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Original Article

Cefepime monotherapy is as effective as ceftriaxone plus amikacin in pediatric patients with cancer and high-risk febrile neutropenia in a randomized comparison

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Background and purpose: The empirical use of antibiotic therapy is widely accepted for patients with fever and neutropenia during cancer chemotherapy. The use of intravenous monotherapy with broad-spectrum antibiotics in patients at high risk for complications is an appropriate alternative. However, few data are available for pediatric patients. The aim of this study was to compare the efficacy and safety of cefepime (CFP) monotherapy with ceftriaxone plus amikacin (CFT+AK) in children and adolescents with febrile neutropenia (FN).

Methods: A prospective randomized open study of patients with lymphoma or leukemia who had fever and neutropenia during chemotherapy was conducted. Patients were randomized to receive CFP or CFT+AK. The randomization was based on number lists.

Results: Fifty seven patients with 125 episodes of fever and neutropenia were evaluated (CFP, 62 episodes; CFT+AK, 63 episodes). The mean neutrophil count at admission to hospital was 118.6 cells/mm^3 for patients in the CFP group and 107 cells/mm^3 for patients in the CFT+AK group. The mean duration of neutropenia was 9 days for the CFP group and 8 days for the CFT+AK group. Analysis of only the first episodes for each patient showed that CFP treatment was successful for 65.5% of episodes and CFT+AK was successful for 64.3% of episodes. The overall rates of success with modification were 90% for the CFP group and 89% for the CFT+AK group. No major treatment-emergent toxicity was reported.

Conclusion: Monotherapy with CFP seems to be as effective and safe as CFT+AK for initial empirical therapy in children and adolescents with FN.

Key words: Cefepime; Leukemia; Lymphoma; Neutropenia; Risk

Introduction

Fever is the most prominent sign of infection in patients with neutropenia and is often the only sign of infection. The prompt initiation of empirical antibiotics has been the most important advance in the management of patients with febrile neutropenia (FN) [1-3]. Combination therapy with a β-lactam and an aminoglycoside antibiotic has traditionally been recommended for febrile episodes in high-risk neutropenic patients, but there is now evidence that monotherapy with a broad-spectrum cephalosporin such as ceftazidime, cefepime (CFP), or carbapenem is as effective as combination therapy [4-8]. Monotherapy offers the advantages of decreased toxicity (mainly for patients treated with many nephrotoxic drugs), lower cost, and easy administration when compared with multidrug regimens [5,9-12].

CFP is an extended spectrum fourth-generation cephalosporin. CFP is active against a broad spectrum

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**Kátia Verônica Torres Barros da Silva has died since this work was performed.*

of Gram-positive and Gram-negative bacteria, including methicillin-sensitive *Staphylococcus aureus*, α-hemolytic streptococci, and some strains of *Pseudomonas aeruginosa* [13,14]. Recent reports have shown that CFP is effective and safe for empiric treatment of pediatric patients with FN [6,15,16]. However, there are only limited studies comparing CFP monotherapy with combination therapies in children with cancer and FN [15]. The aim of this study was to compare the efficacy and safety of CFP monotherapy with ceftriaxone plus amikacin (CFT+AK) in children and adolescents with FN.

Methods

This was a prospective randomized open study conducted at the Pediatric Oncology Institute, Grupo de Apoio à Criança com Câncer, Federal University of São Paulo, São Paulo, Brazil. The hospital ethics committee approved the study protocol, and written informed consent was obtained from each child's parents or legal guardian.

Patients

The eligible populations were children and adolescents (0 to 21 years) with acute leukemia and stage III and IV Hodgkin and non-Hodgkin lymphomas, who were considered to be at high risk for infectious complications, and had been admitted to hospital with FN. Fever was defined as an axillary temperature above 38.0°C or 3 measurements between 37.5°C and 38.0°C at intervals of at least 4 h over a 24-h period. Neutropenia was defined as an absolute neutrophil count (ANC) <500 cells/mm^3 or between 500 and 1000 cells/mm^3 before the nadir of chemotherapy.

Exclusion criteria were history of hypersensitivity to β-lactam antibiotics, pregnancy or breastfeeding, hepatic dysfunction (total serum bilirubin >3-fold the upper limit of normal), or liver enzymes (alanine aminotransferase/aspartate aminotransferase, >5-fold the upper limit of normal) and renal insufficiency (creatinine level increased 50% above the upper limit of normal for age), patients who developed fever during transfusion of blood products or bone marrow transplantation, and patients who had received antibiotics within 2 weeks of the start of the study.

