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Open Randomized Study of Cefepime versus Piperacillin-Gentamicin for Treatment of Febrile Neutropenic Cancer Patients

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An open-label randomized trial comparing the efficacy and safety of cefepime versus piperacillin plus gentamicin (P+G) given intravenously for the treatment of febrile episodes in neutropenic patients with underlying malignancy was conducted at two oncology centers. Over a 30-month period 111 patients were enrolled and 99 patients were found to be suitable for evaluation. At the 72-h time of evaluation, cefepime monotherapy and P+G combination therapy produced comparable clinical response rates (78% for both). P+G and cefepime produced comparable response rates in microbiologically documented (78 versus 71%), clinically documented (100 versus 100%), and possible (75 versus 79%) infections. The P+G and cefepime treatments achieved comparable microbiological eradication of gram-negative (100 versus 71%) ($P = 0.09$) and gram-positive (44 versus 70%) ($P = 0.37$) organisms. There were no statistically significant differences in the rates of superinfection between the groups; however, more superinfections of fungal origin were noted in the P+G group. Cefepime was demonstrated to be an effective and safe treatment for febrile episodes in neutropenic patients with malignancies, and its lack of nephrotoxicity compared to P+G was noteworthy. Cefepime appears to be a candidate for monotherapy in febrile neutropenic cancer patients.

Management of the febrile neutropenic period in patients with malignancies requires prompt therapy with empiric broad-spectrum antimicrobial agents. While substantial morbidity and mortality results from gram-negative infections, infections with gram-positive organisms appear to predominate (15, 19, 25, 26). Accepted empiric antimicrobial treatment strategies for these febrile episodes include combination therapy with a broad-spectrum antipseudomonal penicillin and an aminoglycoside, monotherapy with an antipseudomonal cephalosporin or a carbapenem, double beta-lactam combinations, and a beta-lactam and quinolone combination (1, 8, 9, 11, 15–18, 23, 27). Although there are advantages and drawbacks to each empiric treatment strategy, monotherapy with an antipseudomonal cephalosporin remains a very attractive option because of its efficacy, ease of administration, and lack of toxicity (2, 16, 23).

Cefepime, a new alpha-methoxyiminoaminothiozolyl cephalosporin with extended gram-negative and gram-positive activities is a potential candidate for empiric monotherapy in febrile neutropenic cancer patients (3, 7). Its enhanced spectrum is due to several factors. Cefepime permeates the outer membrane of gram-negative bacilli more rapidly than other cephalosporins (7, 14, 21). It is also relatively resistant to Bush group 1 beta-lactamase-producing organisms, while being a relatively poor inducer of type 1 beta-lactamases for gram-negative bacteria (7, 13, 21, 22). In vitro studies have demonstrated that cefepime has activity against *Staphylococcus aureus* and *Streptococcus* spp. which is comparable to that of ceftriaxone (13, 21). It is also potent against both *Pseudomonas* spp. and *Enterobacter* spp.

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Cefepime has proven efficacy in the treatment of a wide range of infections (5, 10, 24). However, only one published, noncomparative clinical trial has evaluated cefepime monotherapy in febrile neutropenic cancer patients (3). Therefore, this study was undertaken to compare the efficacy and safety of cefepime monotherapy to those of the combination regimen of piperacillin and gentamicin (P+G) in the empiric management of febrile episodes in neutropenic cancer patients.

MATERIALS AND METHODS

Patients. This study was conducted from June 1989 to November 1991 at Roswell Park Cancer Institute, Buffalo, N.Y., and at Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, N.Y. Ethical approval was obtained from the protocol review committee at each hospital. Patients were eligible for the trial if they had underlying malignancies, had absolute neutrophil counts of $\leq 1000/mm^3$, were 18 years of age or older, and had temperatures of $\geq 38.5°C$ or two temperature readings of $>38°C$ in a 24-h period preceded by an afebrile period of at least 72 h. All patients provided informed consent. Each subject was enrolled only once in the protocol.

