Cefepime plus amikacin versus piperacillin–tazobactam plus amikacin for initial antibiotic therapy in haematology patients with febrile neutropenia: results of an open, randomized, multicentre trial

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Background: Standard therapy for suspected infections in patients with profound neutropenia is the combination of a β-lactam antibiotic plus an aminoglycoside. Cefepime’s broad-spectrum activity makes it an option for initial empirical therapy in neutropenic patients. The aim of this study is to evaluate the efficacy and safety of cefepime plus amikacin compared with piperacillin–tazobactam plus amikacin for initial empirical treatment of fever in adult haematology patients with severe neutropenia.

Methods: In this prospective multicentre trial, 969 patients with 984 febrile neutropenic episodes were randomized to receive iv amikacin (20 mg/kg every 24 h) combined with either cefepime (2 g every 8 h) or piperacillin–tazobactam (4 g/500 mg every 6 h). Clinical response was determined at 72 h and at completion of therapy.

Results: Eight hundred and sixty-seven episodes were assessable for efficacy (432 cefepime, 435 piperacillin–tazobactam). The frequency of success without modification of the empirical therapy was nearly identical for cefepime plus amikacin (49%) compared with piperacillin–tazobactam plus amikacin (51%). Similar rates of success were found for microbiologically documented infection: 40% versus 39%, respectively. Antibiotic modification was necessary in 49% of cefepime and 44% of piperacillin–tazobactam patients. The overall response rate, with or without modification of the assigned treatment, was 94% in both groups. Drug-related adverse events were reported in 10% of cefepime plus amikacin versus 11% of piperacillin–tazobactam plus amikacin patients. Mortality due to infection occurred in a total of 10 patients (two cefepime, eight piperacillin–tazobactam).

Conclusion: The empirical regimen of cefepime plus amikacin is equivalent to piperacillin–tazobactam plus amikacin in febrile adult haematology patients with severe neutropenia.

Keywords: cefepime, piperacillin–tazobactam, amikacin, empirical antibiotic therapy, febrile neutropenia, haematological malignancy

Introduction

Infectious complications are an important cause of morbidity and mortality, especially in patients with cancer with profound and prolonged neutropenia following intensive chemotherapy for haematological malignancies. Thus, prompt administration of empirical broad-spectrum antibiotics at the onset of fever in neutropenic patients with cancer has been the standard care since the 1971 report by Schimpff et al.1 documenting reduction in mortality rates. Combination therapy with an aminoglycoside plus an anti-pseudomonal β-lactam has commonly been recommended because this approach
provides broad-spectrum coverage, bactericidal activity and potential synergic effects, and minimizes the development of resistance during treatment.²

The optimal empirical combination antibiotic regimen for treating febrile, high-risk granulocytopenic patients has not been clearly established. A key trial of the International Antimicrobial Therapy Cooperative Group (IATCG) of the European Organization for Research and Treatment of Cancer (EORTC) reported that the combination of piperacillin–tazobactam plus amikacin was more effective than ceftazidime plus amikacin in the empirical treatment of febrile granulocytopenic patients with cancer.³ Based on the findings of this pivotal trial, piperacillin–tazobactam plus amikacin became the standard regimen used in Spain to treat high-risk haematology patients with granulocytopenia.

Cefepime is a new cephalosporin with a broader spectrum of activity against Gram-negative organisms than ceftazidime and other extended-spectrum cephalosporins. It is also more active than third-generation cephalosporins against Gram-positive cocci, such as Streptococcus pneumoniae and most other streptococcal species, as well as staphylococcal species.⁴ A broad and potent spectrum of activity, together with advanced pharmacological properties (e.g. long elimination half-life), make cefepime a suitable antibiotic for initial empirical therapy for febrile episodes in neutropenic patients.⁴ Several studies have demonstrated the effectiveness of cefepime, either alone or as part of combination therapy, for empirical treatment of febrile neutropenic episodes;⁵⁻¹³ however, cefepime has only been evaluated against piperacillin–tazobactam in a pilot study.⁹

In the present study, we report the results of a large, prospective, randomized, multicentre trial designed to evaluate the efficacy and safety of cefepime plus amikacin compared with piperacillin–tazobactam plus amikacin for the empirical treatment of fever in haematology patients with severe neutropenia.

