

Clinical Experience with Three Combination Regimens for the Treatment of High-risk Febrile Neutropenia

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Abstract

Introduction: The objective of this study was to compare the safety and efficacy of ceftazidime (2 g every 8 h), piperacillin/tazobactam (4 g/500 mg every 6 h), and meropenem (1 g every 8 h), when combined with amikacin (15 mg/kg once daily), in the empirical treatment of high-risk febrile neutropenic episodes in patients with haematological malignancy. **Materials and Methods:** A prospective, comparative study designed in the haematology unit of a university hospital in Turkey. **Results:** A total of 89 febrile episodes in 60 neutropenic patients were treated; 29 febrile episodes in 23 patients with ceftazidime plus amikacin (group 1), 30 episodes in 25 patients with piperacillin/tazobactam plus amikacin (group 2), and 30 episodes in 25 patients with meropenem plus amikacin (group 3). The 3 groups were comparable in terms of age, sex, underlying malignancy, pretherapy neutrophil counts, duration of neutropenia and types of infections. Neutropenia, since the start of fever, persisted for ≥ 10 days in all of the episodes in the 3 study groups. Nearly all of the episodes were seen in patients with acute leukaemia. In 25.8% (23/89) of the febrile neutropenia episodes, an aetiologic organism was isolated, with gram-negative bacteria being the most commonly isolated. The success without modification rates were 34.5%, 30% and 36.7% for groups 1, 2 and 3, respectively ($P > 0.05$). After modification with a different class of antimicrobial therapy, the response rates increased to 65.5%, 63.3% and 70% for groups 1, 2 and 3, respectively ($P > 0.05$). The mean duration of treatment and the time to defervescence were also comparable in all groups. In all arms, side effects were minimal. **Conclusions:** It is concluded that the 3 regimens were equally effective and safe in the empirical treatment of high-risk febrile neutropenic episodes.

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Introduction

Cancer patients who become severely neutropenic as a result of intensive myelosuppressive chemotherapy are at high risk for developing life-threatening infections, and unless they are treated at the first sign of infection, the rate of mortality is high.^{1,2} Because of the defect in the inflammatory response, the classic signs of infection such as pain, heat, redness and swelling are often absent in neutropenic patients. Since fever is generally the first and frequently the only sign of infection,³ prompt initiation of empirical antimicrobial therapy at the onset of fever is compulsory.⁴ Combination of antibiotics, namely, an antipseudomonal beta-lactam (piperacillin-tazobactam,

ticarcillin-clavulanic acid, cefepime, ceftazidime, meropenem, or imipenem-cilastatin) plus an aminoglycoside (amikacin, tobramycin, or gentamicin) continues to be one of the recommended regimens in the treatment of high-risk febrile neutropenic patients.⁵

Despite extensive clinical studies since the 1970s, no single empirical therapeutic regimen for the initial treatment of febrile patients with neutropenia has been recommended. The results from previous studies are often not comparable, because the definitions of infectious diseases and the criteria used to assess the response to therapy vary considerably. Differences in the local patterns of infection and antibiotic susceptibilities may also

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influence the efficacy of the antibiotic regimens at some institutions.⁵ We present the first prospective study that compares the efficacy and safety of piperacillin-tazobactam, ceftazidime, and meropenem in combination with amikacin for the empirical treatment of high-risk febrile neutropenic patients.

Material and Methods

Study Design

Patients (≥ 16 years old) with fever and a neutrophil count of $< 0.5 \times 10^9/L$ with an expected duration of neutropenia of ≥ 7 to 10 days after intensive chemotherapy for a haematological malignancy at the Department of Hematology, Inonu University, Turkey were enrolled in the prospective study. Fever is defined as a single temperature of $\geq 38.3^\circ C$ ($101^\circ F$) or a temperature of $\geq 38.0^\circ C$ ($100.4^\circ F$) for at least 1 hour, and was not related to the administration of blood products or known pyrogenic substances.

To include a patient additional times, at least 7 days had to pass since recovery from the prior episode. Patients were excluded if they had been exposed to antibacterial agents (including those on prophylactic regimens) within the preceding 48 hours. Patients with end-stage underlying disease in whom bone marrow recovery was not anticipated, with a serum creatinine > 250 mmol/L, severe hepatic disease – defined as an increase (> 6 times the upper limit of normal) in the level of serum aspartate aminotransferase, or serum alanine aminotransferase – and allogeneic bone marrow transplantation (since the patients all received prophylactic ciprofloxacin and fluconazole) were excluded.

