Infectious Disorders

Cefpirome as empirical treatment for febrile neutropenia in patients with hematologic malignancies

Cefpirome, a fourth generation cephalosporin, was administered during 154 episodes of febrile neutropenia in 106 patients. We assessed the clinical efficacy of cefpirome and its activity against isolated pathogens in neutropenic patients with hematologic malignancies. In addition, the pharmacokinetics and optimal dosing regimen of cefpirome during neutropenia were investigated.

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Cefpirome is a fourth generation cephalosporin, with a broad spectrum of antibacterial activity. As compared with third generation cephalosporins the drug has better activity against Gram-positive micro-organisms and greater stability to beta-lactamases. Moreover, cefpirome is generally well tolerated. In view of these properties cefpirome may be suitable for the empirical treatment of fever in neutropenic patients. Open trials, as well as some randomized studies, have shown promising results.[1-3]

The dosage of cefpirome recommended by the manufacturer for infections in neutropenic patients is 2 g twice daily. However, though pharmacokinetics have been investigated in healthy volunteers, data during neutropenia are lacking.

We performed an open label, non-randomized clinical study to assess the clinical efficacy of cefpirome and its activity against isolated pathogens in neutropenic patients with hematologic malignancies. In addition, the pharmacokinetics and optimal dosing regimen of cefpirome in this population were investigated.

During a two-year study period cefpirome was administered during 154 neutropenic episodes in 106 patients. The dose given was 2g twice daily, intravenously. Patients were eligible if they were admitted to the hematology ward of our hospital for chemotherapeutic treatment of hematologic malignancies and became febrile (T>38.5°C) during the neutropenic episode (neutropenia defined as an absolute neutrophil count (ANC) $<0.5\times10^9$/L). For prevention purposes all patients had initially received systemic antimicrobial prophylaxis, comprising oral ciprofloxacin, azithromycin, fluconazole and nasal amphotericin B. The patients' characteristics, disease and treatment variables are given in Table 1. Patients were evaluated for causes of fever and clinical outcome. A microbiologically documented infection (MDI) was evidenced in 55 (36%) of episodes, a clinically documented infection (CDI) in 40 (26%) and fever of unknown origin (FUO) in 59 (38%) (Table 2). Cefpirome treatment was considered to have been successful if the patient survived the episode of fever and neutropenia without any modification of the cefpirome regimen, and without signs of remaining active infection.[4] Treatment was successful in 81 (53%) of the 154 episodes. The rate of success was highest in the episodes of FUO (45/59; 76%), less in the episodes of CD1 (21/40; 53%) and lowest in the episodes of MDI (15/55; 27%). The toxicity profile of cefpirome appeared to be favorable. Skin rash, possibly caused by cefpirome, occurred in 14 episodes.

Table 1. Characteristics of the patients and infections episodes.

Characteristics	*Number of episodes (%) Unless otherwise specified*
General characteristics	
Number of neutropenic episodes	154
Number of patients	106
Male/ female	63/ 43 (59/ 41)
Age (years, mean ± SD)	50.2±13.6
Diagnoses (in 106 patients)	
Acute myeloid leukemia	44 (41)
Acute lymphoblastic leukemia	8 (7)
Myelodysplastic syndrome	6 (6)
Lymphoma	21 (20)
Multiple myeloma	20 (19)
Chronic myeloid leukemia	6 (6)
Hairy cell leukemia	1 (1)
Treatment (in 154 neutropenic episodes)	
Autologous stem cell transplantation	58 (38)
Central venous access catheter	148 (96)
Neutropenic episode# (days, mean ± SD)	24.8±9.5
Duration of fever (days, mean ± SD)	4.5±4
Duration of fever (days, range)	1-25
Cefpirome	
Treatment days (mean ± SD)	9.8±6.2
Treatment days (range)	1-42

#Duration of the neutropenia is calculated from the start of chemotherapy until absolute neutrophil count (ANC) >0.5×10⁹/L.

No other toxicities of the study treatment were observed. Seven patients died during the study period. Four were still febrile (MDI n=3, CDI n=1), three others died of disease progression (n=2) or cerebral hemorrhage (n=1).

Susceptibility patterns of isolated pathogens were determined by standard microbiological techniques, which classified strains as sensitive (S), intermediate susceptible (I) or resistant (R), and are given in Table 2. The majority of the Gram-positive cocci and Gram-negative rods isolated were susceptible to cefpirome. However, all isolates of enterococci (*E. faecium* and *E. faecalis*), *Corynebacterium jeikeijum* and *Stenotrophomonas maltophilia* were resistant. *Pseudomonas aeruginosae* were susceptible to cefpirome *in vitro*. However, MIC_{90} values between 12.5 and >32 mg/L have been reported, indicating borderline susceptibility or resistance.[5,6]

Cefpirome serum levels were measured in a subgroup of 24 patients, randomly selected from the total of 106 patients entered in the study. On the final day of cefpirome treatment the standard dosing regimen was switched to one of three different dosing regimens. Group I (n=8) continued to receive cefpirome 2 g twice daily, group II (n=8) received cefpirome 1 g three times daily and group III (n=8) received a single dose of 500 mg followed by 3 g cefpirome continuously i.v. A two-compartment model was constructed to predict the duration of time between cefpirome administration and the moment that the serum concentration dropped below 4 mg/L, for each of the different dosing regimens. The concentration of 4 mg/L was defined as a target concentration to be exceeded, being the MIC_{50} and a breakpoint for *Pseudomonas aeruginosa*.[7] Group I patients had serum concentrations >4 mg/L for a mean of 87.5% of the time, group II for 92.6% of the time (p=0.4) and group III for 100% of the time (p=0.01). Cefpirome 2 g twice daily is recommended by the manufacturer as a dosing regimen

Table 2. Pathogens isolated and their susceptibility patterns.

Causes of fever	*No. of episodes*	*No. of strains sensitive (S), intermediate (I) or resistant (R) to cefpirome*		
		S	*I*	*R*
Microbiologically documented infections	55 (36%)			
Bloodstream infections	40			
Coagulase negative staphylococci	10	10		
Viridans group (VG) streptococci	16	15		1
Enterococci	7			7
Corynebacterium jeikeijum	3			3
Pseudomonas aeruginosa	2	2		
Candida tropicalis	1			
Other	1			1
Respiratory tract infections	10			
Pseudomonas aeruginosa	3	3		
Stenotrophomonas maltophilia	2		1	1
Serratia marcescens	2	2		
E. coli	1	1		
Aspergillus fumigatus	2			
Urinary tract infections	3			
Enterococci	2			2
Proteus mirabilis	1	1		
Other	2	1		1
Clinically documented infections	40 (26%)			
Lungs	14			
Ear, nose, throat	8			
Sinuses	10			
Skin	3			
Genital or (peri) anal	4			
Other	1			
Fever of unknown origin (FUO)	59 (38%)			

for infections in neutropenic patients and our data confirm that this may be adequate.

In view of the available efficacy data, its broad antibacterial coverage and favorable toxicity profile, cefpirome, at the recommended dose of 2 g twice daily, appears to be a valuable addition to the therapeutic arsenal available for febrile neutropenia. However, limited activity against *Pseudomonas spp.* may in the long run hamper its use as single agent therapy

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