**Patients and methods**

**Study design and criteria for eligibility**

This open, comparative, unblinded, randomized, multicentre study was conducted in 18 Spanish institutions ascribed to the PETHEMA group (see Acknowledgements). The trial was designed in accordance with guidelines issued by the Immunocompromised Host Society (IHS) consensus conference and the European Society of Clinical Microbiology and Infectious Disease (ESCMID).¹⁴,¹⁵ Adult patients over 18 years of age who received chemotherapy for haematological malignancy [leukaemia, myelodysplastic syndrome (MDS), lymphoma, multiple myeloma] or who had undergone haematopoietic stem cell transplantation for malignant disease were evaluated for enrolment. Patients were eligible for study participation if they had fever attributable to neutropenia and presumed infection. Fever was defined as an axillary temperature ≥38°C on two occasions at least 1 h apart or 38.5°C on one occasion. Neutropenia was defined as an absolute neutrophil count of <0.5 × 10⁹/L or if ≥1 × 10⁹/L, expected to fall below 0.5 × 10⁹/L within 24–48 h because of preceding chemotherapy. Only patients with presumed infectious causes of fever were included in the trial. The trial was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of each participating centre. Each patient provided written informed consent before enrolment.

Patients were excluded if they met any of the following criteria: known allergy to any of the study antibiotics (cefepime, piperacillin, tazobactam, amikacin) or history of β-lactam allergic reactions, pregnant or lactating women, serum creatinine level >200 µmol/L or creatinine clearance <40 mL/min, concomitant treatment with an iv antibiotic or administration of an iv antibiotic within 96 h before study entry, or known HIV infection.

Patients receiving oral antibacterial prophylaxis, such as fluoroquinolones or co-trimoxazole, were allowed to participate in the study. However, oral antibiotics were discontinued at study entry with the exception of co-trimoxazole when given as prophylaxis for Pneumocystis carinii pneumonia.

**Randomization and antibiotic treatments**

Patients were randomly allocated to one of the arms of the trial, stratified by centre, by consecutive opening of computer-generated sealed envelopes. Patients could be randomized more than once into the trial if they had completed the previous treatment at least 4 weeks before. Patients received intravenously either cefepime (2 g every 8 h) or piperacillin–tazobactam (4 g/500 mg every 6 h). Intravenous amikacin was administered to all patients as a single daily dose of 20 mg/kg body weight (to a maximum of 1.5 g). Patients received antibiotic therapy for a minimum of 7 days in total or at least 4 days beyond their last day of fever. Amikacin was stopped at day 7 in patients responding to therapy and β-lactam monotherapy could be continued, if clinically indicated. In patients who remained febrile after 72 h, antibiotic therapy was modified as part of a multistep strategy by successive addition of a glycopeptide (vancomycin or teicoplanin). If at any time during the study the patient’s clinical status worsened (e.g. development of septic shock, progression of initial infection or detection of new clinical sites of infection), the β-lactam was discontinued and changed to another β-lactam or a carbapenem (i.e. imipenem–cilastatin or meropenem). Antifungal therapy was also started if the patient remained febrile or if their clinical status worsened after 4–6 days of antibiotic therapy. In patients with a microbiologically documented infection (MDI), therapy was modified, if appropriate, according to susceptibility testing.
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Clinical and laboratory evaluation

A complete medical history and physical examination, as well as a complete blood cell and differential count, routine chemistry, at least two sets of blood cultures obtained from two different sites and a chest X-ray were performed before starting antibiotic treatment. One set of blood culture consisted of two bottles with 10 mL of blood added to each. Cultures of any other sites of infection were performed as clinically indicated.

Patients were monitored daily for clinical signs and symptoms and intercurrent events during antibiotic treatment. Complete blood cell counts, coagulation and chemistry parameters, and urinalysis were performed at least three times a week. Microbiological specimens were obtained before and during therapy, as clinically indicated. When possible, a bronchoalveolar lavage or a fibrobronchoscopy brushing was performed in patients with suspected pneumonia. Blood cultures were obtained daily from patients with persistent fever; in patients with established bacteraemia, blood cultures were repeated until negative.

