Piperacillin-tazobactam plus amikacin as an initial empirical therapy of febrile neutropenia in paediatric cancer patients

Hamidah A, Rizal A M, Nordiah A J, Jamal R

ABSTRACT

Introduction: We evaluated piperacillin-tazobactam in association with amikacin in the initial empirical therapy of febrile neutropenic children.

Methods: An open-labelled, non-randomised, prospective trial to assess the efficacy and safety of this association was conducted from June 1, 2001 to December 31, 2002. Children and adolescents were treated for a haematological malignancy or a primary, refractory or relapsed solid tumour, and presented with febrile neutropenia. Patients received intravenous piperacillin-tazobactam (90 mg/kg/dose every eight hours) plus a single daily dose of amikacin at 15 mg/kg/day, maximum 250 mg. If fever persisted, second-line therapy with carbapenem was administered. Teicoplanin was added for gram-positive isolates or for unremitting fever after 48 hours, if clinically indicated. Amphotericin B was added at 96 hours, if fever and neutropenia persisted.

Results: 155 episodes of fever and neutropenia in 76 patients were evaluable. 40 (25.8 percent) episodes were a microbiologically-documented infection, 30 (19.4 percent) were clinically-documented, and 85 (54.8 percent) were unexplained fever. 77 (49.7 percent) episodes responded to piperacillin-tazobactam plus amikacin without a need for treatment modification. A higher success rate (63.5 percent) was observed in episodes with unexplained fever. The predominant pathogens isolated in our study were gram-negative organisms (70.7 percent). A mild gastrointestinal intolerance occurred in 35 out of 155 (22.6 percent) episodes.

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

Keywords: amikacin, childhood cancer, febrile neutropenia, piperacillin-tazobactam

Singapore Med J 2008; 49(1): 26-30

INTRODUCTION

Empirical broad-spectrum antibiotic therapy remains the cornerstone of treatment for febrile neutropenic patients. This approach has been shown to significantly reduce the morbidity and mortality from severe infection in particular gram-negative bacteraemias.[1] The guidelines of the Infectious Diseases Society of America (IDSA) published in 2002 recommend either monotherapy with cefepime, ceftazidime, a carbapenem, or duotherapy with an antipseudomonal ß-bactam antibiotic in combination with an aminoglycoside as empirical antimicrobial therapy in febrile neutropenic patients.[2] Piperacillin is a broad-spectrum ureido-penicillin, active against many gram-positive pathogens, particularly Streptococci and most gram-negative pathogens, including *Escherichia coli* and *Bacteroides* species. Hence, piperacillin offers an alternative therapeutic option for empirical treatment as a component of combination therapy. Association of piperacillin and beta-lactamase inhibitor, tazobactam, allow to overcome resistances observed with piperacillin alone.[3] Studies on the use of a combination of piperacillin-tazobactam and amikacin in the management of children with febrile neutropenia are limited in number. We therefore conducted an open-labelled, non-randomised prospective trial evaluating the efficacy of piperacillin-tazobactam associated with amikacin.

METHODS

All febrile and neutropenic children and adolescents, who had been treated for a haematological malignancy or a

Department of Paediatrics, Hospital Universiti Kebangsaan Malaysia, Faculty of Medicine, Jalan Yaacob Latif, Bandar Tun Razak, Cheras 56000, Kuala Lumpur, Malaysia

Hamidah A, BMedSc, MD, MMed
Associate Professor

Jamal R, MD, MRCP, PhD
Professor

Department of Microbiology

Nordiah AJ, MD, MSc
Professor

Department of Community Health

Rizal AM, MD, MPH
Associate Professor

Correspondence to:
Dr Hamidah Alias
Tel: (60) 3 9170 2177
Fax: (60) 3 9173 7827
Email: midalias@mail.hukm.ukm.my

primary, refractory or relapsed solid tumour from June 1, 2001 to December 31, 2002 at the Paediatric Haematology/Oncology Unit, Hospital Universiti Kebangsaan Malaysia (HUKM), were eligible for the study. All consecutive patients with fever (≥ 38.5ºC once or ≥ 38ºC at least twice after an interval of four hours) and neutropenia (absolute neutrophil count [ANC] ≤ 0.5×10^9/L) were included. Orally-administered trimethoprim /sulfomethoxazole or fluconazole were 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 > 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 in all patients prior to administering antibiotics. Blood cultures were drawn from all lumens of an indwelling central venous catheter or Port-a-Cath® (Bard Access Systems, Salt Lake City, UT, USA), 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.[4] 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 three times a week. Blood cultures were repeated every other day while fever and other signs of infection persisted, before any escalation or modification of the antibiotics, and until the cultures were negative.

