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Cefepime Monotherapy is as Effective as Ceftriaxone Plus Amikacin in Pediatric Patients with Cancer and High-Risk Febrile Neutropenia: A Randomized Comparison

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Abstract: The empirical use of antibiotic therapies is widely accepted in patients with fever and neutropenia during cancer chemotherapy. The use of intravenous monotherapy with broad-spectrum antibiotics in patients with high-risk of complications is an appropriate alternative. However, few data are available in pediatric patients. We conducted a prospective, randomized, open study in patients with lymphoma or leukemia who had fever and neutropenia during chemotherapy. Patients were randomized to receive cefepime (CFP) or ceftriaxone plus amikacin (CFT+AK). A total of 57 patients with 125 episodes of fever and neutropenia were evaluated (CFP, 62 and CFT + AK, 63 episodes). The mean neutrophil count at admission was 118.6 cells mm^{-3} (CFP) and 107 cells mm^{-3} (CFT+AK). The mean duration of neutropenia was 9.0 days (CFP) and 8.0 days (CFT+AK). Analyzing only the first episodes of each patient, CFP treatment was successful in 65.5% of the episodes and CFT+AK were successful in 64.3%. Overall rates of success with modification were 90% (CFP) and 89% (CFT+AK). No major treatment-emergent toxicity was reported. Monotherapy with CFP seems to be as effective and safe as the combination of CFT+AK for initial empirical therapy in children and adolescents with NF.

Key words: Febrile neutropenia, cefepime, high-risk, leukemia, lymphoma.

INTRODUCTION

Fever is the most prominent sign of infection in neutropenic patients and very often may be the only evidence of infection. The prompt initiation of empirical antibiotics in Febrile Neutropenic (FN) patients has been the most important advance in the management of these patients[1-3].

Combination therapy with a beta-lactam and an aminoglycoside has been traditionally recommended for febrile episodes in high-risk neutropenic patients, but there is now evidence that monotherapy with broad-spectrum cephalosporin such as ceftazidime, cefepime or carbapenem is as effective as combination therapy[4-8]. Monotherapy offers the advantages of decreased toxicity (mainly in patients treated with many nephrotoxic drugs), lower cost and easy administration when compared with multidrug regimens[5,9-12].

Cefepime (CFP) is an extended spectrum fourth generation cephalosporin. It is active against a broad spectrum of gram-positive and gram-negative bacteria, including methicillin-sensitive *S. aureus*, alpha-hemolytic streptococci and some strains of *P. aeruginosa*[13,14]. Recent reports showed that CFP is effective and safe for empiric treatment of FN pediatric patients[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 monotherapy with CFP versus CFT+AK in children and adolescents with FN.

MATERIALS AND METHODS

This was a prospective randomized open study conducted at the Pediatric Oncology Institute-GRAACC-Federal University of São Paulo-Brazil. The Ethics Committee approved the protocol and written informed consent was obtained from each child's parents or legal guardian. The eligible populations were

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children and adolescents (0-21 years) with acute leukemia and stage III and IV Hodgkin and non-Hodgkin lymphomas (considered at high-risk for infectious complications) hospitalized with FN. Fever was defined as an axillary temperature above 38°C or three measurements between 37.5°C and 38°C, at intervals of at least 4 h, over a 24 h period. Neutropenia was defined as an absolute neutrophils count (ANC) below 500 cells mm^{-3}, or between 500 and 1000 cells mm^{-3} before the nadir of chemotherapy. Exclusion criteria were: history of hypersensitivity to beta-lactamics, pregnancy or breastfeeding, hepatic dysfunction (total serum billirubins >3-fold the upper limit of normality) or liver enzymes (ALT/AST) >5-fold the upper limit of normality) and renal insufficiency (creatinine level increased 50% above the upper limit of normality for age), those who developed fever during transfusion of blood products, bone narrow transplantation and patients who had received antibiotics within 2 weeks of the study start.

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

Randomization: All the 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^{-1} day^{-1} TID, CFT was given at the dose of 100 mg kg^{-1} day^{-1} BID and AK at 15 mg kg^{-1} day^{-1} QD, as intravenous infusion. The randomization was based on number lists and a patient could be randomized more than once if he/she had a distinct episode of FN and prior antibiotic treatment had been completed at least 2 weeks before.