All bacterial isolates were tested for in vitro susceptibility to cefepime, piperacillin–tazobactam and amikacin by the Kirby–Bauer disc diffusion method or by determination of MICs as recommended by the NCCLS.16

Classification of febrile episodes

Primary febrile episodes were classified according to guidelines issued by the IHS consensus conference and the ESCMID as follows: (i) MDI with or without bacteraemia; (ii) clinically documented infection (CDI); (iii) fever of unknown origin (FUO); and (iv) non-infectious fever. Single blood culture isolates were sufficient to classify an episode as bacteraemic, except for coagulase-negative staphylococci (CNS) and Corynebacterium spp. other than Corynebacterium jeikeium, which required at least two positive blood culture specimens.14,15

Evaluation of response

Response was assessed both at 72 h (early evaluation) and at completion of therapy (overall evaluation). Response was categorized as a success if all of the following criteria were met: afebrile (<38°C) for 4 consecutive days, clearance of signs and symptoms of infection, infecting microorganism eradicated (whenever isolated) and no recurrence of the primary infection within 1 week after treatment completion. Failure was defined by one of the following criteria: (i) death from primary infection; (ii) modification of or addition of antibiotic(s) to the antibacterial treatment in an attempt to eradicate the primary infection; and (iii) in vitro resistance to the β-lactam agent. A patient was considered non-assessable for response in the following circumstances: (i) co-existent fungal or viral infection; (ii) febrile episode not related to infection; and (iii) protocol violation (e.g. non-adherence to protocol; early discontinuation secondary to severe adverse effects).

Adverse events

Adverse events were graded according to the World Health Organization (WHO) grading system.17 Nephrotoxicity was defined as an increase in serum creatinine by ≥50% from baseline value. Hepatotoxicity was assessed on the basis of transaminase, bilirubin and alkaline phosphatase levels; abnormal values were defined as 1.5–2 times above the baseline value and normal range. Secondary infection was defined as a new infection caused by a microorganism not recognized as the initial pathogen occurring either during antibiotic therapy or within 1 week of the discontinuation of study antibiotics. Death was attributed to infection when it occurred as a direct consequence of either the presenting infection or a secondary infection.

Statistical analysis

The primary objective of this study was to compare clinical success rates of both study drug regimens. According to previous experience, the expected response rates to piperacillin–tazobactam plus amikacin and cefepime plus amikacin were 61% and 71%, respectively.3,5 To demonstrate such a difference by a one-tailed hypothesis test based on a χ² distribution with a continuity correction (type I error level, 5%; power, 90%), the inclusion of 486 patients in each treatment arm was required. The latter assumed a possible 20% patient attrition rate.

Each case report form was systematically reviewed by two of the authors (L. Larrea and I. Jarque). Selected case report forms with conflicting data or controversial interpretation of response were also reviewed by the Data Review Committee. All data were entered into a computerized database and analysed using the Biomedical Data Package (BMDP).18

An intent-to-treat analysis was used to assess success rates (i.e. clinical response without modification plus eradication of pre-therapy pathogen when present). Differences between proportions of response within each group were analysed by χ² test and Fisher’s exact test, if appropriate.

Results

Characteristics of the study population

From May 1998 to April 2000, a total of 984 episodes of febrile neutropenia occurring in 969 adult patients from 18 Spanish institutions were randomized into the study. Twenty-four episodes were not eligible (12 cefepime,
12 piperacillin–tazobactam), and 93 were not assessable for efficacy (51 cefepime, 42 piperacillin–tazobactam). The reasons for non-eligibility and for being excluded from the efficacy analysis are given in Table 1. The remaining 867 febrile episodes (432 cefepime, 435 piperacillin–tazobactam) were assessable for response to antibacterial therapy in the intent-to-treat analysis (Figure 1). One hundred and eighty of these febrile episodes occurred in patients who had been entered into the study during a previous episode.

Demographic and baseline medical characteristics were well balanced between the two treatment groups (Table 2). The majority of patients had acute leukaemia or lymphoma as their underlying disease; approximately one-third had undergone stem cell transplantation. At enrolment, the median polymorphonuclear leucocyte count was $0.02 \times 10^9$ cells/L in both treatment groups.

