Cefepime plus amikacin as an initial empirical therapy of febrile neutropenia in paediatric cancer patients

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ABSTRACT

Introduction: We evaluated the efficacy of cefepime in association with amikacin in the initial empirical therapy of febrile neutropenic children.

Methods: The study was an open-labelled, non-randomised prospective trial to assess the efficacy and safety of this association, from January 2003 to December 2003. Children and adolescents were treated for a haematological malignancy or a primary, refractory or relapsed solid tumour, and presented with febrile neutropenia. Patients received cefepime (50 mg per kg per dose every 8 hours for children weighing less than or equal to 40 kg; and 2 g every 8 hours for those weighing more than 40 kg) plus a single daily dose of amikacin at 15 mg per kg per day, up to a maximum 250 mg. If fever persisted, a second-line therapy with carbapenem was administered. Amphotericin B was added at 96 hours if fever and neutropenia persisted.

Results: 103 episodes of fever and neutropenia were evaluated in 54 patients. 18.4 percent of the episodes were microbiologically-documented infections, 24.3 percent were clinically documented, and 57.3 percent were episodes with unexplained fever. 54.4 percent of the episodes responded to cefepime plus amikacin without a need for treatment modification. A higher success rate (74.6 percent) was observed in episodes with unexplained fever. In all cases of persistent fever, the antibiotics were changed to carbapenem within 72 hours and all patients survived. One patient died because of culture-negative septic shock within 24 hours of admission. A mild gastrointestinal intolerance occurred in three patients.

Conclusion: This study suggests that cefepime plus amikacin presents a satisfactory efficacy and a good tolerance as an initial empirical therapy for febrile neutropenic children.

Keywords: amikacin, cefepime, childhood cancer, febrile neutropenia

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INTRODUCTION

Empirical use of broad-spectrum antibiotics in febrile neutropenic children has been shown to significantly reduce the morbidity and mortality from severe infection, in particular gram-negative bacteraemia.[1] A combination of a beta-lactam antibiotic and an aminoglycoside has been used for many years as empirical therapy, because of the spectrum of activity against likely pathogens. Cefepime, a fourth generation cephalosporin antibiotic, has been shown to have similar in-vitro activity to that of ceftazidime against *Pseudomonas aeruginosa*, and a better activity than ceftazidime against gram-positive cocci and Enterobacteriaceae.[2] Hence, cefepime offers an alternative therapeutic option for empirical treatment, as a component of combination therapy. Studies on the use of the combination of cefepime and amikacin in the management of children with febrile neutropenia are limited in number. Most comparative studies are done on adult patients. We therefore conducted an open-labelled, non-randomised prospective trial to evaluate the efficacy of cefepime associated with amikacin.

METHODS

Eligible subjects for the study were all febrile and neutropenic children and adolescents who had been treated for a haematological malignancy, or a primary, refractory or relapsed solid tumour, from January 2003 to December 2003, at the Paediatric Haematology/Oncology Unit, Hospital Universiti Kebangsaan Malaysia (HUKM). All

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consecutive patients who presented with fever (≥ 38.5ºC once or ≥ 38.0ºC at least twice after an interval of four hours) and neutropenia (absolute neutrophil count ≤ 0.5 × 10^9/L) were included in the study. Orally administered trimethoprim/sulfomethoxazole or fluconazole was allowed as prophylaxis. Patients were excluded if they had received any intravenous antibiotics during the preceding five days; had a known allergy to any of the protocol antibiotics; had terminal illness; had significant renal impairment (serum creatinine level greater than 300 μmol/L or an estimated creatinine clearance below 20 ml/min); were less than two months of age; or had refused consent.

A complete medical history and physical examination, as well as laboratory tests, were performed on all patients prior to administering antibiotics. Blood cultures were drawn from all lumens of an indwelling central venous catheter or port-a-cath, and from a peripheral vein, before the initiation of antibiotics therapy. Bacteria were isolated and identified by standard techniques in the Department of Microbiology, HUKM and were tested for antimicrobial susceptibilities by the Kirby-Bauer disc diffusion method according to recommendations of the National Committee for Clinical Laboratory Standards.[3] Production of extended spectrum beta-lactamase (ESBL) was inferred on the basis of a positive synergy test between ceftazidime and amoxycillin-clavulanate on double-disc diffusion testing. Other cultures were performed as clinically indicated, and a routine chest radiograph was also obtained within 24 hours. During follow-up, haematological analysis was repeated each day, and blood chemistries were measured three time a week. Blood cultures were repeated every other day when fever and other signs of infection persisted, before any escalation or modification of the antibiotics, and until the cultures presented negative results.