Clinical and Laboratory Studies

Before the initiation of therapy, cultures of blood and specimens from other suspected sites of infection were performed. If the patient had an indwelling venous catheter, at least 1 blood culture was taken from each lumen of the catheter and 1 from another peripheral vein. Coagulase-negative staphylococci were defined to be the causative infectious agent only if at least 2 positive blood cultures had been found. Blood cultures were repetitively taken daily for persistent fever until culture results became negative. Standard techniques were applied for bacteriological analysis and antibiotic susceptibilities were determined by the Kirby-Bauer disk diffusion method. A chest radiograph was obtained, and urinalysis performed within the first 12 h. Radiographic examinations were performed throughout the course of therapy as appropriate. Routine haematological investigations and biochemical analysis were carried out before treatment was started and weekly during the course of therapy. Before the empirical regimen was started, a detailed physical examination was made and repeated daily.

Antibiotic Treatment

The study comprised 3 groups of patients: Group 1 was treated with ceftazidime (2 g every 8 h) plus amikacin (15 mg/kg once daily), group 2 with piperacillin/tazobactam (4 g/500 mg every 6 h) plus amikacin (15 mg/kg once daily), and group 3 with meropenem (1 g every 8 h) plus amikacin (15 mg/kg once daily). The antibiotics were given in 20-min to 30-min infusions and the drugs in the combination regimens were infused 30 min apart. No prophylactic antibiotics including antibacterial, antiviral and antifungal drugs were allowed before and during the trial.

Patients were assessed at 24 hours, 96 hours and at the cessation of study therapy. Modification of study therapy was allowed if there was (a) a deterioration in the clinical state after 24 hours, (b) no objective improvement after 96 hours, (c) evidence of a severe adverse event that was possibly related to study drug therapy, or (d) cultures grew a causative pathogen that was resistant to study therapy. When patients were deemed to be improving after 96 h, the study therapy was stopped in patients without fever for 5 days, and who were clinically well, with no discernible infectious lesions and radiographic or laboratory evidence of infection. A minimum of 7 days' therapy was given in total. Otherwise, antibiotics were given until recovery from neutropenia or until disappearance of clinical, radiographic or laboratory evidence of infection. Improvement at 96 hours was defined as the lysis of fever ($< 38.0^\circ C$) and/or the disappearance of the initial symptoms of infection. If the patient remained febrile for 96 hours after the administration of the antibiotics or if a new episode of fever of undetermined nature occurred, amphotericin B was started at 1 mg/kg/day.

Classification of Febrile Episodes and Evaluation of Response

Febrile episodes were divided into 3 groups: a) microbiologically defined infection, when bacteraemia was verified or cultures showed growth from a site of infection; b) clinically defined infection, when a suspected site of infection such as cellulitis was identified without microbiological confirmation; and c) unexplained fever, when no site was identified and no microbiological evidence of infection was found.

Responses were divided into 3 categories: a) success without modification – if fever and clinical signs and symptoms (whenever present) resolved and the infecting microorganism (whenever isolated) was eradicated without recurrence of the signs and symptoms of the primary infection for at least 5 days after completion of the initial regimen; b) success with modification – if the initial infection was successfully eradicated with the primary therapy, but a second infection arose that fell outside the

spectrum of the initial regimen and thus required the addition of another antimicrobial (i.e., antifungal, antiviral, or antiparasitic); c) failure – if there is the lack of response requiring addition to, or change in the initial regimen or death due to infection. Total success referred to success with or without modification.

Statistical Analysis

Statistical significance was calculated using the chi-square test.

Results

Between 1 January 2001 and 1 September 2003, a total of 89 febrile episodes in 60 neutropenic patients were treated; 29 febrile episodes in 23 patients with ceftazidime plus amikacin, 30 episodes in 25 patients with piperacillin/tazobactam plus amikacin, and 30 episodes in 25 patients with meropenem plus amikacin.

The characteristics of patients with febrile episodes are shown in Table 1. The 3 treatment groups were comparable in terms of age, number of episodes, underlying malignancy, type of infection and initial neutrophil count. Neutropenia since the start of fever persisted for ≥ 10 days in all of the episodes in the 3 study groups. Nearly all of the episodes were seen in patients with acute leukaemia (96.6% in group 1, 100% in group 2 and 96.7% in group 3).

In group 1, out of 29 episodes, 7 (24.2%) were defined microbiologically and 6 (20.7%) of these had bacteraemia. Clinically defined infections and unexplained fever were diagnosed in 9 (31%) and 13 episodes (44.8%), respectively. Out of 30 episodes in group 2, 8 (26.7%) were defined

microbiologically, and 6 (20%) of these had bacteraemia. Clinically defined infections and unexplained fever were diagnosed in 10 (33.3%) and 12 episodes (40%), respectively. In group 3, out of 30 episodes, 8 (26.7%) were defined microbiologically, and 7 (23.3%) of these had bacteraemia. Clinically defined infections and unexplained fever were diagnosed in 9 (30%) and 13 episodes (43.3%), respectively.