### Table 1. Randomized episodes of febrile neutropenia

<table>
<thead>
<tr>
<th></th>
<th>Cefepime + amikacin</th>
<th>Piperacillin–tazobactam + amikacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>495</td>
<td>489</td>
</tr>
<tr>
<td>Non-eligible (%)</td>
<td>12 (2.4)</td>
<td>12 (2.4)</td>
</tr>
<tr>
<td>previous iv antibiotic</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>enrolled in concomitant investigational trial</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>&lt;18 years old</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>diagnosis criteria not fulfilled</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Non assessable (%)</td>
<td>51 (10.3)</td>
<td>42 (8.6)</td>
</tr>
<tr>
<td>protocol violation</td>
<td>19 (37)</td>
<td>10 (24)</td>
</tr>
<tr>
<td>non-infectious fever</td>
<td>6 (12)</td>
<td>11 (26)</td>
</tr>
<tr>
<td>fungal/viral infection</td>
<td>15 (29)</td>
<td>12 (29)</td>
</tr>
<tr>
<td>other</td>
<td>11 (22)</td>
<td>9 (21)</td>
</tr>
<tr>
<td>Assessable</td>
<td>432</td>
<td>435</td>
</tr>
</tbody>
</table>

### Type of infection and infecting organisms

There were no significant differences between the two treatment groups in the occurrence of any type of febrile episode according to clinical and microbiological records. Three hundred and eight febrile episodes (35%) were proven bacterial infections (161 cefepime, 147 piperacillin–tazobactam). A total of 252 of 308 (82%) MDI episodes were bloodstream infections; the majority caused by single infecting pathogens (212 of 252; 84%). Bacteraemia was caused by a single Gram-positive organism in 58% of febrile episodes and a single Gram-negative organism in 42% of episodes. CNS were the most common Gram-positive organisms, isolated in 35% of bacteraemic episodes, and *Escherichia coli* was the most common Gram-negative organism, isolated in 24% of these bacteraemia cases.

A total of 231 episodes (27%) were categorized as CDI (106 cefepime, 125 piperacillin–tazobactam). The most frequent sources of infection were mucous membrane (9%), lower respiratory tract (7%), skin and soft tissues, including catheter tunnel infections (5%), and gastrointestinal tract (4%). Febrile episodes were classified as FUO for 328 episodes (165 cefepime, 163 piperacillin–tazobactam).

### Clinical outcome per protocol

**Overall.** A successful outcome occurred in approximately half of the febrile episodes, with similar success rates in both treatment groups: 49% in the cefepime group and 51% in the piperacillin–tazobactam group (Figure 2). The distribution of the causes of failure was not statistically different between the treatment groups.

**MDI.** For bacteriologically confirmed episodes, the overall response rate was 40% for cefepime compared with 39% for piperacillin–tazobactam (Figure 2). The success rate in the
Cefepime plus amikacin in febrile neutropenics

Table 2. Characteristics of assessable episodes according to treatment group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cefepime + amikacin [episodes (% of all episodes)]</th>
<th>Piperacillin–tazobactam + amikacin [episodes (% of all episodes)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>227 (53)</td>
<td>221 (51)</td>
</tr>
<tr>
<td>female</td>
<td>205 (47)</td>
<td>214 (49)</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>acute leukaemia</td>
<td>211 (49)</td>
<td>208 (48)</td>
</tr>
<tr>
<td>lymphoma</td>
<td>108 (25)</td>
<td>104 (24)</td>
</tr>
<tr>
<td>multiple myeloma</td>
<td>27 (6)</td>
<td>32 (7)</td>
</tr>
<tr>
<td>solid tumour</td>
<td>31 (7)</td>
<td>28 (6)</td>
</tr>
<tr>
<td>MDS</td>
<td>20 (5)</td>
<td>28 (6)</td>
</tr>
<tr>
<td>other</td>
<td>35 (8)</td>
<td>35 (8)</td>
</tr>
<tr>
<td>Graft recipients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>autologous</td>
<td>117 (27)</td>
<td>114 (26)</td>
</tr>
<tr>
<td>allogeneic</td>
<td>22 (5)</td>
<td>25 (6)</td>
</tr>
<tr>
<td>Status of underlying disease (excluding graft recipients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>complete remission</td>
<td>106 (36)</td>
<td>103 (35)</td>
</tr>
<tr>
<td>active disease</td>
<td>187 (64)</td>
<td>193 (65)</td>
</tr>
<tr>
<td>Haematopoietic growth factors</td>
<td>232 (54)</td>
<td>236 (54)</td>
</tr>
<tr>
<td>Fluoroquinolone prophylaxis</td>
<td>267 (62)</td>
<td>282 (65)</td>
</tr>
<tr>
<td>Nosocomial origin</td>
<td>319 (74)</td>
<td>321 (74)</td>
</tr>
<tr>
<td>Intravenous catheter</td>
<td>353 (82)</td>
<td>355 (82)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± S.D.</td>
<td>48.4 ± 16.4</td>
<td>48.6 ± 16.1</td>
</tr>
<tr>
<td>median (range)</td>
<td>52 (18–83)</td>
<td>50 (18–83)</td>
</tr>
<tr>
<td>Days of neutropenia at entry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± S.D.</td>
<td>8.8 ± 37.2</td>
<td>8.4 ± 24.2</td>
</tr>
<tr>
<td>median (range)</td>
<td>4 (0–730)</td>
<td>4 (0–395)</td>
</tr>
<tr>
<td>Granulocyte count at entry (×10⁹ cells/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (range)</td>
<td>20 (0–1000)</td>
<td>20 (0–1000)</td>
</tr>
<tr>
<td>patients with PMN &lt; 0.1 × 10⁹ cells/L</td>
<td>309 (74)</td>
<td>313 (74)</td>
</tr>
</tbody>
</table>

