided that the previous infective episode had completely resolved and the two infective episodes were more than 4 weeks apart.

Initial assessment included history and physical examination, urinalysis, complete blood counts, blood biochemistry, and chest X ray. Specimens for bacterial and fungal cultures were collected from the nose, throat, urine, stool, sputum (if available), blood, and any other appropriate sites before commencement of antibiotic treatment. After the initial evaluation, patients were randomized to receive either ceftazidime or imipenem. Ceftazidime (2 g; Fortum; Glaxo Pharmaceuticals, Ltd., Greenford, United Kingdom) dissolved in normal saline was given by intravenous infusion over 30 min at 8-h intervals. Imipenem-cilastatin (500 mg; Tienem; Merck Sharp & Dohme, West Point, Pa.) dissolved in normal saline was infused intravenously over 30 min at 6-h intervals. The imipenem-cilastatin that we used was available as a mixture containing imipenem and cilastatin in a 1:1 ratio.

Patients were assessed daily for changes in symptoms and signs. Complete blood counts and blood biochemistry were determined at least every other day. Repeated specimens from blood and other appropriate sites were obtained for cultures if patients remained febrile. Chest radiographs were performed at least twice weekly. Invasive diagnostic proce-

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dures (e.g., fiber-optic bronchoscopy) were performed when indicated. The organisms isolated from cultures were identified by routine microbiological methods, and susceptibilities of the organisms to antimicrobial agents were determined by the break-point method on agar dilution or by the disk diffusion technique. Break points greater than 4 and 8 μg/ml were used to denote resistance to imipenem and ceftazidime, respectively.

All patients were treated with ceftazidime or imipenem and were assessed at 72 h for their response to therapy. For patients who had good responses, either drug was continued for at least a total of 7 days or for 4 days after the patient became afebrile, whichever was longer, unless an adverse reaction, clinical deterioration, or death occurred. For those who did not respond or who had clinical deterioration, cloxacillin given at 1 g intravenously every 6 h and amikacin given at 5 mg/kg of body weight intravenously every 8 h were given in addition to the original monotherapy (ceftazidime or imipenem). Amikacin levels in serum were determined (pre- and postinfusion) within 48 h, and the dose of amikacin was adjusted accordingly. The three antibiotics were continued for at least another 72 h for the second assessment of response, unless there was an adverse reaction, clinical deterioration, or death. For those patients who responded to the combination antibiotics, the drugs were continued for at least another 4 days after they had become afebrile or a total of 7 days, whichever was longer. For those who had not responded, further management such as empiric amphotericin B therapy was considered (6). Vancomycin was used if there were clinically suspected or microbiologically documented gram-positive infections. No patient was given a leukocyte transfusion at any time (17).

If a primary focus of infection was apparent or a positive culture was obtained during the study, the same antibiotic regimen was continued if the patient was responding to therapy. Otherwise, the antibiotic therapy was altered according to the susceptibility of the organism or the clinical setting.

Fever of unknown origin was diagnosed when no clinical, radiological, or bacteriological evidence of infection was found. Patients were considered to have clinically suspected infection if they had fever and other clinical evidence of an infection, even though the infective organisms were not isolated. Response was defined as complete disappearance of all clinical and laboratory evidence of infection, including fever. Relapse was defined as the reappearance of the same infection within 7 days after discontinuation of the antibiotics. Superinfection was defined as an infection by a different organism or at a different site if no organism could be isolated from the original site and which occurred during treatment with the antibiotics. The chi-square test with the Yates correction was used to compare response rates and proportions.

Informed consent was obtained from all patients. The study protocol was approved by the Ethics Committee of the Faculty of Medicine, University of Hong Kong.