Initial assessment

All the patients were assessed for their medical history and underwent a complete physical examination. The following laboratory tests were performed: complete blood cell count, electrolytes, liver and renal function, urinalysis, and urine and blood cultures from catheters and peripheral veins. In addition, cultures of the presumptive site of infection for patients with skin and soft tissue infections, diarrhea, or any localized infection, and chest and sinus X-rays were performed.

Randomization

All patients who developed fever and neutropenia were randomly assigned to receive either CFP or CFT+AK. CFP was administered at a dose of 150 mg/kg/day given 3 times daily, CFT was given at a dose of 100 mg/kg/day given twice daily, and AK was given at a dose of 15 mg/kg/day. All drugs were administered in an intravenous infusion. The randomization was based on number lists, and a patient could be randomized more than once if he/she had had a distinct prior episode of FN and prior antibiotic treatment had been completed at least 2 weeks previously.

Patients were evaluated daily by physical examination and complete blood count and weekly by electrolytes and hepatic and renal function tests. Blood cultures were obtained each day for as long as the patient remained febrile. Chest X-rays were taken when clinically indicated.

Therapy was modified with the inclusion of new antibacterial, antifungal, or antiviral agents, according to the patients' clinical status, development of clinically or microbiologically documented infections, or persistence of fever. Amphotericin B was started when FN persisted for more than 5 days, or earlier for suspected or documented fungal infection. Vancomycin was added when Gram-positive cocci were isolated, when there was documented catheter-related infection, skin infection, or pulmonary infection, or when infection was associated with hypotension. Antibiotics were discontinued after the second consecutive day without fever for patients with an absolute neutrophil count >500 cells/mm^3 without an identified source of infection. Patients were treated for a minimum of 5 days.

Bacterial isolates were identified according to standard techniques and antibiotic susceptibilities were determined by disk diffusion, according to the National Committee for Clinical Laboratory Standards [17]. The FN episodes were classified at the end of the treatment period as: microbiologically documented infection (MDI), including bacteremia; clinically documented infection (CDI); or fever of unknown origin (FUO) if no clinical or microbiological infection was identified. CDI or MDI were treated for as long as necessary.

Bloodstream infection was defined as 1 or more blood cultures positive for a bacterial pathogen except for coagulase-negative staphylococci (CoNS), which required 2 or more positive blood cultures.

Diagnostic criteria and outcome

Therapeutic success was defined as resolution of all signs and symptoms without modification of the initial empirical antibacterial treatment; failure was defined as death due to infection, or the administration of any additional antibacterial agent due to persistent fever, persistent fever in a patient with signs of clinical deterioration, microbiological evidence, clinical progression of the presumed infection, or adverse event associated with the antibiotic regimen [18,19]. Fever was considered as an isolated cause of failure only after 7 days of treatment, or 2 days after the introduction of amphotericin B [19]. The definition of therapeutic success with modification was used if FN resolved with the addition of another antibiotic, antiviral, or antifungal agent to the initial treatment. Breakthrough infection was defined as any infection occurring between 72 h after treatment started and 1 week after discontinuation of the antibiotic regimen [20].

Statistical analysis

The Student's *t* test was used to evaluate the difference between any 2 means (duration of neutropenia, duration of fever, and age). The difference between proportions was used to categorize the febrile episodes (FUO, CDI, or MDI). Chi-squared test with Yates correction and Fisher exact test were used to evaluate the difference in the sex distribution, drug modifications, and treatment outcome. A p value of <0.05 was considered statistically significant.

Results

From January 2000 to May 2002, 57 patients (29 in the CFP group and 28 in the CFT+AK group) had 130 episodes of FN. Of the 57 patients, 22 (38.6%) had 1 episode, 11 (19.3%) had 2 episodes, 16 (28.1%) had 3 episodes, and 8 (14.0%) had more than 3 episodes. Two episodes in the CFP group and 3 in the CFT+AK group were excluded because ANC did not fall below 500 cells/mm^3. Therefore, there were 62 and 63 episodes in the CFP and CFT+AK groups, respectively.

