A Randomized, Open-Label, Multicenter Comparative Study of the Efficacy and Safety of Piperacillin-Tazobactam and Cefepime for the Empirical Treatment of Febrile Neutropenic Episodes in Patients with Hematologic Malignancies

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Background. The empirical treatment of febrile, neutropenic patients with cancer requires antibacterial regimens active against both gram-positive and gram-negative pathogens. This study was performed to demonstrate the noninferiority of monotherapy with piperacillin-tazobactam, compared with cefepime.

Methods. We conducted a randomized-controlled, open-label, multicenter clinical trial among high-risk patients from 34 university-affiliated tertiary care medical centers in the United States, Canada, and Australia who were undergoing treatment for leukemia or hematopoietic stem cell transplantation and were hospitalized for empirical treatment of febrile neutropenic episodes. Patients received piperacillin-tazobactam (4.5 g every 6 h) or cefepime (2 g every 8 h) intravenously. The primary outcome was success (defined by defervescence without treatment modification) at 72 h of treatment, end of treatment, and test of cure in the modified intent-to-treat analysis. Secondary outcomes included time to defervescence, microbiological efficacy, the additional use of glycopeptide antibiotics, emergence of resistant bacteria, and safety.

Results. For 528 subjects (265 received piperacillin-tazobactam and 263 received cefepime), success rates were 57.7% and 48.3%, respectively (P = .04) at the 72-h time point, 39.6% and 31.6% (P = .06) at end of treatment, and 26.8% and 20.5% (P = .11) at the test-of-cure visit. The analyses demonstrated noninferiority for piperacillin-tazobactam at all time points (P < .0001). Treatment with piperacillin-tazobactam was independently associated with treatment success in multivariate analysis (odds ratio, 1.65; 95% confidence interval, 1.04–2.64; P = .035). Both regimens were well tolerated.

Conclusions. This study demonstrates the noninferiority and safety of piperacillin-tazobactam monotherapy, compared with cefepime, for the empirical treatment of high-risk febrile neutropenic patients with cancer.

Clinical practice guidelines published by the Sociedad Española de Quimioterapia in Spain [1], the Infectious Diseases Society of America [2], the Infectious Diseases Working Party of the German Society of Hematology and Oncology [3], and the National Comprehensive Cancer Network [4] recommend the prompt administration of empirical broad-spectrum antibacterial...
therapy for the management of high-risk febrile neutropenic patients with cancer. Recommendations for combination therapy based on an extended spectrum antipseudomonal β-lactam agent plus an aminoglycoside remain prominent in the American [2, 4] and German [3]—but not in the Spanish [1]—guidelines. Despite this, the weight of clinical trial experience supports the adoption of monotherapy as the standard of treatment of febrile neutropenic patients with cancer [5, 6].

There is no consensus with regard to the optimal agent for monotherapy. Broad-spectrum antipseudomonal cephalosporins (such as ceftazidime [7] and cefepime [8–14]), carbapenems (such as imipenem-cilastatin [15, 16] and meropenem [17–29]), and β-lactam–β-lactamase inhibitor combinations (such as ticarcillin-clavulanate [13, 30, 31] and piperacillin-tazobactam [10, 17, 32–37]) have been evaluated as monotherapy in this setting. The Spanish and German guidelines support choices from each antibiotic class, whereas the American guidelines have not recommended β-lactam–β-lactamase inhibitor agents, such as piperacillin-tazobactam, as monotherapy, citing limited experience with these agents when the guidelines were published in 2002 [2]. Since then, further studies have been published that show that these agents have an important role in treatment [10, 13, 17, 30–37]. Here, we report the results of a large, multicenter, multinational, open-label, randomized-controlled clinical trial that examines the safety and efficacy of piperacillin-tazobactam monotherapy, compared with cefepime, for the empirical treatment of fever in neutropenic patients with cancer.