The febrile episodes were classified as microbiologically-documented infections (MDI) with or without bacteraemia, clinically-documented infections (CDI), and unexplained fever (FUO), according to previously-published definitions.[4,5] The treatment was regarded as a success if fever and clinical signs of infection resolved, and if blood or infection sites were cleared from isolated pathogens without any change in the treatment. The treatment was regarded as a failure if: (i) the primary infection recurred within one week after discontinuation of the antibiotics therapy; (ii) death resulted from the primary infection; (iii) there was an addition to, or modification of the antibiotics therapy, such as antifungals; and (iv) occurrence of a primary pathogen resistant in vitro to cefepime-amikacin or isolation of methicillin-resistant *Staphylococcus aureus*.

Patients received intravenous cefepime (50 mg/kg/dose every 8 hr for children ≤ 40 kg, and 2 g every 8 hr for those > 40 kg) plus a single daily dose of amikacin at 15 mg/kg/day, maximum 250 mg. Patients were re-evaluated at 48 hours after the initiation of the antibiotics. In cases of non-response, i.e. persistent fever > 38.0ºC or clinical deterioration, the antibiotics were changed to meropenem. When a resistant pathogen was isolated, the antibiotic therapy was individually adapted depending on the antimicrobial susceptibility test results of the isolated strain. Amphotericin B was added at 96 hours if fever and neutropenia persisted. Patients responding to the antibiotics would continue to receive the antibiotics, until resolution of the fever, for at least four consecutive days. Thereafter, the antibiotics were discontinued regardless of the duration of neutropenia. Teicoplanin was added for gram-positive isolates or for unremitting fever after 48 hr if clinically indicated.

Nephrotoxicity and hepatotoxicity were defined as a rise in serum creatinine, transaminases, bilirubin, or alkaline phosphatase by at least twice the upper limit of the normal range. Blood chemistries were measured at least three times per week during the antibiotic therapy. Assessment of ototoxicity was done at the bedside. Evaluation criteria for signs of inner ear dysfunction, included checking for vertigo with vomitting, nystagmus and tinnitus. Adverse effects were recorded in the case report form and assumed to be antibiotic-related if they occurred in the absence of other toxic agents or predisposing factors.

The data of this study was analysed using the Statistical Package for Social Sciences for Windows version 11.5 (SPSS Inc, Chicago, IL, USA). Descriptive statistical methods (median, ranges, frequencies, and percentages) were used to evaluate the data.

RESULTS

During the study period, 104 episodes of fever and neutropenia were documented in 55 patients. One patient was excluded from the analysis because of clinical course precluding evaluation. Therefore, 103 episodes in 54 patients were evaluated for response to antibiotic therapy. Table I shows the characteristics and demographical data of the 103 episodes of febrile neutropenia. Of these 103 episodes, 19 (18.4%) were classified as MDI with or without bacteraemia, 25 (24.3%) as CDI, and 59 (57.3%) as FUO. The most frequent CDI was bronchopneumonia (21/25), followed by local abscess (1/25) and mucositis (1/25).

Of the 19 episodes of MDI, eight were due to gram-positive bacteria, and 13 were gram-negative bacteria. MDIs were caused by multiple organisms in two episodes and single organisms in 17 episodes. The species of bacteria isolated are shown in Table II. The results of antimicrobial susceptibility testing were documented: all seven (100%) gram-positive bacteria (one not tested)

Table I. Clinical characteristics of the 54 patients with 103 febrile episodes.

	Patients	Febrile episodes
Total no.	54	103
Median age (range)(years)		6.0 (1.0–19.0)
Gender (Male/Female)	28/26	57/46
Underlying cancer		
Leukaemia	37	66
Lymphoma	4	14
Solid tumours	11	18
Others	2	5
Treatment phase		
Induction and consolidation		59
Maintenance		18
Relapse		26
G-CSF administration		51
Central venous line		29
Median ANC at study entry, × 10^9/L (range)		0.10 (0.00–0.50)
Classification of episodes		
FUO		59
MDI		19
with bacteraemia		15
without bacteraemia		4
CDI		25

G-CSF: granulocyte-colony stimulating factor; ANC: absolute neutrophil count

Table II. Microbiological documentation in blood cultures and in-vitro susceptibilities of bacterial isolates during the study period.

	No. of isolates	Cefepime sensitive/tested	Amikacin sensitive/tested
Escherichia coli	2	1/2	2/2
Staphylococcus aureus	4	4/4	4/4
Pseudomonas aeroginosa	3	3/3	3/3
Klebsiella pneumoniae	2	2/2	2/2
Acinetobacter spp.	2	2/2	0/1
Enterobacter spp.	1	0/1	1/1
Enterococcus faecium	1	0/1	1/1
Streptococcus viridans	1	1/1	1/1
Bacillus	2	1/1	2/2
MRSE	1	NA	NA
Coagulase-negative *Staphylococcus*	2	2/2	2/2
Total	21*		

* Two episodes of polymicrobial infection; NA: not available; MRSE: methicillin-resistant *Staphylococcus epidermidis*

and eight out of 11 (73%) gram-negative bacteria (two not tested) exhibited in-vitro susceptibility to cefepime plus amikacin. There were three ESBL-producing organisms isolated: *Escherichia coli*, *Enterococcus faecium* and *Enterobacter* species. One organism was resistant to amikacin: *Acinetobacter* species. Six fungal superinfections (four aspergillus, two candida) occurred during the study period.