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.[5] The treatment was regarded as a success if fever and clinical signs of infections 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 from the primary infection; (iii) an addition to or modification of the antibiotics therapy, such as antifungal treatment; and (iv) occurrence of a primary pathogen resistant *in vitro* to piperacillin-tazobactam-amikacin or isolation of methicillin-resistant *Staphylococcus aureus*.

Patients received intravenous piperacillin-tazobactam (90 mg/kg/dose every eight hours) 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 > 38.0°C, or clinical deterioration, the antibiotics were changed to carbapenem. 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 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 hours, 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, evaluating for vertigo with vomiting, nystagmus, and tinnitus as signs of inner ear dysfunction. Adverse effects were recorded in the case report form and assumed to be probably antibiotic-related, if they occurred in the absence of other toxic agents or predisposing factors. The study data were analysed using the Statistical Package for Social Science for Windows version 11.5 (SPSS Inc, Chicago, IL, USA).

RESULTS

During the study period, 155 episodes of fever and neutropenia were documented in 76 patients. Table I shows the characteristics and demographic data of the 155 evaluable episodes of febrile neutropenia. Of the 155 episodes, 40 (25.8%) were classified as MDI with or without bacteraemia, 30 (19.4%) as CDI, and 85 (54.8%) as FUO. The most frequent CDI was bronchopneumonia (20/30), followed by urinary tract infection (3/30), local site abscess/infection (2/30), acute tonsillitis (2/30), otitis media (1/30), postoperative intraabdominal infection (1/30), and mucositis (1/30).

Of the 40 episodes of MDI, 11 were gram-positive bacteria, and 30 were gram-negative bacteria. MDI were

Table I. Clinical characteristics of the 155 febrile episodes.

Clinical characteristics	Febrile episodes
Median age (range)(years)	5.0 (0.8–20.0)
Gender (male/female)	84/71
Underlying cancer, no.(%)	
Leukaemia	124 (80.0)
Lymphoma	2 (1.3)
Solid tumours	29 (18.7)
G-CSF administration, no.(%)	
Yes	52 (33)
No	103 (67)
Central venous line, no.(%)	
Present *in situ*	67 (43.2)
Absent	88 (56.8)
Prophylaxis, no.(%)	
Yes	99 (63.9)
No	56 (36.1)
Median ANC at study entry	0.10 (0.00–0.70)
$\times 10^9$/L (range)	
Classification of episodes, no.(%)	
FUO	85 (54.8)
MDI	40 (25.8)
CDI	30 (19.4)

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

due to multiple organisms in one episode and to single organisms in 39 episodes. The bacteria isolated are shown in Table II. The results of antimicrobial susceptibility testing were documented: all ten (100%) gram-positive bacteria (one not tested) and 23 out of 28 (82.1%) gram-negative bacteria (two not tested) exhibited *in vitro* susceptibility to piperacillin-tazobactam plus amikacin. One isolate each of *Klebsiella pneumoniae* and *Enterobacter cloacae,* showed partial sensitivity to piperacillin-tazobactam. There were two ESBL-producing organisms isolated: *Pseudomonas aeruginosa* and *Serratia mascucense*; these organisms were resistant to piperacillin-tazobactam and amikacin. Eight fungal superinfections (two aspergillus, six candida) occurred during the study period.

The response rate achieved without a need for treatment modification was 49.7%. The overall response rate with or without modification of therapy was 98.7%. The success rate for MDI was 27.5%, 41.4% for CDI, and 63.5% for FUO. The causes of failure in 78 (50.3%) episodes included, persistent or relapsing fever after 48 hours in 56 (71.8%) episodes, culture and sensitivity results in 11 (14.1%) episodes, fungal sepsis in eight (10.3%) episodes, perianal abscess in one (1.3%) episode, and death due to overwhelming *Pseudomonas* septicaemia in one episode (1.3%). One patient died due to progressive malignancy.