In 25.8% (23/89) of the febrile neutropenia episodes, an aetiologic organism was isolated, with gram-negative bacteria being the most common (Table 2). The most common aetiologic microorganism was *Escherichia coli*, followed by *Klebsiella oxytoca*. In one episode, bacteraemia was polymicrobial and caused by *Streptococcus* group C and *Acinetobacter lwoffii*.

The mean duration of treatment and the time to defervescence were comparable in all the groups. The mean durations of treatment in groups 1, 2 and 3 were 10.7 days (range, 7 to 14), 11.6 days (range, 7 to 17) and 10.9 days (range, 7 to 15), respectively ($P > 0.05$). The mean times to defervescence in the groups 1, 2 and 3 were 3.4 days (range, 1 to 9), 4.2 days (range, 1 to 11) and 4 days (range, 1 to 11), respectively ($P > 0.05$).

Antibiotic therapy was modified in more than half the episodes in the 3 treatment groups. Because some episodes had more than one addition, the sum of individual antimicrobial additions exceeds the total number of patients that required at least one addition. Eighteen (62.1%) episodes in group 1, 19 (63.3%) in group 2 and 17 (56.7%) in group 3 required a modification of the original empiric antimicrobial regimen ($P > 0.05$). Antifungals, primarily

Table 1. Characteristics of Patients with Febrile Episodes

	Ceftazidime + Amikacin Group 1		Pip/Taz + Amikacin Group 2		Meropenem + Amikacin Group 3	
	n	%	n	%	n	%
No. of patients	23		25		25	
No. of episodes	29		30		30	
Age (median/range) (y)	40/18-66		37/18-68		39/19-68	
Female/Male	13/10		13/12		14/11	
Underlying neoplasm*						
Acute myeloid leukaemia	24	82.8	25	83.3	27	90
Acute lymphoid leukaemia	4	13.8	5	16.7	2	6.7
Non-Hodgkin lymphoma	1	3.4	–	–	–	–
Multiple myeloma	–	–	–	–	1	3.3
Entry ANC*						
<100/mm ³	25	86.2	24	80	26	86.7
100-500/mm ³	4	13.8	6	20	4	13.3
Type of infection*						
Microbiologically defined	7	24.2	8	26.7	8	26.7
Clinically defined	9	31	10	33.3	9	30
Unexplained fever	13	44.8	12	40	13	43.3

ANC: absolute neutrophil count; Pip/Taz: piperacillin/tazobactam

* No. of episodes

Table 2. Pathogens Isolated at Entry

Isolates	Group 1 (n = 29)		Group 2 (n = 30)		Group 3 (n = 30)		
	Blood	Urine	Blood	Urine	Blood	Urine	Wound
<i>Escherichia coli</i>	2	–	1	1	3	–	–
<i>Klebsiella oxytoca</i>	2	–	1	–	1	–	–
<i>Proteus mirabilis</i>	1	1	–	–	–	–	–
<i>Pseudomonas aeruginosa</i>	–	–	–	1	–	–	1
<i>Acinetobacter lwoffii</i>	–	–	–	–	1	–	–
<i>Enterobacter cloacae</i>	–	–	1	–	1	–	–
<i>Klebsiella pneumoniae</i>	–	–	1	–	–	–	–
MRSA	–	–	1	–	–	–	–
MSSA	–	–	–	–	1	–	–
<i>Streptococcus</i> group C	–	–	–	–	1	–	–
<i>Streptococcus</i> spp.	1	–	–	–	–	–	–
<i>Enterococcus</i> spp.	–	–	1	–	–	–	–

MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-sensitive *Staphylococcus aureus*

amphotericin B, were the most common antimicrobial agents used for modification in all the 3 groups. They were administered to 10 (34.5%), 13 (43.3%) and 12 (40%) episodes in groups 1, 2 and 3, respectively. The antibiotics used for modification were glycopeptide (thrice, twice and thrice in groups 1, 2 and 3, respectively), metronidazole (thrice, five times and twice, respectively) and betalactam other than the initial study drug (once in groups 2 and 3). Acyclovir was administered to 4, 7 and 6 episodes in groups 1, 2 and 3, respectively.

The clinical outcome of febrile episodes in the 3 treatment groups was similar (Table 3). The success without modification rates were 34.5% (10), 30% (9) and 36.7% (11) for groups 1, 2 and 3, respectively ($P > 0.05$). After modification, the total success rates became 65.5% (19), 63.3% (19) and 70% (21) for groups 1, 2 and 3, respectively ($P > 0.05$).