The response rate achieved without a need for treatment modification was 54.4%. The overall response rate with or without modification of therapy was 99.0%. The success rates were 26.3% for MDI, 28.0% for CDI, and 74.6% for FUO. The causes of failure in 47 episodes included persistent fever after 48 h in 30 (29%) episodes,

lack of clinical response in 15 (14.6%) episodes, and culture and sensitivity results in two (2%) episodes. An early death (within 24 hours and while still on unmodified initial empirical antibiotic therapy) due to culture-negative septic shock occurred in one patient.

Overall, second-line therapy with carbapenem was chosen to treat 37 out of 47 episodes (78.7%), a triple antibiotic combination (cefepime plus amikacin and teicoplanin) was chosen in four episodes (8.5%), and a combination of two antibiotics and antifungal (cefepime plus amikacin and antifungal) was chosen in six episodes (12.8%). Ten febrile episodes that received carbapenem needed an addition of empirical antifungal treatment due to persistent fever. Mild gastrointestinal intolerance occurred in three out of 103 episodes. Side effects were generally mild and did not lead to any discontinuation of treatment. During our study, no nephrotoxicity or hepatotoxicity was detected.

Table III. Response rates after 48 hours by type of infection.

Type of infection	Response/Total no. (%)
FUO	44/59 (74.6)
MDI	5/19 (26.3)
CDI	7/25 (28.0)
Total	56/103 (54.4)

DISCUSSION

The use of broad-spectrum antibiotics in combination with aminoglycosides as an empirical treatment for febrile neutropenic episodes has been well documented in various published studies.[6,7] In our unit, a combination of ceftazidime and amikacin has been the empirical antibiotic therapy since the early 1990s. However, there has since been a rising number of resistant gram-negative pathogens to the third generation cephalosporin after its prolonged use.[8] A similar phenomenon was also reported in another local study conducted at the Universiti Hospital Kuala Lumpur.[9]

Cefepime offers a promising therapeutic option for the empirical treatment either as a component of combination therapy or as monotherapy. It has a wide range of activity against gram-positive pathogens and gram-negative pathogens, including *S. pneumoniae*, *P. aeruginosa*, oxacillin-susceptible Staphylococci and Enterobacteriaceae, all of which produce chromosomally- and plasmid-mediated beta-lactamases.[2] In this study, in-vitro susceptibility testing showed that all (100%) gram-positive pathogens and eight out of 11 (73%) gram-negative pathogens (two not tested) were sensitive to cefepime and amikacin. In all cases of persistent fever, the antibiotics were changed to carbapenem within 72 hours and all patients survived. A higher success rate was observed in episodes classified as FUO, compared to CDI and MDI (Table III). Our study results supported the findings of other reports that cefepime plus amikacin are effective as an empirical treatment of febrile neutropenia in children with cancer.[10]

In our study, the response rate was comparable to those of other beta-lactam-aminoglycoside regimens tested in such a paediatric population. In a prospective noncomparative open study of piperacillin plus gentamicin for treatment of 239 febrile episodes in neutropenic children, Fleischhack et al reported an overall response rate of 55.2%.[11] In a prospective, open-labelled, single-centre study of single-daily dose ceftriaxone plus amikacin for treatment of 191 febrile episodes in neutropenic children, Ariffin et al reported an overall response rate of 55.5%.[12] In a randomised study comparing ceftriaxone plus amikacin, and ceftazidime plus amikacin, for treatment of 364 febrile episodes in neutropenic children, Charnas et al reported an overall response rate of 66% in each therapeutic arm.[13] The efficacy of the cefepime plus amikacin therapy has also been reported in adult neutropenic patients.[14] In addition, no renal or hepatic toxicity was reported in our study.

As in other studies, the modification of antimicrobial therapy in our study was more often indicated in patients with MDI or CDI, than in FUO. Antimicrobial modifications were required in 45.6% of all episodes. About 60% of the treatment modification performed in this study was due to persistent fever lasting longer than 48 hours from the beginning of the antimicrobial therapy. This is certainly due to the more stringent definitions of failure of empirical therapy used in this trial. In most trials, the evaluation of response is usually performed at 72 hours.

The predominant pathogens isolated in our study were gram-negative organisms (61.9%). This is in contrast to previous studies that reported predominance of gram-positive organisms isolated in neutropenic cancer patients.[7] A probable explanation for this is that a smaller proportion of patients in our unit use the central venous line. In conclusion, this study suggests that cefepime plus amikacin provides an alternative option in treating febrile neutropenic episodes in children with cancer, with satisfactory efficacy and a good tolerance. To our knowledge, this is the first study performed to assess the efficacy of cefepime plus amikacin on a large series of chemotherapy-induced neutropenic children in Malaysia. Further randomised controlled trials in this group of patients are required.

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