**PATIENTS AND METHODS**

**Patients.** Eligible subjects included those patients at high risk for medical complications [38–40] who were ≥18 years old, severely neutropenic (defined as having an absolute neutrophil count [ANC] of <0.5 × 10⁹ cells/L or a count of <1.0 × 10⁹ cells/L with the expectation that it will decrease to <0.5 × 10⁹ cells/L after cytotoxic therapy), hospitalized for the management of a febrile episode complicating the course of cytotoxic therapy for a hematological malignancy or for a hematopoietic stem cell transplant (HSCT), and who had provided written, informed consent according to institutional protocol. The protocol was approved through the ethics review process of each
of the participating university-affiliated institutions. Exclusion criteria included a history of hypersensitivity to β-lactam antibiotic agents, evidence of hepatic dysfunction (defined as a total serum bilirubin level ≥3 times the upper limit of the normal range or as a serum transaminase level ≥5 times the upper limit of the normal range), severe renal insufficiency requiring dialysis, or a positive test result for HIV antibodies.

**Antibacterial regimens.** Patients were randomly allocated to receive piperacillin-tazobactam (Zosyn, Wyeth Ayerst; 4.5 g intravenously every 6 h) or cefepime (Maxipime, Bristol-Myers Squibb; 2 g intravenously every 8 h). Regimens were assigned using a centralized randomization procedure in a 1:1 ratio and were stratified according to receipt of prophylactic antibiotic agents. Antibacterial prophylaxis was discontinued at the time of study entry. Study regimens were administered for up to 21 days and were modified at the investigator’s discretion. Adherence to published management guidelines was encouraged [41].

**Study design.** The study was conducted as an open-label, randomized-controlled, multicenter, noninferiority clinical trial. Calculation of the sample size was based on the assumption that the study agents were equally effective. Assuming an evaluable rate of at least 50%, ~528 patients were to be enrolled to obtain 264 evaluable patients. If the 2 treatments were equally effective, with success rates of 50% at the test-of-cure visit, ~132 clinically evaluable patients per treatment group would be required.

**Definitions.** The primary outcome was treatment success without regimen modification assessed at 72 h of therapy, end of therapy, and the test-of-cure review among the modified intent-to-treat population (patients receiving at least 1 dose of the study agents), in accordance with recommendations [42–44]. Treatment success was assessed at the test-of-cure assessment (defined as at least 7 days posttreatment). Fever and febrile episodes were defined and classified in accordance with current guidelines [2, 45]. Defervescence was defined as a reduction in body temperature to <38°C when measured orally, sustained over at least 48 h. Treatment success was defined as resolution of all signs and symptoms of infection without modification of the initial empirical antibacterial regimen. Initial treatment response but with a modified regimen was defined as recrudescence of fever within 48 h of defervescence because of a viral, fungal, or parasitic pathogen outside the spectrum of activity of the antibacterial study agents that required regimen modification. Treatment failure was defined as death due to infection or the administration of any additional antibacterial agent for persistent fever, lack of improvement, progressive infection, or new bacterial infection. Indeterminate status was defined as loss to follow-up; an instance in which the etiology of the initial febrile episode was determined to be due to a viral, fungal, parasitic, or mycobacterial pathogen; or an instance in which the patient received concomitant antibacterial therapy for reasons other than treatment failure.

**Statistical analysis.** The primary objective was to demonstrate piperacillin-tazobactam to be noninferior to cefepime in the modified intent-to-treat analysis. One-sided 95% CIs (corrected for continuity) were calculated for the difference in treatment success to evaluate noninferiority between treatment groups. Noninferiority was concluded if the lower bound of the 95% CI for the difference in success was ≥−0.20. Secondary outcome analyses included microbiological success; treatment success by prestudy use of antibacterial prophylaxis, by classification of infection, or by neutrophil recovery profile; time (in days) to defervescence; emergence of vancomycin-resistant enterococci or extended-spectrum β-lactamase–producing gram-negative bacteria in rectal surveillance cultures; and the emergence of *Clostridium difficile*–associated diarrhea. Success rates with 95% CIs were compared between treatment groups using the Cochrane-Mantel-Haenszel statistic stratified across study centers. Time-to-event analyses were conducted using Kaplan-Meier product limit estimates. Differences by allocation were examined using the log-rank test.