The failure rates were 34.5% (10), 36.7% (11) and 30% (9) for groups 1, 2 and 3, respectively ($P > 0.05$). The distribution of the number of failures of initial treatment is as follows: (i) 4 episodes in both groups 1 and 3 and 6 in group 2 did not respond to initial therapy; (ii) antibiotic was added for 4, 3 and 2 episodes in groups 1, 2 and 3, respectively; (iii) only 1 post-therapy infection occurred in groups 1 and 3; and (iv) 1 patient in group 1 and 2 patients

in both groups 2 and 3 died from infection.

One (3.4%) patient in group 1 and 2 (6.7%) in both groups 2 and 3 died from an undocumented infection. One death in each treatment group was due to the initially treated infection. The remaining 2 deaths in groups 2 and 3 were attributed to superinfection.

All drugs were well tolerated, and clinical safety was similar in all 3 groups. The adverse events were mainly diarrhoea, nausea/vomiting and rash. Diarrhoea was noted in 2 patients in group 1, 5 patients in group 2, and 3 patients in group 3. Nausea/vomiting occurred in 1 patient in group 1 and 2 patients in group 3. Rash occurred in 1 patient in group 2. Discontinuation of the therapy due to adverse effects did not take place in any of the groups.

Discussion

This study compared the safety and efficacy of ceftazidime, meropenem, and piperacillin/tazobactam, in combination with amikacin, as empiric therapy for the treatment of high-risk febrile neutropenic patients. Examination of all parameters of efficacy (success without modification, total success and modification rates, mean time to defervescence and duration of treatment, and survival) indicated no significant differences among the 3 treatment groups.

Table 3. Clinical Outcome of Febrile Episodes*

	Group 1 (n = 29)		Group 2 (n = 30)		Group 3 (n = 30)	
	n	%	n	%	n	%
Success without modification	10	34.5	9	30	11	36.7
Success with modification	9	31	10	33.3	10	33.3
Total success	19	65.5	19	63.3	21	70
Failure	10	34.5	11	36.7	9	30

* No significant difference was found between the 3 treatment groups

Comparisons between meropenem, ceftazidime, and piperacillin/tazobactam, plus amikacin, have not been reported previously in a single study. Also, our trial is the first study to evaluate the efficacy of meropenem in combination with an aminoglycoside (amikacin) for the treatment of febrile neutropenic patients. For many years, empiric antibiotic therapy has consisted mainly of a combination of an aminoglycoside with either an antipseudomonal penicillin or a cephalosporin. However, in the last decade, monotherapy with broad spectrum antibiotics has become an alternative choice to classic antimicrobial combinations in the treatment of febrile neutropenic patients and meropenem has been preferred in this setting, and shown to be successful.⁶⁻¹⁰ The combination of ceftazidime plus amikacin has been a widely used empirical approach and established as a standard regimen.^{11,12} The use of piperacillin/tazobactam plus amikacin has not been studied as extensively as that of ceftazidime plus amikacin, but it has also been found to be effective for the empirical treatment of episodes of fever in neutropenic patients.¹²⁻¹⁵ Comparing the results from the present trial with those of other studies may be inappropriate, mainly because of considerable variations in the duration of neutropenia, the definitions of infectious diseases, the criteria used to assess the response to therapy, and the local patterns of infection and antibiotic susceptibilities.^{16,17} For example, several studies have indicated that not all beta-lactam antibiotics are equally effective.¹⁸⁻²⁰

In the past decade, many cancer centres have experienced a major change in the aetiology of bacterial infections occurring in neutropenic patients. While gram-negative bacteria were predominant in the 1970s and early 1980s, gram-positive bacteria have recently increased in frequency, and seem to have largely superseded gram-negative bacilli in many institutions.^{8,11,14,21-23} Contributory risk factors for the increased incidence of gram-positive infections in neutropenic cancer patients include the frequent presence of oropharyngeal mucositis following intensive cytotoxic chemotherapy, altered skin integrity due to long-term indwelling vascular catheters, and the use of quinolone prophylaxis.^{24,25} In contrast, gram-negative bacteria were predominant in the present study, accounting for 81.8% (18/22) of monomicrobial infections. This may in part be attributable to avoiding the use of quinolone prophylaxis in our patients. In fact, a more parsimonious use of quinolone prophylaxis has already been accompanied by a reversal of the gram-positive shift, with the re-emergence of a larger number of gram-negative infections in several centres.²⁶

Safety profiles of the 3 therapeutic regimens were similar. The study regimens were generally well tolerated and adverse effects, when present, were mild, easily tolerated, and reversible.

In conclusion, ceftazidime, piperacillin/tazobactam, and meropenem, when combined with amikacin, were equally effective and safe in the empirical treatment of high-risk febrile neutropenic episodes. No significant difference in duration of treatment, the need for modification of the initial empiric antibiotic regimen, time to defervescence and success rates were determined among the 3 groups ($P>0.05$). Different combinations might be considered for empiric therapy, depending on their efficacy, the nosocomial bacterial flora and resistance patterns and the cost.

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