None of the characteristics differed significantly between the groups (P > 0.05).

cefepime and piperacillin–tazobactam groups was slightly different for those with bacteraemic infections (38% and 33%, respectively). Bacteraemic patients treated with the cefepime regimen had slightly higher success rates compared with the piperacillin–tazobactam regimen when the infection was due to either a single Gram-negative species (60% and 50%) or when due to several pathogens (48% and 33%) (Table 3). However, these differences were not found to be statistically significant. Response rates for specific Gram-positive and Gram-negative organisms causing bacteraemia are shown in Table 3.

CDI. The observed success rates were similar in both treatment groups with CDIs (47% cefepime, 54% piperacillin–tazobactam) (Figure 2). The corresponding success rates for the most frequent infections were 53% and 64% for severe mucositis, 41% and 52% for lower respiratory tract infections, and 60% and 48% for skin and soft tissue infections, including catheter tunnel infections.

FUO. No significant differences in response rates were observed between the two treatment groups for patients with FUO (58% and 56%, respectively) (Figure 2).

Clinical response following antibiotic modification

Therapy modification was frequently required (47%), regardless of the initial treatment assigned (49% cefepime, 44% piperacillin–tazobactam). Antibiotic modifications were similar between the treatment groups for all categories of infection: MDI (57% cefepime, 54% piperacillin–tazobactam), CDI (49% cefepime, 41% piperacillin–tazobactam) and FUO (41% cefepime, 42% piperacillin–tazobactam). The most frequent modification of antibacterial study drug therapy consisted of the addition of a glycopeptide, vancomycin or
teicoplanin (47% cefepime, 43% piperacillin–tazobactam), followed by substitution of a carbapenem (imipenem or meropenem) for the assigned β-lactam (9% each treatment group). The addition of antifungal therapy did not differ between the cefepime (66 episodes; 15%) and the piperacillin–tazobactam (72 episodes; 16%) groups. Antibacterial therapy modification preceded the addition of antifungal therapy in all episodes.

The initial antibiotic regimen was modified because of documentation of an organism resistant to the assigned β-lactam in 12 of 432 episodes (3%) treated with cefepime plus amikacin and in 19 of 435 episodes (4%) treated with piperacillin–tazobactam plus amikacin. Most of the causative bacteria that were resistant to the assigned β-lactam were Gram-positive, primarily CNS.

Susceptibility to cefepime, piperacillin–tazobactam and amikacin was, respectively, 32% (13/41), 32% (13/41) and 62% (32/52) for CNS; 63% (5/8), 63% (5/8) and 75% (6/8) for *S. aureus*; 100% (31/31), 75% (21/28) and 100% (39/39) for *E. coli*; and 92% (12/13), 62% (8/13) and 93% (13/14) for *Pseudomonas aeruginosa*.

Overall, the response rate of the multistep anti-infective strategy, with or without modification of the treatment assigned initially, was 96% in both treatment groups. Mean duration of treatment was 15.8 ± 9.6 days in the cefepime group and 15.7 ± 8.8 days in the piperacillin–tazobactam group. No significant differences in success rate were observed between the treatment groups according to type of infection (Table 3).