Logistic regression was used to assess the influence of potential prognostic factors on treatment success. In univariate analysis, variables associated with treatment success, including demographic covariates, such as age and country of residence (P = .05), were entered into a stepwise multivariate logistic regression model. Those variables with a P value ≤ .15 were subsequently entered into the final model. The final model was developed with variables (P ≤ .1) retained from the first model. Similarly, variables associated with defervescence and with prolonged neutropenia were entered into multivariate Cox regression models in order to identify predictors. Such variables included age (≥65 years vs. <65 years), sex, underlying diagnoses (acute leukemia, lymphoma, or other), treatment (HSCT vs. chemotherapy), characteristics of the HSCT (autologous vs. allogeneic; stem cell source [peripheral blood vs. bone marrow]), use of hematopoietic growth factors either prior to or concomitantly with the initiation of empirical antibacterial therapy, neutrophil recovery profile from baseline to end of treatment (ANC < 0.5 x 10⁹ cells/L at baseline to > 0.5 x 10⁹ cells/L at end of treatment; ANC < 0.5 x 10⁹ cells/L at baseline remaining through the end of treatment; ANC > 0.5 x 10⁹ cells/L at baseline to < 0.5 x 10⁹ cells/L at end of treatment; ANC > 0.5 x 10⁹ cells/L at baseline remaining through the end of treatment), classification of infection (unexplained fever, clinically documented infection, and microbiologically documented infection with and without bacteremia), pathogens in bacteremic patients (gram-positive organisms vs. gram-negative organisms), country of residence, and randomization to the piperacillin-tazobactam or cefepime arm.

Safety was evaluated by analyzing adverse events, vital signs,
Table 1. Baseline characteristics of the modified intent-to-treat population.