RESULTS

During a 12-month period (August 1988 to July 1989), 92 neutropenic patients entered the study, and there were 103 febrile episodes. Only 100 episodes (in 89 patients) were evaluable. The other three episodes (in three patients) were excluded because they had previously received antibiotics. There were 44 males (49%) and 45 females (51%). The median age was 38 years (mean age, 36.8 years; range, 16 to 76 years). All patients had neutropenia following cytotoxic chemotherapy. Ceftazidime was used as initial monotherapy in 52 febrile episodes and imipenem in the remaining 48 febrile episodes. The clinical characteristics of the two groups of patients are given in Table 1. Clinical parameters, including sex, age, primary disease, primary disease status, prior steroid therapy, indwelling catheters, inpatient status, nadir neutrophil counts, and days of neutropenia, were comparable between the two groups of study patients. None of the differences that we observed were statistically significant (Table 1). Although patients who received imipenem appeared to have more microbiologically documented infections, the difference was not statistically significant.

TABLE 1. Patient characteristics

Characteristic	Ceftazidime	Imipenem
No. of episodes	52	48
Sex (no. [%])		
Male	27 (52)	21 (44)
Female	25 (48)	27 (56)
Age (yr)		
Mean	36.3	39.5
Range	16–74	16–76
Primary blood disease (no. [%])		
Acute leukaemia	36 (69)	32 (67)
Lymphoma	14 (27)	12 (25)
Other	2 (4)	4 (8)
Status of primary disease (no. [%]) at:		
Diagnosis	22 (42)	22 (46)
Remission	14 (27)	12 (25)
Relapse	16 (31)	14 (29)
Prior steroid therapy (no. [%])		
Yes	23 (44)	19 (40)
No	29 (56)	29 (60)
Indwelling central venous catheter (no. [%])		
Yes	29 (56)	22 (46)
No	23 (44)	26 (54)
In hospital before fever (no. [%])		
Yes	23 (44)	19 (40)
No	29 (56)	29 (60)
Nadir neutrophil count (10^6/liter)		
Mean ± SEM	182 ± 14.1	171 ± 13.4
Range	10–420	10–450
Days of neutropenia of $<0.5 \times 10^9$/liter		
Mean ± SEM	16.4 ± 1.9	15.3 ± 1.7
Range	7–38	7–42
No. (%) with:		
Fever of unknown origin	33 (63)	23 (48)
Clinically suspected infection	4 (8)	4 (8)
Microbiologically documented infection	15 (29)	21 (44)

The overall clinical response rate to monotherapy (ceftazidime or imipenem) was 66%. An additional 22% of patients responded to the addition of cloxacillin and amikacin. Table 2 compares the clinical responses of the ceftazidime and

TABLE 2. Clinical responses of patients to therapy

Clinical response	No. responding/total (%)		P value
	Ceftazidime	Imipenem	
Response to initial monotherapy	29/52 (56)	37/48 (77)	0.04
Fever of unknown origin	22/33 (67)	17/23 (74)	NS[a]
Clinically suspected infection	2/4 (50)	3/4 (75)	NS
Microbiologically documented infection	5/15 (33)	17/21 (81)	0.02
Response to subsequent antibiotic combinations	12/52 (23)	10/48 (21)	NS
Response to other alternative therapies	9/52 (17)	1/48 (2)	NS
Death during study	2/52 (4)	0/48 (0)	NS
Response to monotherapy or combination[b]	41/52 (79)	47/48 (98)	0.01
Relapse after responding to monotherapy or combination	1/41 (2)	3/47 (6)	NS
Superinfection after responding to monotherapy or combination	7/41 (17)	7/47 (15)	NS
Response of first episodes			
Initial therapy	24/45 (53)	35/44 (80)	0.02
Combination antibiotics	10/45 (22)	9/44 (20)	NS

[a] NS, Not significant.
[b] Combination indicates the responses to initial monotherapy and subsequent antibiotic combinations, the first two main entries in this table.

imipenem groups. Patients who received imipenem as monotherapy had a significantly better response than did those who received ceftazidime alone (81 versus 33%, respectively; $P = 0.02$). Similarly, for patients with microbiologically documented infection, those who received imipenem also had a better response (81 versus 33%, respectively; $P = 0.02$). On the other hand, for patients with fever of unknown origin and clinically suspected infection, the responses of the two groups were similar. An additional 23 and 21% of the febrile cases in the ceftazidime and imipenem groups, respectively, responded to combination antibiotics following the failure of monotherapy. The overall response rate to either monotherapy or combination therapy was also higher in the imipenem group (98 versus 79%, respectively; $P = 0.01$). When the second infective episode was excluded and only the first episode was counted ($n = 89$) in each patient, similar response rates were observed (Table 2).

