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Original Article

An observational study on the empiric use of cefpirome in febrile neutropenia

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Background and Purpose: The objective of this study was to document the clinical experience of cefpirome use in the treatment of febrile neutropenia in everyday medical practice.

Methods: This was an open, non-controlled multicenter study. Patients with fever and neutropenia were started on cefpirome empirically. Response to therapy was evaluated 72 to 96 h after the beginning of treatment. The primary endpoint, clinical response, was classified as: improvement (disappearance of fever and the other signs and symptoms of infection) or failure (the patient died during the therapy or had no response to the antibiotic regimen; i.e., fever persisted and the patient's clinical condition was not improving, requiring a change in antibiotic therapy). The secondary endpoints were time to the resolution of fever and improvement of neutropenia, and microbiological response evaluated on-treatment or post-treatment.

Results: 140 patients were enrolled in this study; clinical response was analyzed on the clinically evaluated population after 72 to 96 h of treatment. Among the 69 evaluated patients, 58 patients (84.1%) were improved and 11 patients (15.9%) failed. Overall, among the enrolled 140 patients, 124 patients' clinical outcomes were improved after treatment and 16 patients failed. The mean time to fever resolution was 3.1 days. Mean temperature reduced from a baseline reading of 38.7°C to 37.2°C ($p<0.0001$). Moreover, the mean neutrophil count (342.7/mm^3 at baseline) increased significantly to 3664/mm^3 ($p<0.0001$) after 72 to 96 h of treatment. Twenty five pathogens were isolated from 20 patients (13 Gram-positive and 9 Gram-negative). The eradication rate was 72% on-treatment or post-treatment, and the mean time to eradication was 5 days.

Conclusions: Cefpirome improves clinical signs and symptoms of infection and offers improved coverage against some Gram-positive and Gram-negative pathogens in patients with febrile neutropenia. Thus, cefpirome is likely to be a valuable and cost-effective extended-spectrum agent for the empiric treatment of severe infections.

Key words: Bacterial infections; Cephalosporins; Fever; Neutropenia; Treatment outcome

Introduction

Over the past several decades, there have been important advances in the field of antimicrobial therapy [1]. Nevertheless, the incidence of severe bacterial infection has increased and such infections remain an important cause of mortality, especially in neutropenic patients. Development of new antibiotics has allowed clinicians to combat this type of infection with improved results [2].

Cefpirome is a new fourth-generation injectable cephalosporin [3]. The drug is an aminothiazolemethoxyimine cephalosporin, with a positively charged quarternary ammonium moiety in the cephem nucleus position 3, beside a carboxyl group with negative charge

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in position 4, which provides the molecule with the properties of zwitterions [4]. These characteristics give cefpirome the combination of remarkable anti-Gram-positive activity and the anti-Gram-negative activity of third-generation cephalosporins [5]; in addition, these structural features help prevent resistance caused by problematic pathogens such as *Enterobacter* spp. and *Citrobacter* spp. Moreover, cefpirome is stable against a great deal of beta (β)-lactamase producing bacteria [6].

Clinical studies and susceptibility tests have shown that cefpirome is active against bacterial pathogens that cause urinary tract infections, lower respiratory tract infections, skin and soft tissue infections, septicemia, serious infections in patients in intensive care units (ICU) and infections in neutropenic patients [7]. The spectrum of cefpirome includes common Gram-negative organisms such as *Escherichia coli*, *Klebsiella* spp., *Pseudomonas aeruginosa*, *Enterobacter* spp. and Gram-positive organisms such as staphylococci and streptococci. Cefpirome's serum elimination half-life of 2 h, combined with good tissue penetration, allows a twice-daily dosage regimen. Kinetic parameters are linear and there is good bioavailability. As with other β-lactams, gastrointestinal disorders, such as diarrhea, nausea and vomiting have occasionally occurred in clinical trials with cefpirome. Rash and superficial phlebitis have been reported as well, with a frequency of over 1%. Cefpirome, by virtue of its enhanced antimicrobial activity against Gram-positive pathogens and β-lactamase stability, is a promising option among broad-spectrum β-lactams for use in the empiric management of febrile episodes in neutropenic patients [8].

The objective of this clinical observation project is to document the clinical experience of cefpirome use in the treatment of febrile neutropenia in everyday medical practice.