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

Therapy was modified with the inclusion of new antibiotics, antifungal or antiviral agents, according to 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, in case of 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 in cases associated with hypotension. Antibiotics were discontinued after the second consecutive day without fever in patients with ANC > 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 (1) Microbiologically documented infection, including bacteremia (MDI), (2) Clinically Documented Infection (CDI) or (3) Fever of Unknown Origin (FUO) if no clinical or microbiological infection was identified. Clinical or MDI were treated for as long as necessary. At least 2 sets of positive blood cultures were required in case of infection with coagulase-negative *Staphylococci* (CoNS).

Diagnostic criteria and outcome: Therapeutic success was defined as resolution of all signs and symptoms without modification of the initial empirical antibacterial regimen, 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 regime[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. We also used the definition of therapeutic success with modification 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 72h after treatment start and one week after discontinuation of the antibiotic regime[20].

Data analysis: The Student's t-test was used to evaluate the difference between any two means (duration of neutropenia, duration of fever and age). The difference between proportions was used to categorize the febrile episodes (FUO, CDI or MDI). The Chi-square test with Yates correction was used to evaluate the difference in the gender distribution and treatment outcome. A p-value < 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

From January 2000 to May 2002, 57 patients were included (29 in the CFP and 28 in the CFT+AK group) corresponding to a total of 130 episodes of FN. From the 57 patients, 22 (38.6%) had one episode, 11 (19.3%) had two, 16 (28.1%) had three and 8 (14%) had more than three episodes. Two episodes in the CFP group and 3 in CFT+AK group were excluded, because the ANC never fell below 500 cells mm^{-3}. The study included, therefore, 62 and 63 episodes, respectively in the CFP and CFT+AK groups. The mean age of the patients treated with CFP was 8.9±4.9 years (range 1-18.0) and it was 8.9±4.8 years (1.8-7.9) in the CFT+AK group. Table 1 shows demographic characteristics of the study patients and disease profile at inclusion. There was a higher prevalence of AML in the CFP group and of ALL in the CFT+AK group, but without statistic significance. In 67 (53.6%) of the 125 episodes, an indwelling CVC was present. Of these, 31 (46.3%) cases were randomized to CFP and 36 (53.7%) to CFT+AK (Table 1).

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

Table 1: Demographic and baseline characteristics of patients by treatment groups

	Cefepime		Ceftriaxone+ Amikacin	
	N	(%)	N	(%)
Number of patients	29.0	50.9	28.0	49.1
Number of episodes	62.0	49.6	63.0	50.4
Episodes excluded	2.0	1.5	3.0	2.3
Gender				
Female	26.0	41.9	23.0	36.5
Male	36.0	58.1	40.0	63.5
Race				
Caucasian	42.0	67.7	45.0	71.4
Black	20.0	32.3	17.0	27.0
Others	0.0		1.0	1.6
Neutrophil count average (cells mm^{-3})	118.6		107.0	
Underlying Diseases (UD)				
ALL	31.0	50.0	36.0	57.1
AML	23.0	37.1	16.0	25.4
Non Hodgkin III	3.0	4.8	6.0	9.5
Non Hodgkin IV	4.0	6.4	2.0	3.2
Hodgkin Disease	1.0	1.6	3.0	4.8
Activity U D				
Activity	13.0	20.9	19.0	30.2
Remission	49.0	79.1	44.0	69.8
Indwelling venous catheter	31.0	46.3	36.0	53.7

Fifty-four agents were isolated, thirty-seven in blood, 8 in urine and 8 from a catheter. CoN*S*, *E. coli* and *Streptococcus* sp. were the agents most frequently isolated. All gram-negative bacilli were susceptible to CFP, CFT and AK, except for one strain of *P. aeruginosa* (susceptible only to polimyxin B). Before 72 h of treatment, blood cultures were positive in 14.5% of the episodes for CFP and 14.3% for CFT+AK and gram-positive bacteremia was predominant in both groups (55.6 and 66.7%). After 72 h of treatment, blood cultures were positive in 9/62 (14.5%) and in 10/63 (15.9%) patients in the CFP and CFT+AK groups, respectively, with a predominance of gram-negative isolates (60%) in the CFT+AK group and gram-positives (55.6%) in the CFP group. Considering all positive blood cultures, 23/37 (62.2%) had gram-positives, 14/37 gram-negatives (37.8%) and 3 were positive for fungi (8.1%). The 3 fungal infections were isolated in the CFP group. In the overall analysis, the blood stream was considered as the site of infection in 18/62 (29%) episodes for CFP patients and in 19/63 (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 (65.6%) episodes of documented infections in both groups. FOU occurred in 43 (34.4%) episodes. There were no differences between the two 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 = NS) and were microbiologically documented in 3 episodes in each group.