Exclusion criteria included the following: a diagnosis of aplastic anemia or chronic myelogenous leukemia in blast crisis; the administration of any systemic antibiotic within 72 h prior to enrollment, thus precluding the use of oral antibacterial prophylaxis; a history of a serious hypersensitivity reaction to cephalosporins or penicillins; pregnant or lactating women; hypotension; a creatinine level of ≥ 2.0 mg/dl; anticipated treatment with the study medication for >28 days; the presence of signs and symptoms of a central nervous system infection, endocarditis or *Bacteroides fragilis* infection; evidence of a medically significant disease which would impact the outcome of the study; and any patient placed on "do not resuscitate" status. Patients with lower respiratory tract infections were excluded if they had cystic fibrosis, empyema, lung abscess, or pneumonia distal to an obstructive carcinoma. Also, patients with severe burns (20% or greater full thickness affected) or infected prostheses were ineligible for enrollment.

Eligible patients were randomized to one of two treatment arms by sealed envelopes assigned in sequence. When the medications were to be dispensed, the sealed envelope was opened and the drugs were given on an open-label basis.

Treatment. Patients received either cefepime, 2 g every 8 h, or piperacillin, 3 g every 4 h, plus gentamicin, 1.5 mg/kg of body weight every 8 h, intravenously. After the initial dose of gentamicin was administered, the dosage interval was adjusted according to each patient's creatinine clearance. Doses were administered to obtain peak serum gentamicin levels of 4 to 7 μg/ml and trough levels of <2 μg/ml. Serum gentamicin concentrations were assessed at least twice weekly and as necessary. Patients received a minimum of 4 days of treatment and

TABLE 1. Patient characteristics

Treatment arm	No. of patients suitable for evaluation/total no. of patients enrolled	Mean age (yr) ± SD	No. of patients (%)		Mean duration of neutropenia (days) ± SD	Mean initial neutrophil count ± SD	No. of patients with:					
			Male	Female			Hematological malignancy[a]					Solid tumors[b]
							ANL	NHL	HD	ALL	MS	
Cefepime	50/56	48.2 ± 17.4	23 (46)	27 (54)	9.0 ± 7.7	252.0 ± 285.3	16	13	5	2	1	13
P+G	49/55	51.3 ± 17.3	25 (51)	24 (49)	9.6 ± 7.5	244.1 ± 281.0	10	11	2	4	0	22
P value		0.37	0.62		0.72	0.89						0.06[c]

[a] Abbreviations: ANL, acute nonlymphocytic leukemia; NHL, non-Hodgkin's lymphoma; HD, Hodgkin's disease; ALL, acute lymphocytic leukemia; MS, myelodysplastic syndrome. Total number of malignancies: cefepime arm, 37; P+G arm, 27.

[b] Solid tumors included breast, lung, gastrointestinal, bladder, central nervous system, ovarian, adrenal, renal, testicular, and esophageal tumors, Wilms tumor, leiomyosarcoma, melanoma, Ewing's sarcoma, and carcinomas of unknown primary.

[c] Hematological malignancies versus solid tumors between treatment arms.

a maximum of 28 days. Concomitant treatment with vancomycin at a dose of 1 g every 12 h administered over 1 h was permitted if fever persisted for more than 72 h after the initiation of treatment with either of the two study regimens or if the pretherapy causative pathogen was resistant to the study drug(s) but susceptible to vancomycin. However, this modification to the regimen was only allowed after 72 h of treatment with the study medication. Antifungal and antiviral agents were permitted and administered as needed based on the patient's clinical condition. No hematopoietic growth factors were employed in the study.

Microbiological data. Microbiological confirmation was obtained by culture of blood or any body site suspected of being a focus of infection. Cultures were obtained within 72 h of commencing the study medications. Blood cultures were performed and processed by standard laboratory procedures. Lower respiratory tract secretions were obtained for culture by an expectorated sputum, endotracheal aspirate, or bronchoscopy. Urine cultures were clean midstream specimens or were aseptically aspirated via urethral catheterization.

Susceptibility testing was performed on all causative pathogens by the disk diffusion method with cefepime (30-μg), piperacillin (100-μg), gentamicin (10-μg), and vancomycin (30-μg) disks according to laboratory standards (4, 12).