The mean (± standard deviation [SD]) age of the patients was 8.9 ± 4.9 years (range, 1 to 18 years) in the CFP group and 8.9 ± 4.8 years (range, 1 to 7 years) in the CFT+AK group. Table 1 shows the demographic characteristics of the study patients and the disease profile at inclusion. There was a higher prevalence of acute myeloid leukemia (AML) in the CFP group and of acute lymphocytic leukemia in the CFT+AK group, but this was not statistically significant. In 67 of the 125 episodes (53.6%), an indwelling central venous catheter was present. Of these episodes, 31 (46.3%) were randomized to CFP and 36 (53.7%) to CFT+AK (Table 1).

The mean duration of fever was 3.9 days (range, 1 to 13 days) and 4.4 days (range, 1-14 days) in the CFP and CFT+AK groups, respectively ($p = 0.35$). The mean duration of neutropenia was 9 days (range, 2-27 days) and 8 days (range, 2-15 days) in the CFP and CFT+AK groups, respectively, ($p = 0.26$), and the average time of treatment with antibiotics was 11.1 days (range, 3-30 days) and 9.7 days (range, 3-24 days) in the CFP and CFT+AK groups, respectively ($p = 0.10$).

Fifty four pathogens were isolated, 37 in blood, 8 in urine, 8 from a catheter, and 1 from skin. CoNS,

Table 1. Demographic and baseline characteristics of patients with febrile neutropenia receiving cefepime or ceftriaxone and amikacin.

	Cefepime No. (%)	Ceftriaxone and amikacin No. (%)
Patients	29	28
Episodes	62	63
Age (years; mean ± SD)	8.9 ± 4.9	8.9 ± 4.8
Sex		
Female	26 (41.9)	23 (36.5)
Male	36 (58.1)	40 (63.5)
Race		
Caucasian	42 (67.7)	45 (71.4)
Black	20 (32.3)	17 (27.0)
Japanese	0 (0)	1 (1.6)
Neutrophil		
Average (cells/mm^3)	118.6	107.0
White blood cell		
Average (cells/mm^3)	1229.0	1333.9
Underlying disease		
Acute lymphocytic leukemia	31 (50.0)	36 (57.1)
Acute myeloid leukemia	23 (37.1)	16 (25.4)
Non-Hodgkin stage III	3 (4.8)	6 (9.5)
Non-Hodgkin stage IV	4 (6.4)	2 (3.2)
Hodgkin disease	1 (1.6)	3 (4.8)
Activity of underlying disease		
Active	13 (20.9)	19 (30.2)
Remission	49 (79.1)	44 (69.8)
Granulocyte colony-stimulating factor	8 (12.9)	9 (14.3)
Indwelling central venous catheter	31 (50.0)	36 (57.0)

Abbreviation: SD = standard deviation.

Escherichia coli and *Streptococcus* spp. were the most frequently isolated organisms. All Gram-negative bacilli were susceptible to CFT+AK, except for 1 strain of *P. aeruginosa*, which was only susceptible to polymyxin B. Within 72 h of treatment starting, blood cultures were positive in 14.5% of episodes for CFP and 14.3% of episodes for CFT+AK, and Gram-positive bacteremia was predominant in both groups (55.6 and 66.7%, respectively). After 72 h of treatment, blood cultures were positive in 14.5% of episodes for CFP and 15.9% of episodes for CFT+AK, with a predominance of Gram-positive isolates (55.6%) in the CFP group and Gram-negative isolates (60%) in the CFT+AK group. Of all positive blood cultures, 19/37 (51.3%) were Gram-positive organisms, 14/37 (37.8%) were Gram-negative organisms, 3 (8.1%) were positive for fungi, and 1 (2.7%) was Gram-positive bacilli. The 3 fungal infections were isolated in the CFP group. In the overall analysis, the bloodstream was considered to be the site of infection in 18 of 62 episodes (29.0%) for patients in the CFP group and 19 of 63 episodes (30.1%) in the CFT+AK group (Table 2).

At the end of the treatment period, 51 episodes (40.8%) were classified as CDI, and 31 (24.8%) as MDI, totaling 82 episodes of documented infection (65.6%) in both groups. FUO occurred in 43 episodes (34.4%). There were no differences between the 2 groups. Breakthrough infections occurred in 22.6% (14/62) of the patients in the CFP group and in 15.9% (10/63) of those in the CFT+AK group (p = 0.34) and were microbiologically documented in 3 episodes in each group.

Adverse events were reported in 21 episodes (16%); 10 in the CFP group and 11 in the CFT+AK group. The main adverse events were diarrhea (1 episode in each group), increased liver enzymes (3 episodes in the CFT+AK group), headache (2 episodes in the CFP group and 3 episodes in the CFT+AK group), and increased creatinine (1 episode in the CFP group and 2 episodes in the CFT+AK group). All changes returned to normal after the end of treatment.