Adverse events were reported in 22 (17.6%) cases, 10 for CFP and 11 for CFT+AK. The main adverse events were diarrhea (1 case in each group), increased liver enzymes (3 cases in the CFT+AK group), headache (2 for CFP and 3 for CFT+AK) and increased creatinine (1 for CFP and 2 for CFT+AK). All changes returned to normal after the end of the treatment.

The initial treatment was modified in 46 (36.8%) cases, being 26 (41.9%) in the CFP group and 20 (31.7%) in the CFT+AK group (p = 0.32). The most

Table 2: Pathogens recovered from 125 episodes of FN

Agent	Blood	Catheter	Urine	Other	Total
CoN*S*	9	6	0	1	16
E. coli	6	1	6	0	13
Streptococcus sp	10	0	0	0	10
Acinetobacter sp	5	1	1	0	7
P.aeruginosa	2	0	0	0	2
Other	2	0	1	0	2
Candida sp	3	0	0	0	3
Total	37	8	8	1	54

CoN*S* = Coagulase Negative *Staphylococcus*

Table 3: Drug modification of initial therapy by study group

	Cefepime		Ceftriaxone+Amikacin	
Associated drugs	N	(%)	N	(%)
Amphotericin B	16	26.0	10	16.0
Vancomycin	11	17.7	11	17.0
Clindamycin	3	4.8	5	7.9
Metronidazole	5	8.0	4	6.3
Amikacin	8	13.0	0	0.0
Other	7	11.0	7	11.0
Episodes with addition*	26	41.9	20	31.7
Total episodes	62	100.0	63	100.0

*: p = 0.32 (Chi square)

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

	Cefepime		Cetriaxone+ Amikacin	
	N	(%)	N	(%)
Success	19	65.5	18	64.3
With modification	27	93.1	25	89.0
Failure	11	34.5	10	35.7
Fever and clinical deterioration	1	3.5	2	7.1
Fever without clinical deterioration	4	13.8	3	10.3
Microbiological evidence	3	10.3	3	10.3
Clinical progression of infection	1	3.5	1	3.6
Adverse event	0	0.0	0	0.0
Death	1	3.5	1	3.6
Total	29	100.0	28	100.0

frequent drugs added, in both groups, were amphotericin B and vancomycin (Table 3).

Analyzing only the first episodes of each patient (29 in the CFP group and 28 for CFT+AK), as recommended by the Multinational Association for Supportive Care in Cancer, success was achieved in 19 (65.53%) and 18 (64.3%) and failure in 10 (34.5%) and 10 (35.7%) with CFP and CFT+AK, respectively. The main causes of failure in both groups were persistent fever without clinical deterioration and microbiological evidence. Success with modification occurred in 27 (93.0%) and 25 (89.0%) cases in the CFP and CFT+AK groups, respectively. Analyzing all episodes, 3 cases (4.8%) in the CFP group and 4 (6.3%) in the CFT+AK group required modification of the initial therapy and one child died in each group (Table 4).

Patients with acute leukemia and stage III and IV lymphomas have a higher risk of infectious complications[1,2,21-23]. The underlying disease and intensive chemotherapy lead to prolonged neutropenia, more frequent bacteremia, secondary infection and higher risk of death[24,25].

The standard therapy for FN is a combination of antibiotics, which allows to treat a broad range of possible pathogens, achieves bactericidal serum concentrations, exerts a synergistic effect against some gram-negative bacilli and has a minimal risk of drug resistance during treatment[7,26]. However, with the worldwide decrease in the frequency of gram-negative infections in neutropenic patients and the availability of new antibiotics with extended spectrum of activity, the treatment of FN with a single antibiotic (monotherapy) is an alternative to combinations of beta-lactams plus aminoglycosides[5,7,10,11,27,28].