Patient evaluation. All patients underwent a history and physical examination, had appropriate cultures performed, and had a chest X ray and laboratory studies completed. Hematologic, coagulation, urinalysis, and biochemical studies were performed at baseline and then repeated at 3- to 5-day intervals for the first week and weekly thereafter. Similarly, any positive baseline culture was repeated 3 to 5 days later and weekly thereafter. Patients were also evaluated clinically at 3- to 5-day intervals during the first week, and then a minimum of weekly thereafter. An end-of-treatment assessment included a clinical evaluation of signs and symptoms, a physical examination, repeat cultures, a chest X ray if pneumonia was present, and measurement of all laboratory parameters. In addition, 10 to 14 days after the completion of therapy, an assessment was conducted for all patients except for those with urinary tract infections, who were evaluated 5 to 9 days and 4 to 6 weeks after the completion of therapy.

The definition of a bloodstream infection required that at least one blood culture be positive for one or more clinically significant organisms. Documentation of pneumonia required a chest X ray with radiologic evidence consistent with pneumonia. A colony count of $\geq 10^5$ CFU/ml was necessary for the diagnosis of a urinary tract infection.

Efficacy and safety. All febrile episodes were classified as microbiologically documented infection (both the site of infection and the organism were identified), clinically documented infection (the site of infection was identified, but no organism was isolated), or possible infection (infection was suspected in a febrile patient, but no site or organism was identified).

Efficacy was determined by clinical response. A clinical response was classified as (i) success if fever and/or all clinical signs and symptoms relevant to the infection were resolved or if they improved and no new clinical signs or symptoms occurred in the 72-h evaluation period; (ii) unsatisfactory if fever and/or clinical signs and symptoms persisted for 72 h or more after the initiation of therapy, resulting in the clinical decision to change antimicrobial agents, or if, following initial improvement, recurrence or worsening of any fever or clinical signs or symptoms relevant to the original site of infection was observed; or (iii) unsuitable for evaluation if no follow-up evaluation of the clinical signs and symptoms was conducted or if the response could not be classified according to the previously mentioned clinical response categories because of a protocol violation. A superinfection occurred when new, persistent, or worsening symptoms and/or signs of infection were associated with the isolation of a new pathogen or the development of a new site of infection.

Patients had to receive the study medication for at least 96 h to be considered suitable for evaluation. All modifications to initial antibacterial therapy were reported. Patients were withdrawn from the analysis and considered protocol violations if antimicrobial therapy other than antifungal or antiviral medication was initiated prior to the 72-h period of evaluation.

In addition, the microbiological response was assessed. The microbiological response was defined as (i) eradication if the pretherapy causative pathogens were not isolated in follow-up cultures or if there was no source to culture during therapy or at the posttherapy evaluation or (ii) failure if the causative pathogen was present in the microbiological evaluation at the 72-h evaluation.

Although all clinical adverse events were recorded, only laboratory parameters deviating significantly from normal were included in this report. In particular, hypokalemia was defined as a decrease of at least 0.5 meq/liter from the baseline value to <3.5 meq/liter. Hypokalemia temporally related to amphotericin B or diuretic drug administration was excluded from the analysis. Antibiotic-related nephrotoxicity was defined as an increase of at least 0.5 mg/dl in the serum creatinine level when other causes of nephrotoxicity (hypotension and other nephrotoxic drugs, etc.) had been excluded. Hypoprothrombinemia was present if the prothrombin time was more than 2 s above the baseline value.

Analysis. All continuous variables in each arm were analyzed by Student's *t* test. Categorical variables in each group were compared by means of chi-square or Fisher exact tests. The Mantell-Haenszel test of homogeneity was used to assess the effect of each subject's underlying diagnosis on treatment outcome. A two-way analysis of variance was performed to evaluate any interaction between the treatment allocation and underlying tumor type with respect to the duration of neutropenia and initial neutrophil count. Statistical significance was determined at $P \leq 0.05$.

RESULTS

Overall, 111 patients were enrolled over 30 months. Fifty-six patients received cefepime, and 55 received P+G. Due to protocol violations prior to the 72-h evaluation period, 11 patients were unsuitable for evaluation. One additional patient (cefepime arm) was withdrawn from the study prior to the time of evaluation because of a drug rash. Thus, a total of 12 patients were unsuitable for evaluation, 6 each in the cefepime and P+G arms.