**Secondary infections**

The occurrence of secondary infections did not differ between the two treatment groups: 54 episodes (12.5%) in the cefepime group versus 53 episodes (12.2%) in the piperacillin–tazobactam group. Among the total 107 secondary infections, 25 (23%) episodes were MDIs, 11 (20%) in the cefepime group and 14 (26%) in the piperacillin–tazobactam group. There were 19 bacterial infections: nine single Gram-positive organisms (seven and two, respectively), three single Gram-negative organisms (one and two, respectively) and seven polymicrobial infections (one and six, respectively). A fungal infection was documented in six additional episodes (two and four, respectively).

**Mortality**

Overall mortality rates at day 10 and at day 30 were 1.2% and 5.3%, respectively. Mortality due to infection (presenting or secondary infection) occurred in a total of 10 patients: death occurred in four patients before day 10 (one cefepime, three piperacillin–tazobactam) and six additional patients at day 30 (one cefepime, five piperacillin–tazobactam). An additional 36 patients died of non-infectious causes, including underlying disease progression (n = 14), fatal haemorrhage (n = 11) and other causes (n = 11).

**Adverse events**

The overall rate of adverse effects considered related or probably related to study antibiotics was similar in the two treatment groups: 10% for the cefepime group versus 11% for the piperacillin–tazobactam group. Moderate to severe nephrotoxicity probably attributable to the aminoglycoside developed in seven episodes in the cefepime group and six in the piperacillin–tazobactam group. Mild nephrotoxicity was observed in 12 additional episodes. A cutaneous allergic reaction was observed following treatment in 22 febrile episodes (14 cefepime, eight piperacillin–tazobactam). Drug-induced hypokalaemia was reported for 12 episodes in the cefepime group and 13 in the piperacillin–tazobactam group. Hepatotoxicity, gastrointestinal intolerance and other intercurrent side effects were rarely associated with either of the antibiotic regimens.

**Discussion**

Our intent-to-treat analysis in this large trial established that cefepime or piperacillin–tazobactam, both in combination with amikacin, were equally effective for the initial management of febrile haematological cancer patients with severe neutropenia. The standard treatment of febrile neutropenic episodes in patients with cancer has changed over the past 30 years in response to the emergence of new pathogens, recognition of different types of neutropenic patients and the availability of new drugs. During the last two decades, since the reported study from the IATCG supporting the combined use of ceftazidime and amikacin in patients with severe neutropenia,19 the combination of a β-lactam plus an aminoglycoside has become one of the most commonly prescribed antibiotics.
Cefepime plus amikacin in febrile neutropic patients. Use of this potent, but sometimes toxic, combination is based on the need for rapid bactericidal killing, enhanced synergy against difficult-to-treat pathogens (e.g., \textit{P. aeruginosa}) and the attempt to minimize the emergence of resistance.\textsuperscript{2} These suppositions are best supported in cancer patients with severe (WBC < 0.1 × 10^9 cells/L) and persistent neutropenia in which Gram-negative and streptococcal bacteraemia are likely.\textsuperscript{20,21}

The empirical antibiotic approach to managing febrile episodes in neutropenic patients with cancer continues to evolve. This evolution has been especially apparent over the past decade due to a significant reduction in the incidence of Gram-negative bacteraemia and the availability of new broad-spectrum antibiotic agents, leading to the use of monotherapy in the treatment of febrile neutropenia as an interesting approach. One study conducted by the EORTC reported similar overall success rate comparing meropenem with ceftazidime plus amikacin.\textsuperscript{22} Moreover, monotherapy with meropenem has also been shown to be as effective as ceftazidime in trials that included a substantial number of patients with underlying haematological malignancy.\textsuperscript{23} Although piperacillin–tazobactam has proved to be effective as monotherapy,\textsuperscript{9,24} its use has not been studied as extensively as that of ceftazidime, cefepime or carbapenems. However, combination antibiotic regimens may be considered more efficacious for patients with prolonged and severe neutropenia, especially when Gram-negative infection is suspected.