| Characteristic                      | Piperacillin-tazobactam recipients (n = 265) | Cefepime recipients (n = 263) |
|-------------------------------------|---------------------------------------------|-------------------------------|
| **Age, years**                      |                                             |                               |
| Mean ± SD                           | 50.2 ± 15.1                                 | 50.1 ± 14.5                   |
| Median (range)                      | 52 (17–83)                                  | 52 (18–79)                    |
| **Sex**                             |                                             |                               |
| Male                                | 166                                         | 146                           |
| Female                              | 99                                          | 117                           |
| **Body weight, kg**                 |                                             |                               |
| Mean ± SD                           | 80.95 ± 20.37                               | 76.34 ± 17.36                 |
| Median (range)                      | 78.1 (42.2–172.5)                           | 73.1 (45.0–146.36)            |
| **Underlying disease**              |                                             |                               |
| Acute leukemia                      | 103d                                        | 99o                           |
| Acute myeloid leukemia              | 76                                          | 82                            |
| Acute lymphoblastic leukemia        | 27                                          | 16                            |
| Chronic leukemia                    | 12                                          | 11                            |
| Chronic lymphocytic leukemia        | 6                                           | 7                             |
| Chronic myeloid leukemia            | 6                                           | 4                             |
| Myelodyplasia                       | 8                                           | 7                             |
| Non-Hodgkin lymphoma                | 76f                                         | 68                            |
| Hodgkin lymphoma                    | 16                                          | 14                            |
| Myeloma                             | 50f                                         | 66                            |
| Other                               | 6g                                          | 0                             |
| **Underlying disease treatment**    |                                             |                               |
| Chemotherapy                        | 131                                         | 116                           |
| Hematopoietic stem cell transplant  | 134 (50.6)                                  | 147 (55.9)                    |
| Autologous BMT                      | 0                                           | 1                             |
| Autologous PBSCT                    | 57                                          | 65                            |
| Autologous, stem cell source specified | 29                                          | 29                            |
| Allogeneic BMT                      | 4                                           | 3                             |
| Allogeneic PBSCT                     | 16                                          | 13                            |
| Allogeneic, stem cell source specified | 23                                          | 22                            |
| PBSCT, not otherwise specified      | 5                                           | 14                            |
| **Hematopoietic growth factors**    |                                             |                               |
| Total                               | 171 (64.5)                                  | 182 (69.2)                    |
| Administered prior to study entry   | 72                                          | 100                           |
| Administered concomitant with study entry | 99                                           | 82                            |
| **Antibacterial prophylaxis**       |                                             |                               |
| Receiving at least 1 agent          | 141 (53.2)                                  | 150 (57.0)                    |
| Trimethoprim-sulfamethoxazole       | 45 (17.0)                                   | 51 (19.4)                     |
| Fluoroquinolone                     | 102 (38.5)                                  | 108 (41.1)                    |
| Duration, mean days ± SD (median)   | 9.3 ± 5.2 (9)                               | 9.7 ± 9.1 (9)                 |
| **Central venous catheter**         |                                             |                               |
| Total                               | 259 (97.7)                                  | 250 (95.1)                    |
| **Myelosuppression at study entry, median ANC × 10^9 cells/L** |                                             |                               |
| <0.1                                | 209 (78.9)                                  | 217 (82.5)                    |
| 0.1–0.499                           | 46 (17.4)                                   | 35 (13.3)                     |
| 0.5–1.0                             | 5 (1.9)                                     | 7 (2.7)                       |
| >1.0                                | 5 (1.9)                                     | 4 (1.5)                       |
| **Duration of myelosuppression, mean days ± SD (median)** |                                             |                               |
| ANC, <0.1 × 10^9 cells/L            | 9.18 ± 6.96 (7)                             | 8.20 ± 6.07 (7)               |
| ANC, 0.1–0.499 × 10^9 cells/L       | 4.17 ± 5.04 (2)                             | 3.66 ± 4.23 (2)               |
| ANC, 0.5–9.99 × 10^9 cells/L        | 11.71 ± 7.97 (10.5)                         | 10.25 ± 6.53 (9)              |
| ANC, 0.5–9.99 × 10^9 cells/L        | 5.29 ± 6.72 (1)                             | 4.27 ± 5.50 (1)               |
| ANC, <1.0 × 10^9 cells/L            | 13.92 ± 8.64 (13)                           | 11.98 ± 7.50 (11)             |
(continued)
| Characteristic                          | Piperacillin-tazobactam recipients (n = 265) | Cefepime recipients (n = 263) |
|---------------------------------------|---------------------------------------------|-----------------------------|
| Febrile neutropenic episode           |                                             |                             |
| Unexplained fever                     | 157 (59.2)                                  | 150 (57.0)                  |
| Clinically documented                 | 27 (10.2)                                   | 27 (10.3)                   |
| Oral mucositis                        | 8                                           | 8                           |
| Gastrointestinal mucositis            | 4                                           | 4                           |
| Sinusitis                             | 2                                           | 1                           |
| Pneumonia                             | 6                                           | 10                          |
| Soft tissue infection, NOS             | 1                                           | 0                           |
| CVAD-related cellulitis               | 2                                           | 3                           |
| Perianal cellulitis                   | 2                                           | 0                           |
| Both CVAD and perianal cellulitis     | 0                                           | 1                           |
| Other                                 | 2                                           | 0                           |
| **Microbiologically documented**      |                                             |                             |
| All cases                             | 81 (30.6)                                   | 86 (32.7)                   |
| Bacteremia                            |                                             |                             |
| GNO, total                            | 73 (27.5)                                   | 74 (28.1)                   |
| *Escherichia coli*                    | 17                                          | 21                          |
| *Klebsiella, Enterobacter, and/or Serratia species* | 5 | 11 |
| *Pseudomonas aeruginosa*              | 7                                           | 6                           |
| Other                                 | 3                                           | 2                           |
| GPO, total                            | 41                                          | 39                          |
| *Staphylococcus aureus*               | 13                                          | 14                          |
| Coagulase-negative staphylococci      | 16                                          | 11                          |
| α-Hemolytic streptococci              | 6                                           | 3                           |
| *Streptococcus pneumoniae*            | 4                                           | 3                           |
| Other                                 | 4                                           | 4                           |
| Polymicrobial bacteremia              | 15                                          | 14                          |
| GNO-GNO                               | 6†                                          | 4†                          |
| GNO-GPO                               | 6†                                          | 4†                          |
| GPO-GPO                               | 8†                                          | 4†                          |
| Nonbacteremic infection               | 8 (3.0)                                     | 12 (4.6)                    |

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. ALC, absolute lymphocyte count; ANC, absolute neutrophil count; BMT, bone marrow transplant; CVAD, central venous access device; GNO, gram-negative organism; GPO, gram-positive organism; NOS, not otherwise specified; PBSCT, peripheral blood stem cell transplant.