There were no significant differences between the two patient groups with regard to age, sex, duration of neutropenia, mean initial neutrophil count, and underlying malignancy (Table 1). Sixty-five percent of the patients (72/111) had underlying hematological malignancies.

Microbiologically documented infections were identified in 48% (48/99) of the patients. Bacteremia was the primary source of infection in 26% of the patients. Clinically documented infections were found in only seven patients. Possible infectious etiology existed in 44% (44/99) of the febrile episodes. There was no significant difference in the clinical response between the arms (78% for both) (Table 2). However, this relatively small study would only have been able to reliably detect a true difference in response rate of about 18% between the two treatments.

The respective response rates for microbiologically documented, clinically documented, and possible infections were 71 and 78%, 100 and 100%, and 79 and 75% in the cefepime and P+G arms, respectively. Of note, there were more microbiologically documented urinary tract infections in the P+G arm, while clinically documented infections occurred more frequently in the cefepime arm. Ten study patients had two simultaneously microbiologically and clinically documented in-

TABLE 2. Primary infection source and clinical response in patients suitable for evaluation

Type of infection	No. of patients responding/total no. of patients with infection	
	Cefepime arm (n = 50)	P+G arm (n = 49)
Microbiologically documented	15/21 (71%)	21/27 (78%)
Bacteremia	9/14	7/12
Bronchitis		1/1
Cellulitis	1/2	
Gasteroenteritis		1/1
Pharyngitis	3/3	2/3
Pneumonia		1/1
UTI[a]	2/2	8/8
Vaginal cellulitis		1/1
Clinically documented	5/5 (100%)	2/2 (100%)
Cellulitis	2/2	
Pharyngitis	1/1	1/1
Pneumonia		1/1
Sinusitis	1/1	
Stomatitis	1/1	
Possible	19/24 (79%)	15/20 (75%)
Total[b]	39/50 (78%)	38/49 (78%)

[a] UTI, urinary tract infection.
[b] P = 0.96.

fections. In each case, the primary efficacy analysis was based on the microbiologically documented infection. Eight of these cases involved a bloodstream infection, while the other two cases were a vaginal abscess and a urinary tract infection. Cefepime was employed in eight cases, and P+G was employed in two. One treatment failure occurred in each arm.

Because the underlying diagnosis, i.e., hematological malignancy versus solid tumor, was not equally represented in both treatment groups, an additional analysis was performed. When stratifying the analysis of clinical response by tumor type, it was apparent that cefepime was more successful in patients with hematological malignancies than P+G (78 versus 63%, respectively). On the other hand, P+G attained greater response rates in patients with solid tumors (96 versus 77%, respectively). The formal comparison of treatment effect between patients with hematological malignancies and those with solid tumors yielded a P value of 0.03, indicating strong statistical evidence of a subgroup effect. Further analyses to evaluate any interaction between tumor type and mean duration or mean initial depth of neutropenia were also completed. A two-way analysis of variance revealed no interaction between tumor type and the treatments with regard to mean duration of neutropenia (P = 0.801). In addition, there was no significant interaction between tumor type and treatment allocation with regard to the mean initial neutrophil count (P = 0.279).

The microbiological response for each pathogen in all microbiologically documented infections is shown in Table 3. The microbiological response rate for gram-positive microorganisms tended to be higher in the cefepime arm than in the P+G arm but didn't achieve statistical significance (7/10 [70%] versus 4/9 [44%], respectively; P = 0.37). However, there was a trend of enhanced efficacy with P+G against gram-negative pathogens (15/15 [100%] versus 5/7 [71%] for cefepime; P = 0.09). Each treatment achieved comparable efficacy against mixed gram-positive and -negative infections (3/4 [75%] for cefepime and 2/3 [67%] for P+G).