Tables 3 and 4 show the clinical responses to monotherapy according to clinical sites of infection and the organisms that were isolated, respectively. Multiple clinical sites were involved in 11 of the 100 (11%) febrile episodes (6 episodes in the ceftazidime group and 5 episodes in the imipenem group), and more than one infective organism was isolated in 9 (9%) febrile episodes (5 episodes in the ceftazidime group and 4 episodes in the imipenem group). Because of the small number of cases in each subgroup, the differences observed in Tables 3 and 4 were not statistically significant.

All together, there were 4 patients with relapses and 14 patients with superinfections, with no significant differences between the ceftazidime and imipenem groups (Table 1). Of the 14 episodes of superinfection, 9 (64%) were caused by more than one organism. The patterns of relapse and superinfection are shown in Table 5. They were commonly due to staphylococcal, pseudomonal, or fungal infections. Relapses and superinfections caused by *Pseudomonas* spp. appeared to be more frequent in the imipenem group (6 of 18 versus 1 of 11 in the ceftazidime group), but the difference was not statistically significant.

TABLE 3. Clinical responses to monotherapy by site of infection

Site of infection	No. responding/total (%)	
	Ceftazidime	Imipenem
Blood	5/12 (42)	6/9 (67)
Respiratory tract	3/7 (43)	3/5 (60)
Ear, nose, eye, dental	1/2 (50)	6/6 (100)
Central venous catheter related	0/2 (0)	1/1 (100)
Gastrointestinal tract		4/4 (100)
Skin or soft tissue	2/2 (100)	2/3 (67)
Urinary tract		1/2 (50)

The antibiotic susceptibilities of all the organisms isolated from 44 patients are shown in Table 6. A higher proportion of gram-positive organisms was resistant to ceftazidime (68%), while a smaller proportion (20%) was resistant to imipenem. There appeared to be a higher incidence of resistance of some gram-negative organisms to ceftazidime as well, except that *Pseudomonas* spp. appeared to have a higher incidence of resistance to imipenem. However, all the differences observed were not statistically significant because of the small number of cases in each subgroup. Twenty-five percent of the *Staphylococcus aureus* isolates were resistant to cloxacillin, and 5% of the *Pseudomonas* spp. were resistant to amikacin.

Of the 11 febrile episodes that did not respond to ceftazidime or its combination with the addition of cloxacillin and amikacin, 9 febrile episodes responded to another, alternative therapy (Table 2). There of the febrile episodes responded to vancomycin, one responded to empirical amphotericin B, one responded to high-dose co-trimoxazole, one responded to piperacillin, and three responded to imipenem. The remaining two patients died from progression of their underlying blood diseases. The only patient in the imipenem group who did not respond to either imipenem or its combination was subsequently found to have disseminated candidiasis which responded to amphotericin B therapy (Table 2).

Both ceftazidime and imipenem were well tolerated by patients. Three patients developed skin rashes that required the cessation of antibiotic therapy (two after ceftazidime and one after imipenem therapy). Three patients had significant nausea and vomiting that required antiemetic therapy after imipenem but none after ceftazidime administration. No patients developed central nervous system toxicity.