* P = .111
* P = .006
* Total numbers reflect that some patients who received >1 diagnosis.
* Previous diagnoses of Hodgkin lymphoma, non-Hodgkin lymphoma, and myelodysplasia were recorded in 1, 1, and 2 patients, respectively.
* One patient received a previous diagnosis of myelodysplasia.
* One patient in each case received a previous diagnosis of chronic lymphocytic leukemia.
* Diagnoses of myelofibrosis (1), amyloidosis (1), hairy cell leukemia (1), lymphoreticular malignancy not otherwise specified (2), and breast cancer (1).
* P = .0228
* Infection with *E. coli* and unspecified, gram-negative bacilli.
* Infections with the following: (1) *E. coli* and *Proteus mirabilis*; (2) *Klebsiella pneumoniae* and *Citrobacter freundii*; (3) *E. coli*, *Citrobacter* species, and *Moraxella catarrhalis*; and (4) *P. aeruginosa* and *K. pneumoniae*.
* Infections with the following: (1) *K. pneumoniae*, *Bacillus cereus*, *Enterococcus faecalis*, and α-hemolytic streptococcus; (2) *K. pneumoniae*, *E. faecalis*, and *K. pneumoniae*; (3) *Enterobacter cloacae* and 2 α-hemolytic streptococci; (4) *P. aeruginosa* and 2 coagulase-negative staphylococci; (5) *E. coli* and 2 α-hemolytic streptococci; and (6) *P. aeruginosa* and *Staphylococcus haemolyticus*.
* Infections with the following: (1) *E. coli*, *Klebsiella oxytoca*, and coagulase-negative staphylococci; (2) *K. pneumoniae* and α-hemolytic streptococci; (3) *P. aeruginosa* and 2 α-hemolytic streptococci; (4) *E. coli*, 2 α-hemolytic streptococci, and coagulase-negative staphylococci; (5) *E. coli*, β-hemolytic streptococci, and coagulase-negative staphylococci; and (6) *K. pneumoniae*, *Acinetobacter anitratus*, and *S. aureus*.
* Infection with the following: (1) *Streptococcus mitis* and *Streptococcus oralis*; (2) α-hemolytic streptococcus and coagulase-negative staphylococci; (3) *Staphylococcus epidermidis* and *Staphylococcus warneri*; (4) *E. faecalis* and *S. epidermidis*; (5) *Enterococcus hirae* and *S. epidermidis*; (6) coagulase-negative staphylococcus and *Propionibacterium acnes*; (7) 2 α-hemolytic streptococci; and (8) *S. epidermidis* and *S. haemolyticus*.
* Infection with the following: (1) α-hemolytic streptococcus and coagulase-negative staphylococcus; (2) 2 α-hemolytic streptococci; (3) *S. epidermidis* and *Staphylococcus hominis*; and (4) *S. mitis* and *S. oralis*.
Table 2. Response to treatment, by randomization and by classification of febrile neutropenic episodes at the test-of-cure time point for the modified intent-to-treat population.

| Classification                        | Piperacillin-tazobactam recipients | Cefepime recipients |
|---------------------------------------|------------------------------------|---------------------|
|                                       | (n = 265)                          | (n = 263)           |
| Success                               | 71 (26.8)                          | 54 (20.5)           |
| IR:RM                                 | 7 (2.6)                            | 6 (2.3)             |
| Indeterminate                         | 47 (17.7)                          | 41 (15.6)           |
| Regimen modification                  | 118                                | 134                 |
| Glycopeptide                          | 106                                | 117                 |
| Breakthrough infection                | 10                                 | 13                  |
| No improvement                        | 5                                  | 3                   |
| Not reported                          | 1                                  | 4                   |
| Lost to follow-up                     | 3                                  | 1                   |

Febrile neutropenic episode

| Unexplained fever                     | 53/157 (33.7)                      | 45/150 (30.0)       |
| Clinically documented infection       | 7/27 (25.9)%                       | 2/27 (7.4)%         |
| Microbiologically documented infection|                                    |                     |
| Overall                               | 11/81 (13.6)                       | 7/86 (8.1)          |
| Bloodstream infection                 | 11/73 (16.4)                       | 5/74 (6.8)          |
| With gram-positive organisms          | 60                                 | 27                  |
| With gram-negative bacilli            | 26                                 | 24                  |
| With polymicrobial organisms          | 22                                 | 16                  |
| Other                                 | 0/8                                | 2/12 (16.7)         |

Chemotherapy

| Chemotherapy                          | 38/131 (29.0)                      | 24/116 (20.7)       |

HSCT

| HSCT                                   | 33/134 (24.6)                      | 30/147 (20.4)       |
| Overall                                | 23/86 (26.7)                       | 24/95 (25.3)        |
| Autologous                             | 7/43 (16.3)                        | 3/38 (7.9)          |
| Allogeneic                             | 3/5 (60)                           | 3/14 (21.4)         |