Methods

This was an open-label, single-arm multicenter study in which the clinical experience of intravenously administered cefpirome (Cefrom®, Sanofi-Aventis, France) was documented in patients with febrile neutropenia in medical practice. Between July 2002 and June 2003, a total of 140 patients were enrolled at five hospitals in Taiwan: Buddhist Dalin Tzu Chi General Hospital; Tri-Service General Hospital; National Taiwan University Hospital; Mackay Memorial Hospital; and Chung Shan Medical University Hospital. As judged by the investigators, all patients met the selection criteria, and were included in the final analysis.

For purposes of the study, neutropenia was defined as an absolute neutrophil count of <500 cells/mm^3 or a count of <1000 cells/mm^3 with a predicted decrease to <500 cells/mm^3. Febrile was defined as a single axillary temperature of >38°C. At admission, all patients were assessed clinically and baseline investigations including blood culture, serum creatinine and a full blood count were performed.

Cefpirome was available in the form of 1 g vials for injection. The patient was treated with cefpirome by prescription from the physician as in usual practice. Cefpirome was administered by intravenous injection or infusion, with the dosage, mode of administration and duration of treatment depending upon the severity of the infection, sensitivity of the pathogens, and condition of the patient and renal function. For the treatment of infections in neutropenic patients, 2 g 12-hourly was recommended (daily dose, 4 g) administered as either an intravenous bolus (in 20 mL sterile water for injections) over 3 to 5 min; or an intravenous infusion (in 100 mL sterile water for injections) over 20 to 30 min.

The following infusion solutions were also permitted: 0.9% sodium chloride solution; Ringer's solution; standard electrolyte infusions; 5% and 10% glucose solution; 5% fructose solution; and 6% glucose + 0.9% sodium chloride solution.

In patients with impaired renal function (creatinine clearance, <50 mL/min), the following doses were recommended instead: 2 g loading dose, then 1 g twice daily when the creatinine clearance was 20-50 mL/min; 2 g loading dose, then 1 g daily when the creatinine clearance was 5-20 mL/min; 2 g loading dose, then 1 g daily, plus 0.5 g immediately after hemodialysis, when the creatinine clearance was <5 mL/min and the patient was receiving hemodialysis. All patients were hospitalized until the fever resolved. All data were monitored on site for accuracy and completeness.

Endpoints

The primary endpoint of the study was clinical response. The clinical response was based on clinical evaluations of the patient to determine the effect of therapy on the signs and symptoms of infection, which were evaluated 72-96 h after the start of the empiric treatment, and was classified as: 1) improvement (disappearance of fever and the other signs and symptoms of infection); 2) failure (the patient died during the therapy or had no response to the antibiotic regimen, i.e., fever persisted and the

patient's clinical condition was not improving, requiring a change in antibiotic therapy).

The secondary endpoints were: 1) the time to the resolution of fever and improvement of neutropenia; 2) microbiological response, evaluated on-treatment or post-treatment; and 3) mean days of eradication, the time period between the initiation of antibiotics and the eradication of bacterial pathogen. If the microbiology laboratory identified several pathogens, the microbiological response was separately assessed for each pathogen. Grading was as follows: eradication — eradication of causative organism on-treatment or post-treatment; persistence — presence of causative organism at the end of therapy; and indeterminate — bacterial response not evaluated for any reason (e.g., culture lost or not obtained when indicated).

Statistical analysis

As the objective of this clinical observation project was to document clinical experience with cefpirome, statistical data were analyzed in all patients who met the selection criteria. In the analysis, the clinical data were classified as: 1) improvement and 2) failure. The occurrence of adverse events throughout the study period was assessed. Descriptive analysis was applied for both the efficacy and safety parameters.

Results

Patient characteristics

140 patients were enrolled at five hospitals. As judged by the investigators, all patients met the selection criteria of febrile neutropenia, and were included in the final analysis. The mean age of patients was 55.4 years and 67.1% were male. The mean height was 164 m and mean weight was 60 kg.

Drug administration

A dosage of 2 g 12-hourly was the most commonly employed regimen, used in 132 patients (94.3%), and the average extent of exposure was 7.9 days (range, 1 to 22 days). Two patients changed dose during the treatment period due to the resolution of fever.

Efficacy

Whereas the protocol stated that clinical response should be evaluated 72 to 96 h after the start of empiric treatment, 15 patients were evaluated earlier than 72 h and 56 patients were evaluated later than 96 h. These 71 patients (50.7%) were not included in the clinically evaluated population. Sixty nine patients were evaluated after 72 to 96 h of treatment as suggested by the protocol and were included in the clinically evaluated population.