DISCUSSION

Both ceftazidime and imipenem have been shown to be safe and effective as initial monotherapy for febrile neutropenic patients (1, 2, 10, 14). However, there are considerable differences in their spectra of antibacterial activity. Imipenem appears to be more effective than ceftazidime against gram-positive organisms (7). Both drugs are, in general, very active against gram-negative organisms, including *Pseudomonas* spp., although ceftazidime is probably the more active drug against *Pseudomonas* spp. (3, 12, 14). Patients in this study who did not respond to monotherapy were given additional cloxacillin and amikacin empirically. Cloxacillin was used to cover some of the resistant gram-positive

TABLE 4. Clinical responses to monotherapy by the organism isolated

Organism	No. responding/total (%)			
	Ceftazidime		Imipenem	
	All episodes	Episodes with in vitro susceptible organisms	All episodes	Episodes with in vitro susceptible organisms
Gram positive	2/5 (40)	1/2 (50)	4/5 (80)	4/4 (100)
Staphylococcus aureus	1/2 (50)	0/1 (0)	3/4 (75)	3/3 (100)
Staphylococcus epidermidis			1/1 (100)	1/1 (100)
Streptococcus spp.	1/3 (33)	1/1 (100)		
Gram negative	8/17 (47)	8/12 (67)	16/20 (80)	16/18 (89)
Pseudomonas spp.	4/6 (67)	4/4 (100)	6/8 (75)	6/6 (100)
Enterobacteriaceae family	2/5 (40)	2/4 (50)	7/8 (88)	7/8 (88)
Acinetobacter spp.	1/3 (33)	1/2 (50)	1/1 (100)	1/1 (100)
Flavobacterium spp.	0/2 (0)	0/1 (0)		
Haemophilus influenzae	1/1 (100)	1/1 (100)		
Aeromonas or *Plesiomonas* spp.			2/2 (100)	2/2 (100)
Pasteurella multocida			0/1 (0)	0/1 (0)

organisms such as *Staphylococcus aureus*. Other antimicrobial agents such as vancomycin and teicoplanin are more active against infections caused by gram-positive organisms. The early empirical use of these expensive agents may be justified, as there appeared to be a pattern of increasing incidence of infections caused by gram-positive organisms, in neutropenic patients (8, 15). In this study, the use of vancomycin was reserved for those with documented infections caused by methicillin-resistant staphylococci. Amikacin was used for treatment against some of the resistant gram-negative organisms, especially *Pseudomonas* spp. (5). Because of the possible synergistic effect, ceftazidime or imipenem was continued after cloxacillin and amikacin were added (5, 13, 16).

As neutropenic infection is a serious condition, a relatively high dose of antibiotic is usually used (13, 16). The maximum dose of 6 g of ceftazidime daily was used in this study (14). Although a maximum dose of 4 g daily was used for imipenem in some other trials, this higher dose appeared to be associated with an increased risk of central nervous system toxicity. Since a dose of 2 g of imipenem daily has been shown in our previous pilot study (10) to be safe and effective, this lower dose was used in the present study.

The overall response of fever to imipenem was significantly better ($P = 0.04$) than the response to ceftazidime. The response rate of 77% to imipenem is comparable to the rate of 70% we found in our previous pilot study (10). Also, the response rate of 56% to ceftazidime was comparable to that given in another report (14). The difference in responses was more obvious in patients with microbiologically documented infections. Because of the small number of patients in each subgroup, it was difficult to interpret the differences in responses among the different clinical sites of infection and different infective organisms. However, while the

TABLE 5. Patterns of relapse and superinfection

Type of infection	Ceftazidime		Imipenem	
	Clinical site	Organism	Clinical site	Organism
Relapse	Blood	*Klebsiella pneumoniae*	Skin	*Staphylococcus aureus*
			Blood	*Pseudomonas maltophilia*
			Blood	*Pseudomonas cepacia*
Superinfection				
Gram positive	Skin	*Staphylococcus aureus*	Blood	*Staphylococcus aureus*
	Lung	*Staphylococcus aureus*	Lung	*Staphylococcus aureus*
	Blood	*Staphylococcus epidermidis*	Lung	*Staphylococcus aureus*
	Blood	*Streptococcus faecium*	Blood	*Staphylococcus epidermidis*
	Blood	*Streptococcus faecalis*	Blood	*Staphylococcus epidermidis*
			Blood	*Streptococcus faecium*
Gram negative	Lung	*Pseudomonas maltophilia*	Skin	*Pseudomonas aeruginosa*
	Lung	*Haemophilus influenzae*	Lung	*Pseudomonas* spp.
	Blood	*Acinetobacter* spp.	Lung	*Pseudomonas maltophilia*
			Blood	*Pseudomonas cepacia*
			Lung	*Klebsiella pneumoniae*
			Blood	*Acinetobacter* spp.
			Blood	*Enterobacter* spp.
Fungal	Blood	*Candida* spp.	Blood	*Candida* spp.
	Blood	*Candida* spp.		