HSCT stem cell source

| PBSC                                    | 24/78 (30.8)                       | 25/92 (27.1)        |
| Bone marrow                            | 0/4                                | 0/4                 |
| NOS                                     | 9/52 (17.3)                        | 5/51 (9.8)          |

Hematopoietic growth factors prior to study entry

| Yes                                     | 21/72 (29.2)                       | 28/100 (28.0)       |
| No                                      | 50/193 (25.9)                      | 26/163 (16.0)       |

Hematopoietic growth factors with study entry

| Yes                                     | 19/99 (19.2)                       | 10/82 (12.2)        |
| No                                      | 52/166 (31.3)                      | 44/181 (24.3)       |

ANC recovery profile, ×10⁹ cells/L

| Baseline, <0.5; EOT, <0.5                | 4/32 (12.5)                        | 2/34 (5.9)          |
| Baseline, >0.5; EOT, <0.5                | 0/0                               | 0/4                 |
| Baseline, <0.5; EOT, >0.5                | 58/207 (28.0)                      | 48/197 (24.4)       |
| Baseline, >0.5; EOT, >0.5                | 4/9 (44.4)                         | 1/6 (16.7)          |
| Incomplete data                         | 17                                | 22                  |

NOTE. Data are no. (%) of patients, unless otherwise indicated. ANC, absolute neutrophil count; BSI, bloodstream infection; CVAD, central venous access device; EOT, end-of-treatment; HSCT, hematopoietic stem cell transplant; IR:RM, initial response, regimen modified; NOS, not otherwise specified; PBSC, peripheral blood stem cell.

a Response in clinically documented infection in the piperacillin-tazobactam group are as follows: 2 of 13 cases were oral mucositis, 1 of 4 cases was gastrointestinal mucositis, 4 of 4 cases were pneumonia, 0 of 4 cases were skin and soft tissue–related infection, and 0 of 2 cases were other clinically documented infections that were not otherwise specified.

b Clinically documented infection in the cefepime group are as follows: 5 of 14 cases were oral mucositis, 1 of 4 cases were gastrointestinal mucositis, 6 of 6 cases were pneumonia, 0 of 2 cases were skin and soft tissue infection, and 0 of 1 case was sinusitis.

c Infection with the following: S. aureus, S. epidermidis, α-hemolytic streptococci (3); and Rhodococcus equi.

d Infection with α-hemolytic streptococci (2).

e Infection with α-hemolytic streptococci (2).

f Infection with the following: E. coli and aerobic, gram-negative bacillus.

g Infection with the following: E. coli and P. aeruginosa.

h Infection with the following: α-hemolytic streptococci and E. coli; S. epidermidis and Propionibacterium species; and Klebsiella species and Enterobacter species.

i Infection with S. epidermidis and α-hemolytic streptococci.

j Patients with insufficient data to determine the neutrophil recovery profile.
clinical laboratory results, and physical examination. Treatment-related adverse events were classified by body system and by allocation. Adverse events with an overall incidence of ≥3% were compared using Fisher’s exact test.

RESULTS

A total of 528 eligible subjects were enrolled from 34 institutions in the United States, Canada, and Australia (figure 1 and table 1). Of these, 265 subjects were randomized to receive at least 1 dose of piperacillin-tazobactam, and 263 subjects were randomized to receive at least 1 dose of cefepime over a mean (± SD) of 9 (± 5) days (median, 8 days; range, 1–26 days). The duration of treatment was longer for piperacillin-tazobactam recipients (mean [± SD], 9.9 [± 5.3] days; median, 8 days; range, 1–23 days) than it was for cefepime recipients (mean [± SD], 8.1 [± 4.4] days; median, 7 days; range, 1–26 days; P < .001). Ninety-five percent of patients entered the trial with severe neutropenia.

Treatment success rates were higher among piperacillin-tazobactam recipients than cefepime recipients (26.8% vs. 20.5%; OR, 1.42; 95% CI, 0.95–2.12; χ² = 2.863; P = .09), and treatment failure rates were lower among piperacillin-tazobactam recipients than cefepime recipients (51.7% vs. 61.2%; OR, 0.68; 95% CI, 0.48–0.96; χ² = 4.865; P = .027) (table 2). The response rate for clinically documented infections was marginally higher in the piperacillin-tazobactam group (25.9%) than in the cefepime group (7.4%; χ² = 3.333; P = .068). At each of the response assessment time points of 72 h, end of treatment, and the test-of-cure visit, piperacillin-tazobactam was noninferior to cefepime (table 3).