Clinical response

Statistical analysis of clinical response was performed on the clinically evaluated population initially. Among the 69 patients, 58 (84.1%) improved and 11 (15.9%) failed. All patients (n = 140) were analyzed for the evaluation of efficacy at the time point of observation (from 72 to 96 h). Overall, clinical outcome improved after treatment in 124 patients (88.6%) and the other 16 patients (11.4%) patients failed. The mean time to fever resolution was 3.1 days. When comparing the clinical outcome observed at different time points (<72 h, 72 to 96 h or >96 h), there was no difference between the three groups. However, when the duration of therapy was greater than 96 h, the rate of improvement increased to 94.6%. Among 16 patients who failed therapy, most of them (12 patients, 75%) had no response to the antibiotic regimen (fever persisted), and 4 patients (25%) died during the observation period.

Improvement of fever and neutropenia

Among the 69 patients evaluated at 72-96 h after the start of treatment, the mean temperature reduced from a baseline reading of 38.7°C to 37.2°C (p<0.0001) after 72 to 96 h. The mean neutrophil count was 342.7/mm^3 at baseline. After 72 to 96 h of treatment, the neutrophil count had increased significantly, to 3664.2/mm^3 (p<0.0001) [Table 1].

Microbiological response

Among 140 patients enrolled, bacteria were isolated from blood culture in 20 patients. Twenty five pathogens were isolated from 20 patients (13 Gram-positive and 9 Gram-negative). The majority of them (72%, 18/25) were eradicated on-treatment or post-treatment (Table 2). One patient's pathogen (fungus and normal flora) was isolated post-treatment, but was not clinically significant.

Discussion

Fever is frequently the only clinical sign of infection in patients with neutropenia. In this setting, empirical administration of broad-spectrum antibiotics must be rapid. Cefpirome is an injectable extended-spectrum or 'fourth-generation' cephalosporin. Its antibacterial activity encompasses many of the pathogens involved

Table 1. Summary of change in temperature and neutrophil count

	Baseline Mean ± SD	72 to 96 h Mean ± SD	Change from baseline Mean ± SD	95% confidence interval	*p*
Temperature (°C)	38.7 ± 0.47	37.2 ± 0.8	–1.6 ± 0.83	(–1.74, –0.02)	<0.0001
Neutrophil count (/mm^3)	342.7 ± 26.59	3664 ± 303	3324 ± 306	(2723.81, 3924.79)	<0.0001

Abbreviation: SD = standard deviation

in hospital-acquired infections, such as Enterobacteriaceae, methicillin-susceptible *Staphylococcus aureus*, coagulase-negative staphylococci and viridans group streptococci. Cefpirome also has in vitro activity against *Streptococcus pneumoniae*, regardless of penicillin susceptibility [9-11]. The drug is stable against most plasmid- and chromosome-mediated β-lactamases, with the exception of the extended-spectrum plasmid-mediated SHV enzymes [7]. However, in the current study, among 69 patients whose response was evaluated between 72 and 96 h, 58 patients (84.1%) were improved and 11 patients (15.9%) failed treatment. As the objective of this study was to document clinical experience with cefpirome, we further analyzed all qualified patients for the efficacy evaluation. Overall, 124 patients were improved after treatment and the other 16 patients failed. When comparing the clinical outcome observed at different time points (<72 h, 72-96 h or >96 h), there was no significant difference between the three groups. Among 16 patients who failed therapy, most of them (12 patients, 75%) had no response to the antibiotic regimen (fever persisted), and 4 patients (25.0%) died during treatment. Twenty five pathogens were isolated in 20 patients, of which 13 were Gram-positive and 9 Gram-negative.

The clinical improvement rate we observed is higher than in a previous study, a randomized prospective multicenter trial of cefpirome versus piperacillin-tazobactam in patients with febrile neutropenia, which included 131 men and 77 women aged between 17 and 83 years (median, 49 years). Two days after cefpirome initiation, fever disappearance was observed in 62% of patients and the microbiological success rate was 50% [12].

In the present study, among 69 patients, the mean temperature was 38.7°C at baseline; after 72 to 96 h of treatment, temperature was significantly reduced to 37.2°C (p<0.0001). The mean duration of fever was 3.1 days. The mean neutrophil count, 342.7/mm^3 at baseline, was significantly increased to 3664.2/mm^3 after 72 to 96 h of treatment (p<0.0001).