TABLE 3. Microbiological response in patients suitable for evaluation at 72 h prior to modification of therapy

Fever source	Pathogen	No. of isolates eradicated/total no. of isolates	
		Cefepime arm	P+G arm
Bacteremia	*Staphylococcus aureus*	1/3	0/1
	Staphylococcus epidermidis	1/2	2/3
	Coagulase-negative staphylococci		0/1
	Streptococcus spp.	1/1	0/2
	Enterococcus spp.	1/1	
	Listeria monocytogenes	1/1	
	Clostridium perfringens		0/1
	Escherichia coli	4/4	3/3
	Klebsiella pneumoniae	2/2	2/2
	Enterobacter aerogenes	1/1	
	Pseudomonas aeruginosa	0/1	
	Pseudomonas spp.		1/1
	Acinetobacter calcoaceticus		1/1
Urinary tract infections	Gamma-hemolytic streptococci		1/1
	Diphtheroids	1/1	
	E. coli	2/2	3/3
	K. pneumoniae		3/3
	P. aeruginosa		2/2
Pharyngitis	*Streptococcus* spp.	1/1	2/2
	S. aureus	2/2	0/1
Cellulitis	*Streptococcus agalactiae*	0/1	
	P. aeruginosa	1/2	
Bronchitis	*Haemophilus influenzae*		1/1
Gastroenteritis	Salmonella group D		1/1
Pneumonia	*H. influenzae*		1/1
Vaginal cellulitis	*Enterococcus* spp.		1/1
	P. aeruginosa		1/1

Comparable rates of superinfection were observed in both arms (13/49 [27%] for P+G therapy and 12/50 [24%] for cefepime therapy; P = 0.77). A total of 21 superinfections were noted in 13 P+G patients, with cellulitis and oral stomatitis predominating (Table 4). The most frequently recorded superinfection in the cefepime arm was a bacteremia due to coagulase-negative staphylococci (Table 5). P+G produced more *Candida* spp. superinfections than cefepime (three versus

TABLE 4. Superinfections in patients suitable for evaluation[a]

Source	No. of superinfections in patients in:	
	Cefepime arm	P+G arm
Bacteremia	4	3
Cellulitis	3	7
Oral stomatitis	3	6
Clostridium difficile colitis	2	1
Urinary tract infection	1	0
Esophagitis	1	1
Rectal abscess	0	1
Fever of unknown origin presumed to be due to fungi	0	2

[a] In the cefepime arm, 12 of 50 (24%) patients had superinfections; in the P+G arm, 13 of 49 (27%) patients had superinfections. P = 0.77.

TABLE 5. Superinfection pathogens (more than one pathogen may be present)

Microorganism	No. of isolates in:	
	Cefepime arm	P+G arm
Candida spp.	3	8
Clostridium difficile	2	1
Coagulase-negative staphylococci	2	1
Staphylococcus epidermidis	2	1
Enterococcus spp.	1	2
Staphylococcus aureus	1	0
Corynebacterium spp.	0	1
Staphylococcus warneri	0	1
Klebsiella oxytoca	0	1
Pseudomonas aeruginosa	0	1
Herpes simplex	1	1

eight; $P = 0.12$), but most of these infections were clinically manifested in the gastrointestinal tract.

There was a significant increase in the overall frequency of toxicity experienced with P+G compared with that experienced with cefepime (23/55 [42%] versus 12/56 [21%]; $P = 0.03$). Nephrotoxicity was the most significant adverse event reported for those treated with P+G (15%) compared with 0% for the cefepime arm). Of note, however, five of the eight patients (62.5%) who developed nephrotoxicity also received vancomycin concomitantly. Other adverse events, classified as biochemical laboratory toxicity (hypokalemia, hypophosphatemia, and positive direct Coombs test; 5 with cefepime versus 10 with P+G), gastrointestinal tract toxicity (nausea or vomiting and diarrhea; 5 with cefepime and 9 with C+P), dermatologic toxicity (rash and phlebitis; 1 with cefepime and 5 with P+G), and ototoxicity, which affected 1 patient in each arm, were not significantly different between the two study regimens.