Because of its broad spectrum (including *P. aeruginosa* and gram-positive) and low toxicity, CFP is an excellent candidate for use as an empiric monotherapy[13,14,23]. Based on these features we prospectively randomized 57 high-risk patients with 125 episodes of FN. Considering the first episodes, the therapeutic success was similar (65.5% vs 64.3%) in the CFP and CFT+AK groups. The main causes of failure were persistent fever without clinical deterioration and microbiological evidence, in both groups. Analyzing all episodes, the success rate with modifications was 93.1% in CFP and 89% in the CFT+AK group and mortality was around 3.5% (without statistical difference). Two meta-analyses compared the effectiveness of a beta-lactam monotherapy versus a beta-lactam-aminoglycoside combination for the treatment of FN patients as did the present study. One analyzed 47 randomized trials with 8,803 episodes and another, 29 randomized clinical trials with 4,795 episodes. Similar to our study, both meta-analyses concluded that monotherapy was as effective as aminoglycoside-containing combinations. However, both meta-analyses enrolled adults and children. In the first study, only eight trials included children (5 restricted to children < 16 years old), in the second study, the enrolment of patients younger than 14 years occurred in only four studies and three trials included exclusively patients with low-risk neutropenia (solid tumors and lymphoma). On the other hand, our study evaluated only children with high-risk neutropenia[7,28]. It is worth mentioning that both meta-analyses, as well as our study compared a new beta-lactam with an older one.

CFP was associated with unexpectedly higher all-cause mortality at 30 days, as compared to other beta-lactam antibiotics in another meta-analysis covering 33 randomized trials. Four studies recruited only children. Mortality was also higher with CFP than with ceftazidime and equal to that of meropenem, even when the full recommended dose was used. We did not observe a higher mortality rate in the CFP group, although it must be noticed that we analyzed mortality at the end of the treatment and this was a small study. Regarding treatment, microbiological failure and the need for modifications, these were comparable in the present study and in the above mentioned meta-analysis[8].

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

Studies conducted in children and comparing CFP monotherapy with other beta-lactams as monotherapy (ceftazidime, meropenem or piperacillin/ tazobactam) are more frequent. The therapeutic success rate without modifications in these studies was similar to ours (60-70%) in the CFP arm. However, different from those studies, we analyzed only patients with leukemia and lymphoma (high-risk), the other studies included almost 30% of patients with solid tumors, known to be at a lower risk and to have a higher success rate[6,15,16,23,29,30].

In the past decades, gram-positive pathogens have been isolated more frequently than gram-negatives in patients with FN. In our study, the agents most often isolated were also gram-positive cocci (50%), considering both groups, with CoN*S* being the single most common agent isolated[23,31,32]. Regarding gram-negative bacilli, *E. coli* and *Acinetobacter* sp were the most frequently isolated agents. All isolates were susceptible to the antibiotics studied but one *P. aeruginosa* was only sensitive to Polimyxin B. Three specimens of *Candida* sp were isolated, all of them in the CFP group, where AML was more prevalent although without statistical significance. We had one death in each arm, one was caused by therapeutic failure in a patient with multiresistant *P. aeruginosa* and the other was due to progression of a pulmonary infection. .

The addition of another antimicrobial agent was necessary in 41.9 and 31.7% of the cases, 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 as unequivocal evidence of failure of the initial empiric regimen, but as a consequence of serious and prolonged neutropenia[12]. In our institution, the routine use of glycopeptides as empiric therapy is not recommended[27,34]. In this study, glycopeptides were added in only 17.7% of the episodes in the CFP group, in 7 of them a gram-positive pathogen only susceptible to vancomycin was recovered and in 4 there was clinical deterioration. In the CFT+AK group, there was indication for glycopeptides in 17.0% of the episodes, in 6 due to the isolation of a gram-positive pathogen and in 5 due to clinical deterioration. It is important to consider that an indwelling CVC was present in 53.6% of all episodes.

Combination therapies including aminoglycosides have been associated with a significant higher rate of adverse events, mainly nephrotoxicity[28]. Adverse events were reported in 17.6% of the patients in our 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. We did not observe incremental nephrotoxicity with the combination therapy, but our study evaluated a small number of patients[11]. In conclusion, Monotherapy with CFP is as successful and safe as the combination of CFT+AK. It should be considered an appropriate option for pediatric patients at high risk of infection. There was no major toxicity associated with the study drugs and the therapy was well tolerated.

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