Table II. Microbiological documentation in blood cultures and *in vitro* susceptibilities of bacterial isolates from June 2001 to December 2002.

	No. of isolates	Piperacillin-tazobactam sensitive/tested	Amikacin sensitive/tested
Escherichia coli	9	8/9	8/8
Staphylococcus aureus	8	7/8	7/8
Pseudomonas aeroginosa	4	3/4	3/4
Klebsiella pneumoniae	7	*7/7	7/7
Acinetobacter baumanni	2	2/2	2/2
Enterobacter cloacae	1	*1/1	1/1
Salmonella spp.	1	1/1	1/1
Sphingomonas pancimobilis	1	1/1	NT
Serratia mascucense	1	0/1	0/1
Moraxella	1	1/1	1/1
Corynebacterium	1	1/1	1/1
Sphingomonas spp.	1	1/1	1/1
Chryseomonas meningosepticium	1	NT	NT
Coagulase-negative *Staphylococcus*	3	3/3	3/3
Total	41#		

#:1 episode of polymicrobial infection; *1 isolate of each organism was partially sensitive to piperacillin-tazobactam; NT: not tested

Overall, second-line therapy with carbapenem was chosen to treat 56 (73.7%) out of 76 episodes, a triple antibiotic combination (piperacillin-tazobactam plus amikacin and teicoplanin) was chosen in twelve episodes (15.8%), and a combination of two antibiotics and antifungal (piperacillin-tazobactam plus amikacin and antifungal) was chosen in eight episodes (10.5%). 22 febrile episodes that received carbapenem needed addition of empirical antifungal treatment due to persistent fever. Mild gastrointestinal intolerance occurred in 35 out of 155 (22.6%) episodes. Transient skin rash occurred in one patient. Side effects were generally mild and did not lead to any discontinuation of treatment. During our study, no nephrotoxicity or hepatotoxicity was detected.

DISCUSSION

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

Piperacillin-tazobactam offers a promising therapeutic option for empirical treatment as a component of combination therapy. It has a wide range of activity against gram-positive pathogens and gram-negative pathogens including *Staphylococcus* species, *Escherichia coli*, *P. aeruginosa*, and Enterobacteriaceae, that produce staphylococcal penicillinase, chromosomally- and plasmid-mediated beta-lactamases.[10] In this study, *in vitro* susceptibility testing showed that all (100%) gram-positive pathogens and 23 out of 28 (82.1%) gram-negative pathogens (two not tested) were sensitive to piperacillin-tazobactam and amikacin. In all cases of resistant pathogens, 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. Our study results supported the findings of other researchers that piperacillin-tazobactam plus aminoglycoside is effective as empirical treatment of febrile neutropenia in children with cancer.[11-13] The efficacy of the piperacillin-tazobactam plus amikacin therapy has also been reported in adult neutropenic patients.[11,14]

In our study, the response rate was comparable to those of other beta-lactam-aminoglycoside regimens tested in such a paediatric population. Chastagner et al reported a success rate of 67% of FUO in a series of 64 febrile neutropenia episodes in children with cancer treated with cefepime plus amikacin.[15] 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%.[16] In a prospective, randomised study of meropenem plus amikacin versus piperacillin-tazobactam plus netilmicin as empirical therapy for high-risk febrile neutropenia in children, Aksoylar et al reported an equal efficacy and safety of both antibiotics regimen.[17] In another study, piperacillin-tazobactam plus amikacin was found to be more effective than ceftazidime plus amikacin for the empirical treatment of febrile neutropenia.[11]

In this study, antimicrobials modifications were required in 50% of 154 episodes. 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. About 70% of the treatment modification performed in this study was due to persistent fever longer than 48 hours from the beginning of antimicrobial therapy. This could be due to the more stringent definitions of failure of empirical therapy used in this trial. In many trials, the evaluation of response is usually performed at 72 hours. The predominant pathogens isolated in our study were gram-negative organisms (70.7%). 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 a smaller proportion of patients in our unit use a central venous line.