Table 2. Pathogens recovered from 125 episodes of febrile neutropenia.

Pathogen	Site				Total
	Blood	Catheter	Urine	Skin	
Coagulase-negative staphylococci	9	6	0	1	16
Escherichia coli	6	1	6	0	13
Streptococcus spp.	10	0	0	0	10
Acinetobacter spp.	5	1	1	0	7
Pseudomonas aeruginosa	2	0	0	0	2
Candida spp.	3	0	0	0	3
Other[a]	2	0	1	0	3
Total	37	8	8	1	54

[a]1 *Proteus mirabilis* and 1 *Corynebacterium* sp.

Table 3. Modification of initial drug therapy.

Additional drugs	Cefepime (n = 62) No. (%)	Ceftriaxone and amikacin (n = 63) No. (%)	p
Amphotericin B	16 (26.0)	10 (16.0)	0.17
Vancomycin	11 (17.7)	11 (17.0)	0.97
Clindamycin	3 (4.8)	5 (7.9)	0.49
Metronidazole	5 (8.0)	4 (6.3)	0.71
Amikacin	8 (13.0)	0 (0)	
Other	7 (11.0)	7 (11.0)	0.97
No. of episodes with additional drugs	26 (41.9)	20 (31.7)	0.23

The initial treatment was modified in 46 episodes (36.8%); 26 (41.9%) in the CFP group and 20 (31.7%) in the CFT+AK group (p = 0.23). The most frequent drugs added were amphotericin B and vancomycin for both groups (Table 3).

Analysis of only the first episodes of each patient (29 in the CFP group and 28 in the CFT+AK group), as recommended by the Multinational Association for Supportive Care in Cancer [19], showed that success was achieved for 19 patients (65.5%) and 18 patients (64.3%) in the CFP and CFT+AK groups, respectively; failure was reported for 10 patients (34.5%) and 10 patients (35.7%) in the CFP and CFT+AK groups, respectively. The main causes of failure were persistent fever without clinical deterioration and microbiological evidence for both groups. Success with modification occurred in 27 patients (93.0%) and 25 patients (89.0%) in the CFP and CFT+AK groups, respectively. Analysis of all the episodes showed that 3 patients (4.8%) in the CFP group and 4 patients (6.3%) in the CFT+AK group required modification of the initial therapy, and 1 patient in each group died (Table 4).

Discussion

Patients with acute leukemia and stage III and IV lymphomas are at higher risk for infectious complications [1,2,21-23]. Intensive chemotherapy leads to prolonged neutropenia, increased incidence of bacteremia, secondary infection, and high mortality risk [24,25].

The standard therapy for FN is a combination of antibiotics, which enables treatment of a broad range of pathogens, achieves bactericidal serum concentrations,

Table 4. Overall response of the first episodes to initial therapy.

Response	Cefepime (n = 29) No. (%)	Ceftriaxone and amikacin (n = 28) No. (%)	*p*
Success	19 (65.5)	18 (64.3)	0.92
With modification	27 (93.1)	25 (89.0)	0.60
Failure	10 (34.5)	10 (35.7)	0.92
Fever and clinical deterioration	1 (3.5)	2 (7.1)	0.53
Fever without clinical deterioration	4 (13.8)	3 (10.3)	0.72
Microbiological evidence	3 (10.3)	3 (10.3)	0.96
Clinical progression of infection	1 (3.5)	1 (3.6)	0.98
Adverse event	0 (0)	0 (0)	
Death	1 (3.5)	1 (3.6)	0.98

exerts a synergistic effect against some Gram-negative bacilli, and carries a minimal risk of drug resistance [7,26]. However, with the worldwide decrease in the frequency of Gram-negative infections among patients with neutropenia and the availability of new antibiotics with extended spectra of activity, the treatment of FN with a single antibiotic provides an alternative to the combination of β-lactams plus aminoglycosides [5,7,10,11,27,28].