One of the most important studies published by the IATCG revealed that the combination of piperacillin–tazobactam plus amikacin was more effective than the previous standard combination of ceftazidime plus amikacin.\textsuperscript{3} Based on these findings, piperacillin–tazobactam plus amikacin has been increasingly used in febrile neutropenic patients. The present trial is the largest reported since 1995 comparing the gold standard therapy—piperacillin–tazobactam plus amikacin—with another combination.\textsuperscript{3} Our findings that the combination of cefepime plus amikacin is as effective as piperacillin–

\begin{table}
\centering
\caption{Response to anti-infective strategy by treatment group and type of infection}
\begin{tabular}{lcccc}
\hline
Category                              & Successful response & & & \\
 & cefepime + amikacin & & piperacillin–tazobactam + amikacin & \\
 & without modification & with modification & without modification & with modification \\
\hline
All episodes                         & 211 (49) & 210 (49) & 224 (51) & 191 (44) \\
MDI                                  & 65 (40) & 91 (57) & 57 (39) & 80 (54) \\
bacteraemia                          & 49 (38) & 75 (58) & 40 (33) & 72 (59) \\
single Gram-positive species         & 12 (19) & 49 (75) & 10 (17) & 43 (74) \\
CNS                                  & 9 (23) & 5 (15) & & \\
\textit{S. aureus}                   & 1 (25) & 0 & & \\
streptococci                         & 2 (14) & 3 (43) & & \\
other                                & 0 & 2 (25) & & \\
single Gram-negative species         & 26 (60) & 15 (35) & 23 (50) & 19 (41) \\
\textit{E. coli}                     & 15 (60) & & 13 (52) & \\
KES                                  & 3 (60) & & 4 (50) & \\
\textit{P. aeruginosa}               & 4 (57) & & 2 (29) & \\
other                                & 4 (67) & & 4 (67) & \\
polymicrobial                        & 11 (48) & 11 (50) & 6 (33) & 10 (56) \\
CDI                                  & 50 (47) & 52 (49) & 68 (54) & 51 (41) \\
mucositis                            & 19 (53) & & 27 (64) & \\
lower respiratory tract              & 11 (41) & & 16 (52) & \\
gastrointestinal tract              & 10 (43) & & 5 (36) & \\
skin and soft tissues                & 6 (60) & & 9 (45) & \\
catheter                             & 3 (60) & & 4 (57) & \\
other                                & 1 (20) & & 7 (64) & \\
FUO                                  & 96 (58) & 67 (41) & 91 (56) & 68 (42) \\
\hline
\end{tabular}
\end{table}

KES, \textit{Klebsiella}, \textit{Enterobacter}, \textit{Serratia}.

None of the characteristics differed significantly between groups (\(P > 0.05\)).
tazobactam plus amikacin for high-risk febrile neutropenic patients are consistent with several previous studies in which effectiveness of cefepime, either alone or as part of a combination regimen, for febrile neutropenia has been demonstrated.\(^5\)\(^-\)\(^11\) However, many of these earlier studies differ from the current study due to their small sample size, the small number of patients with haematological malignancy and evaluation of patients with short-duration and less severe neutropenia. In the trial published by Cordonnier et al.,\(^10\) which evaluated the combination of cefepime plus amikacin versus ceftazidime plus amikacin, both empirical regimens were equally effective in treating febrile patients with haematological malignancies (27% cefepime versus 21% ceftazidime) and profound neutropenia. However, although the response rates in both treatment groups were comparable, they were seemingly low. The overall response rate increased to 60% for the cefepime plus amikacin group and 51% for the ceftazidime plus amikacin group following the addition of a glycopeptide. A second trial compared the effectiveness of monotherapy with either cefepime or piperacillin–tazobactam for febrile neutropenic episodes.\(^9\) Unlike the trial presented here, the addition of a second agent (e.g. aminoglycoside, carbapenem, vancomycin) was only started if the initial response was unfavourable. Although the initial response rate was low following cefepime (39%) and piperacillin–tazobactam (43%) monotherapy, 96% of patients receiving both treatments responded following antibiotic modification.\(^9\)

The current trial extends these previous findings, in which 867 of 969 (88%) randomized febrile episodes were assessable for efficacy, exceeding the assumption from previous EORTC IATCG trials.\(^19\)\(^,\)\(^25\)\(^,\)\(^26\) Furthermore, this study is one of a few clinical trials in which the majority of patients had haematological malignancies. As such, this study represents a relatively homogeneous population of patients with a more predictable duration of neutropenia. The majority of the patients in our study who failed to respond initially to either study antibiotic regimen were successfully managed with the addition of a glycopeptide, substitution of a carbapenem for the β-lactam or concomitant use of antifungal therapy. Overall, 96% of patients in both treatment groups responded clinically, with or without antibiotic modification; these data are comparable with previous trials.\(^8\)