TABLE 6. Antibiotic susceptibilities of organisms isolated, including those isolated during relapses and superinfections

Organism	No. of isolates	% Resistant to:	
		Ceftazidime	Imipenem
Gram positive	39	68	20
Staphylococcus aureus	28	64	21
Staphylococcus epidermidis	5	80	0
Streptococcus spp.	6	67	17
Gram negative	61	11	17
Pseudomonas aeruginosa	24	5	10
Pseudomonas maltophilia	7	50	100
Pseudomonas cepacia	4	0	25
Klebsiella spp.	11	9	0
Acinetobacter spp.	8	25	0
Salmonella spp.	5	0	0
Enterobacter spp.	3	0	0
Others	10	10	0

poorer responses to ceftazidime of infections caused by gram-positive organisms was expected from the in vitro activity of ceftazidime, imipenem also appeared to be more effective than ceftazidime in treating infections caused by gram-negative organisms. This finding is not unexpected, given the antibiotic susceptibilities of the organisms isolated in this trial. As shown in Table 6, except for *Pseudomonas* spp., the percentage of some of the gram-negative organisms resistant to ceftazidime was higher than the percentage resistant to imipenem. However, even for pseudomonal infections, ceftazidime did not appear to be more effective than imipenem (Table 4). Also, up to one-third of the patients infected by susceptible gram-negative organisms in vitro did not respond to ceftazidime (Table 4). The relatively high incidence of resistance of gram-negative organisms to ceftazidime may be due to the extensive utilization of the drug in our hospital since 1984. Imipenem was available in our hospital only after 1987.

Approximately 20% of the patients who received either ceftazidime or imipenem responded to the addition of cloxacillin and amikacin after failing monotherapy. This implies that although imipenem is more effective than ceftazidime as monotherapy in treating fever in neutropenic patients, regardless of the kind of initial therapy, an additional approximately 20% of the patients benefited from the addition of cloxacillin and amikacin whenever the initial monotherapy failed.

The subsequent clinical outcomes of patients who did not respond to either monotherapy or combination antibiotic therapy, together with the patterns of relapses and superinfections, suggest that these failures were often due to polymicrobial infections which were related to resistant staphylococcal or pseudomonal sepsis or invasive fungal infections (6, 8, 20). It appears that vancomycin or teicloplanin should be included for infections possibly caused by gram-positive organisms in the initial management of febrile episodes in neutropenic patients, especially if they have an indwelling intravenous catheter (8, 20). Pseudomonal infections remain troublesome and accounted more often for the relapses and superinfections following imipenem therapy (Table 5). This may be the subgroup of patients in whom early use of a combination of two antipseudomonal antibiotics may improve treatment success and prevent relapses (5, 12). Fungal infections have been recognized as important causes of mortality and morbidity in neutropenic patients, and empiric use of amphotericin B is often recommended for those neutropenic patients who have failed to respond to antibacterial agents (4). It remains uncertain whether the prophylactic use of newer agents, such as fluconazole and itraconazole, may prevent this. From the results of this trial, we found that all febrile neutropenic patients must be carefully monitored so that the appropriate modifications of therapy can be instituted.

We conclude that imipenem is more effective than ceftazidime as initial monotherapy for febrile neutropenic patients, especially in patients with microbiologically documented infections. Approximately 20% of patients who failed monotherapy responded to the addition of cloxacillin and amikacin. Treatment failures, relapses, and superinfections were commonly due to resistant staphylococcal or pseudomonal infections or disseminated fungal infections.

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