Owing to its broad spectrum and low toxicity, CFP is used as empiric monotherapy [13,14,23]. Based on these features, a randomized study of 57 high-risk patients with 125 episodes of FN was performed. Considering only the first episodes, the therapeutic success was similar for CFP and CFT+AK at 65.5% and 64.3%, respectively. The main causes of failure were persistent fever without clinical deterioration and microbiological evidence for both treatment groups. Analysis of all episodes showed that the success rate with modifications was 93.1% for the CFP group and 89.0% for the CFT+AK group, and the mortality was approximately 3.5%. Two meta-analyses have compared the effectiveness of β-lactam monotherapy versus a β-lactam–aminoglycoside combination for the treatment of patients with FN [7,28]. Similar to this study, both analyses concluded that monotherapy was as effective as aminoglycoside-containing combinations. However, both meta-analyses enrolled adults and children. In the first analysis, only 8 trials included children (5 were restricted to children younger than 16 years); in the second analysis, the enrolment of patients younger than 14 years occurred in only 4 studies, and 3 trials exclusively included patients with low-risk neutropenia (solid tumors and lymphoma). This study evaluated only children with high-risk neutropenia. It is worth mentioning that both meta-analyses, as well as this study, compared a new β-lactam with an older one.

In another meta-analysis of 33 randomized trials (4 studies included children), CFP was associated with unexpectedly higher all-cause mortality at 30 days than other β-lactam antibiotics [8]. Mortality with CFP was higher than with ceftazidime and was equal to that of meropenem, even when the full recommended dose was used. This study did not show a higher mortality rate in the CFP group, although mortality was analyzed at the end of the treatment and this was a small study.

There has only been 1 study conducted in children with FN treated with CFP as monotherapy and compared with an aminoglycoside-containing combination therapy [11]. In the study by Corapcioglu and Sarper comparing CFP with ceftazidime plus AK, the success rates with unmodified therapy were 52% and 40%, respectively [11]. The worse results in this study were due to the mandatory addition of a glycopeptide if fever persisted for more than 3 days. This study used more strict criteria for the introduction of vancomycin.

Studies conducted in children and comparing CFP monotherapy with other β-lactams as monotherapy are more frequent [6,15,16,23,29,30]. The therapeutic success rate without modifications in these studies was similar to this study at 60% to 70% in the CFP group. However, this study analyzed only high-risk patients with leukemia and lymphoma, while the other studies included patients with solid tumors (up to 30% of patients), who are known to be at a lower risk and to have a higher success rate.

In recent decades, Gram-positive pathogens have been isolated more frequently than Gram-negative organisms in patients with FN. In this study, the pathogens most often isolated were also Gram-positive cocci (50%) in both groups, with CoNS being the most common agent isolated [23,31,32]. Of the Gram-negative bacilli, *E. coli* and *Acinetobacter* spp. were the most frequently isolated pathogens. All isolates

were susceptible to CFP but 1 *P. aeruginosa* isolate was only sensitive to polymyxin B. Three specimens of *Candida* spp. were isolated, all of them in the CFP group in which AML was more prevalent, although this was not statistically significant. There was 1 death in each group; 1 was caused by therapeutic failure in a patient with multiresistant *P. aeruginosa* and the other was due to pneumonia.

The addition of another antimicrobial agent was necessary in 41.9% and 31.7% of episodes in the CFP and CFT+AK groups, respectively. The most frequently used drugs were amphotericin B and vancomycin, in agreement with previous studies [24,33]. These additions were not considered to be unequivocal evidence of failure of the initial empiric regimen, but a consequence of serious and prolonged neutropenia [12]. At the Pediatric Oncology Institute, the routine use of glycopeptides as empiric therapy is not recommended [27,34]. Glycopeptides were added in only 17.7% of episodes in the CFP group; in 64.0% of them a Gram-positive pathogen that was only susceptible to vancomycin was recovered and in 36.0% due to clinical deterioration. In the CFT+AK group, glycopeptides were indicated in 17.0% of the episodes; in 54.0% due to the isolation of a Gram-positive pathogen and in 46.0% due to clinical deterioration. It is important to consider that an indwelling central venous catheter was present in 53.6% of all episodes.

Combination therapies including aminoglycosides have been associated with a significantly higher rate of adverse events, mainly nephrotoxicity, than other therapies [28]. Adverse events were reported in 17.6% of the patients in this study, and were mainly related to the gastrointestinal tract. The drugs were well tolerated and no antimicrobial treatment had to be interrupted due to side effects. There was no incremental nephrotoxicity with the combination therapy, but this study evaluated a small number of patients [11].

Monotherapy with CFP is as successful and safe as the combination of CFT+AK. This therapy should be considered as an appropriate option for pediatric patients at high risk for infection. There was no major toxicity associated with the study drugs and the therapy was well tolerated.

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