The clinical improvement rate was 84% in the current study, higher than the 62% reported in a previous study by Bauduer et al [12]. In both studies, cefpirome was effective in reducing the severity of clinical signs and symptoms in patients with febrile neutropenia. The

Table 2. Summary of isolated pathogens (100% blood isolated)

Pathogen	No. of isolated pathogens	No. of eradicated pathogens	Mean days to eradication
Total	25	18	
Gram-negative organisms	9	7	
Escherichia coli	5	4	5.25
Acinetobacter baumannii	2	2	4.00
Pseudomonas aeruginosa	1	1	7.00
Stenotrophomonas maltophilia	1	0	-
Gram-positive organisms	13	8	
MRSA	6	3	5.67
MSSA	3	3	16.00
MRSE	1	0	-
Micrococcus	1	1	16.00
Sphingobacterium spiritivorum	1	1	3.00
Gram-positive bacilli	1	0	-
Fungus	3	3	
Candida albicans	2	2	2.50
Fungi	1	1	5.00

Abbreviations: MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *S. aureus*; MRSE = methicillin-resistant *Staphylococcus epidermidis*

Table 3. Comparative daily cost of empirical antibiotic therapy for serious infections

Extended-spectrum agents	Product/ formulation	BNHI price (NT$)	Dosage	Daily treatment cost (NT$)	Inducible resistance potential
Fourth-generation cephalosporins	Cefrom® 1g/vial (cefpirome)	541/vial	4-6 g/day	2164-3246	+/–
	Maxipime® 500 mg/vial (cefepime)	505/vial	4-6 g/day	4040- 6060	+/–
Penicillin combinations	Tazocin® 2.25 g/vial (piperacillin-tazobactam)	586/vial	13.5-18 g/day	3516-4688	+/–
	Timentin® 1.6 g/vial (ticarcillin-clavulanate)	484/vial	12.8-19.2 g/day	3872-5808	+++
Carbapenems	Tienam® 250 mg/vial (imipenem)	500/vial	1500-3000 mg/day	3000-6000	+/–
	Mepem® 250 mg/vial (meropenem)	535/vial	1500-3000 mg/day	3210-6420	+/–
Third-generation cephalosporins	Fortum® 500 mg/vial (ceftazidime)	210/vial	6-8 g/day	2520-3360	+++
	Flumarin® 500 mg/vial (flomoxef)	418/vial	4-6 g/day	3344-5016	+++

Abbreviations: BNHI = Bureau of National Health Insurance; NT$ = New Taiwan Dollars; +/– = lower inducible resistance potential; +++ = higher inducible resistance potential

higher clinical improvement rate in this than in the previous study might be due to the small size of this study (and consequent lack of statistical power) and also differences in doses and/or timing of treatment, types of isolated pathogens, bacterial resistance to the study drugs and the severity of illness in the patient populations.

In the present study, among 69 patients evaluated 72 to 96 h after the start of treatment, the mean temperature significantly decreased within 3.1 days and the mean neutrophil count significantly increased during the same period. Moreover, the majority of patients had a successful bacteriological eradication within 5 days. Thus, the majority of treated patients had a successful overall treatment outcome within 5 days. Prolonged treatment with cefpirome was able to increase the proportion of patients with successful clinical outcome. The high rates of clinical success and microbiological success show that cefpirome given empirically may be appropriate in the majority of patients with febrile neutropenia.

The cost of antibiotic treatment is an important consideration in empirical therapy, and subject to the budget control policy of our government. Table 3 shows the daily cost of typical dosages of antibiotics used in empirical therapy, according to Bureau of National Health Insurance prices [13]. Antibiotics with high inducible resistance potency must be avoided in empirical therapy in order to reduce the likelihood of clinical bacterial resistance [5,6]. Cefpirome is likely to have lower potential for inducible resistance and cheaper daily cost compared with alternative extended-spectrum agents for the empiric treatment of severe infections.

In conclusion, cefpirome improves clinical signs and symptoms of infection and offers improved coverage against some Gram-positive and Gram-negative pathogens in patients with febrile neutropenia [14]. Thus, cefpirome is likely to be a valuable extended-spectrum agent for the empiric treatment of severe infections [15].

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