In conclusion, this study suggests that piperacillin-tazobactam plus amikacin provides an alternative option in treating febrile neutropenic episodes of children with cancer, with a satisfactory efficacy and a good tolerance. To our knowledge, this is the first study performed to assess the efficacy of piperacillin-tazobactam plus amikacin on a large series of chemotherapy-induced neutropenic children in Malaysia. Further randomised controlled trials in this group of patients are required.

ACKNOWLEDGEMENT

This study was partially supported by Wyeth Pharma, Malaysia.

REFERENCES

1. Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG. Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. Am J Med 1982; 72:101-11.
2. Hughes WT, Armstrong D, Bodey GP, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 2002; 34:730-51.

3. Payne DJ, Cramp R, Winstanley DJ, Knowles DJ. Comparative activities of clavulanic acid, sulbactam, and tazobactam against clinically important beta-lactamases. Antimicrob Agents Chemother 1994; 38:767-72.
4. National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial disk susceptibility tests. NCCLS Document M2-A4, 4th ed. Villanova, PA: National Committee for Clinical and Laboratory Standards,1990.
5. Immunocompromised Host Society. The design, analysis, and reporting of clinical trials on the empirical antibiotic management of the neutropenic patient. Report of a consensus panel. J Infect Dis 1990; 161:397-401.
6. Ceftazidime combined with a short or long course of amikacin for empirical therapy of gram-negative bacteremia in cancer patients with granulocytopenia. The EORTC International Antimicrobial Therapy Cooperative Group. N Engl J Med 1987; 317:1692-8.
7. Gram-positive bacteremia in granulocytopenic cancer patients. EORTC International Antimicrobial Therapy Cooperative Group. Eur J Cancer 1990; 26:569-74.
8. Latiff Z, Zulkifli SZ, Jamal R. Risk assessment and microbiological profile of infections in paediatric cancer patients with febrile neutropenia. Malays J Pathol 2002; 24:83-9.
9. Ariffin H, Navaratnam P, Lin HP. Surveillance study of bacteraemic episodes in febrile neutropenic children. Int J Clin Pract 2002; 56:237-40.
10. Jones RN, Pfaller MA, Fuchs PC, et al. Piperacillin/tazobactam (YTR 830) combination: Comparative antimicrobial activity against 5889 recent aerobic clinical isolates and 60 Bacteroides fragilis group strains. Diagn Microb Infect Dis 1989; 12:489-94.
11. Cometta A, Zinner S, de Bock R, et al. Piperacillin-tazobactam plus amikacin versus ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer. Antimicrob Agents Chemother 1995; 39:445-52.
12. Fleischhack G, Schmidt-Niemann M, Wulff B, et al. Piperacillin, beta-lactam inhibitor plus gentamicin as empirical therapy of a sequential regimen in febrile neutropenia of pediatric cancer patients. Support Care Cancer 2001; 9:372-9.
13. Le Guyader N, Auvrignon A, Vu-Thien H, et al. Piperacillin-tazobactam and netilmicin as a safe and efficacious empirical treatment of febrile neutropenic children. Support Care Cancer 2004; 12:720-4.
14. Sanz MA, López J, Lahuerta JJ, et al. Cefepime plus amikacin versus piperacillin-tazobactam plus amikacin initial antibiotic therapy in haematology patients with febrile neutropenia - results of a open, randomized, multicentre trial. J Antimicrob Chemother 2002; 50:79-88.
15. Chastagner P, Plouvier E, Eyer D, et al. Efficacy of cefepime and amikacin in the empiric treatment of febrile neutropenic children with cancer. Med Pediatr Oncol 2000; 34:306-8.
16. Ariffin H, Arasu A, Mahfuzah M, et al. Single-daily ceftriaxone plus amikacin versus thrice-daily ceftazidime plus amikacin as empirical treatment of febrile neutropenia in children with cancer. J Paediatr Child Health 2001; 37:38-43.
17. Aksoylar S, Cetingül N, Kantar M, et al. Meropenem plus amikacin versus pipepacillin-tazobactam plus netilmicin as empiric therapy for high-risk febrile neutropenia in children. Pediatr Hematol Oncol 2004; 21:115-23.