Modifications to the empiric therapeutic regimen were somewhat more prevalent for cefepime (25/50, 50%) than P+G (18/49, 37%) ($P = 0.23$). Vancomycin was added to the empiric regimen most frequently (13 patients in the cefepime group and 14 patients in the P+G group). However, vancomycin was never commenced at the initiation of the empiric study regimen. Other common additions included metronidazole (4 patients in the cefepime arm and 7 in the P+G arm) and antifungal therapy (amphotericin B, ketoconazole, and fluconazole), which was provided to 10 patients in each group. Aminoglycosides were added to the cefepime group at the investigator's discretion (five patients), following the completion of the 72-h evaluation period. Similarly, for one patient receiving P+G, ticarcillin-clavulanic acid and gentamicin were substituted for the trial combination after the 72-h evaluation period. Of note, modification to the cefepime treatment arm with an aminoglycoside (two patients), another beta-lactam (two patients) or vancomycin (one patient) occurred in only five instances of microbiologically documented bacterial infection. The bulk of the modifications in the cefepime group were observed in the patients with possible infections.

DISCUSSION

This study evaluated the safety and efficacy of cefepime monotherapy versus the combination of P+G for the empiric therapy of febrile episodes in cancer patients rendered neutropenic by chemotherapy. Overall, there was no significant difference in the clinical response rates between the two arms (78% for both; $P = 0.96$). The observed response rates in microbiologically documented, clinically documented, and infectious fevers of unknown origin were also comparable for both arms. These response rates are similar to those previously reported in the literature for febrile episodes in neutropenic patients with malignancies (2, 8, 11, 17, 18, 27). However, the apparent superiority of cefepime for the empiric treatment of patients with hematological malignancies and that of P+G for those patients with solid tumors cannot be readily explained. The predominance of gram-positive pathogens in patients with hematological malignancies may account for this (15, 20).

Although the P+G arm exhibited somewhat better microbiological eradication rates for gram-negative microorganisms (100% versus 71% for cefepime), and cefepime's activity surpassed that of P+G for gram-positive microorganisms (70 versus 44%, respectively), neither effect was statistically significant. Previously, in an open uncontrolled trial involving 91 patients with cancer, cefepime achieved response rates of 86, 44, and 79% for gram-negative infections, gram-positive infections, and infectious fevers of unknown origin, respectively (3). Cefepime purportedly has enhanced antistaphylococcal activity in vitro. This may have resulted in the response rates observed for gram-positive pathogens, but this observation requires confirmation in a larger trial.

Although no significant difference in the frequency of superinfection was noted between the arms, *Candida* spp. were the most common pathogens producing superinfections in those patients treated with P+G. These infections appeared to originate in the gastrointestinal tract. Fecal concentrations of piperacillin may cause eradication of normal host gastrointestinal flora, with subsequent colonization by *Candida* spp. (6).

Cefepime was demonstrated to be safe treatment for febrile episodes in neutropenic oncology patients. Adverse events were experienced in 12 of 56 patients treated with cefepime (21%) compared to 23 of 55 (42%) patients in the P+G group ($P = 0.03$). Moreover, cefepime's lack of nephrotoxicity and ease of administration make it an attractive alternative to aminoglycoside-containing combination therapy. This may have added relevance since the concomitant use of other nephrotoxins such as vancomycin, amphotericin B, and acyclovir is often necessary in the management of these patients (2, 15).

Cefepime now has demonstrated its efficacy as empiric monotherapy in febrile neutropenic cancer patients. Although it may have a theoretical advantage over ceftazidime because of its enhanced in vitro antistaphylococcal activity, these antimicrobial agents haven't been compared in a randomized clinical trial. As toxicity does not appear to be an issue with either agent, cefepime's resistance to beta-lactamase and poor induction of beta-lactamase in gram-negative bacteria may be of benefit relative to ceftazidime's properties. However, no economic advantage is realized with cefepime monotherapy. In Canada, cefepime's use as monotherapy for febrile neutropenic cancer patients at a dose of 2 g every 8 h produces daily drug acquisition costs of $89.70 (Canadian) compared with $66.04 (Canadian) for combination therapy with P+G for a 70-kg individual. Cefepime's costs also exceed those of ceftazidime at equivalent dosing ($81.72 [Canadian]). In the United States, ceftazidime's daily drug acquisition costs are clearly less than those of cefepime ($47.58 versus $77.10 [American], respectively). Thus, further trials are necessary to substantiate cefepime's role as the preferred agent for monotherapy in febrile neutropenic cancer patients.

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