Direct comparisons of clinical success rates between trials can be difficult because baseline medical characteristics often differ between the study populations. For example, in a study conducted similarly by the EORTC\(^22\) with a large number of enrolled patients, the median age was much younger (38 years) compared with the present trial (48 years). In addition, patients participating in the EORTC trial\(^22\) had a lower incidence of profound neutropenia (67%) compared with the current trial (74%). Despite a seemingly worse prognosis for our study population based on older age and more profound neutropenia, the overall clinical response rates were similar in the two trials.

The large sample size of our study enabled us to perform several subgroup analyses. In patients with proven bacterial infections, clinical success without antibiotic modification was lower compared with the entire sample population, but equivalent between the cefepime and piperacillin–tazobactam groups (40% and 39%, respectively). However, of note was the trend of a higher success rate following cefepime plus amikacin in combination compared with piperacillin–tazobactam plus amikacin in treating patients with bacteraemic infections (38% and 33%, respectively). This was especially true for those with bacteraemia caused by a single Gram-negative species (60% and 50%) or bacteraemia due to multiple pathogens (48% and 33%). These data are consistent with a previous report by Böhme et al.,\(^9\) in which Gram-negative infections responded better to cefepime than to piperacillin–tazobactam. Although numbers were low, cefepime-treated patients infected with *P. aeruginosa* in the current trial were more than twice as likely to respond clinically than those given the piperacillin–tazobactam combination. The reason for these differences may be explained by the *in vitro* superiority of cefepime compared with piperacillin–tazobactam against Gram-negative bacteria.

Another interesting finding from the current trial was the observation of a lower ratio of Gram-positive to Gram-negative bacteraemia (1.37). This ratio is very low, especially compared with ratios observed from the last multicentre randomized trial performed by the IATCG, in which the Gram-positive/Gram-negative bacteraemia ratio was higher (2.25).\(^22\) Data from our trial indicate that the pattern of infecting microorganisms among neutropenic patients may be changing, with a re-emergence of Gram-negative bacteria. Accordingly, a higher rate of Gram-negative bacteraemia could explain the trend of a slightly higher clinical success rate following cefepime plus amikacin versus piperacillin–tazobactam plus amikacin.

Low rates of resistance to cefepime and piperacillin–tazobactam were found during the period our study was conducted. This finding is consistent with data reported by Jacoby & Carreras,\(^27\) who showed that cefepime is highly resistant to the activity of extended-spectrum β-lactamases. The majority of resistant bacteria in the current trial were identified as Gram-positive organisms (e.g. CNS). Accordingly, the initial antibiotic regimen was infrequently modified because of β-lactam resistance—3% of cefepime- and 4% of piperacillin–tazobactam-treated patients. However, because bacteria can rapidly and suddenly mutate, institutions must continually monitor for changing patterns of resistance and adjust empirical antibiotic regimens as needed.

The analyses of safety data from the present trial found that both the cefepime and piperacillin–tazobactam aminoglycoside combinations were well tolerated. Nephrotoxicity, prob...
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ably attributable to the amikacin component, was observed in equal proportions in both treatment groups; approximately half of the episodes were graded from moderate to severe. This adverse effect can be minimized if the aminoglycoside is discontinued early in patients in whom bacteraemia has not been demonstrated. Rates of skin reactions in the present study were similar to those reported by others using either cefepime or piperacillin–tazobactam. Notably, patients treated with either the cefepime or piperacillin–tazobactam plus aminoglycoside combination regimen did not develop gastrointestinal intolerance or pseudomembranous colitis.

In conclusion, the large number of patients participating in this study enables us to confirm that cefepime plus amikacin is as effective as piperacillin–tazobactam plus amikacin for the empirical treatment of fever in patients with haematological malignancies and severe neutropenia. Success rates were slightly lower (40%) for patients with MDI. However, the use of a multistep anti-infective strategy led to an overall 96% clinical success rate. A low rate of infection-related mortality and a low toxicity profile were observed in both treatment groups. This trial supports the role of cefepime plus an aminoglycoside as a safe and effective regimen for patients with severe and persistent neutropenia attributable to haematological malignancies, especially when a Gram-negative bacterial infection is suspected.

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