Table 3 shows the results of the logistic regression analyses of covariates predictive of treatment success. Allocation to piperacillin-tazobactam predicted treatment success (OR, 1.65; 95% CI, 1.04–2.64; P = .034); however, having an indwelling central venous catheter, experiencing failure of neutrophil recovery, having documented infection, and undergoing allogeneic HSCT were associated with poorer outcomes. Treatment success was almost one-half as likely among subjects for whom hematopoietic growth factors were initiated with the empirical antibacterial therapy.

Overall, defervescence occurred at a median of 7 and 10 days for the piperacillin-tazobactam and cefepime groups, respectively (P = .1058; figure 2A). Among patients classified as experiencing treatment success, defervescence at 5 days was observed in each study group (P = .9649; figure 2B), versus 9 days and 14 days among subjects in the piperacillin-tazobactam and cefepime groups, classified as experiencing treatment failure (P = .0202; figure 2C).

Cox proportional hazard models were used to examine factors associated with time to defervescence. Treatment allocation

| Time of evaluation | Piperacillin-tazobactam recipients (n = 265) | Cefepime recipients (n = 263) |
|-------------------|---------------------------------------------|-----------------------------|
| 72 h              | 153 (57.7)                                  | 127 (48.3)                   |
| End of treatment  | 105 (39.6)                                  | 83 (31.6)                    |
| Test-of-cure visit| 71 (26.8)                                   | 54 (20.5)                    |

NOTE. Data are no. (%) of patients. Pnoninferiority = probability that the observed noninferiority of piperacillin-tazobactam, compared with cefepime, is random; Psuperiority = probability that the observed superiority in success rates for piperacillin-tazobactam over cefepime is random.

Table 4 shows the results of the logistic regression analyses of covariates predictive of treatment success. Allocation to piperacillin-tazobactam predicted treatment success (OR, 1.65; 95% CI, 1.04–2.64; P = .034); however, having an indwelling central venous catheter, experiencing failure of neutrophil recovery, having documented infection, and undergoing allogeneic HSCT were associated with poorer outcomes. Treatment success was almost one-half as likely among subjects for whom hematopoietic growth factors were initiated with the empirical antibacterial therapy.

Overall, defervescence occurred at a median of 7 and 10 days for the piperacillin-tazobactam and cefepime groups, respectively (P = .1058; figure 2A). Among patients classified as experiencing treatment success, defervescence at 5 days was observed in each study group (P = .9649; figure 2B), versus 9 days and 14 days among subjects in the piperacillin-tazobactam and cefepime groups, classified as experiencing treatment failure (P = .0202; figure 2C).

Cox proportional hazard models were used to examine factors associated with time to defervescence. Treatment allocation

was included as a forced variable. Glycopeptide antibiotic treatment modification (with vancomycin or teicoplanin) (hazard ratio [HR], 0.71; 95% CI, 0.58–0.87; P = .001) and study enrollment in the United States (HR, 0.54; 95% CI, 0.42–0.70; P < .0001) were less likely to be associated with earlier defervescence, and a diagnosis of lymphoma (HR, 1.25; 95% CI 1.01–1.54; P = .0452) and receipt of piperacillin-tazobactam (HR, 1.24; 95% CI, 1.02–1.51; P = .0332) were more likely to be associated with earlier defervescence.

Regimen modification with glycopeptides for persistent fever was the most frequent reason for treatment failure (table 2). Glycopeptides were added at an overall median of 4 days (range, 1–8 days) for piperacillin-tazobactam recipients and 3 days (range, 1–14 days) for cefepime recipients. Canadian physicians tended to prescribe glycopeptides later (for 96 patients; median, 11 days; 95% CI, 6–15 days) than either the physicians in the United States (for 206 patients; median, 6 days; 95% CI, 5–8 days) or Australia (for 87 patients; median, 4 days; 95% CI, 3–5 days) (P = .0061 by log rank test).

Documented breakthrough infections were uncommon and were evenly distributed between the study groups (piperacillin-tazobactam group, 10 infections; cefepime group, 13 infections). Fewer piperacillin-tazobactam recipients required more systemic antifungal therapy during treatment than cefepime recipients (106 recipients [40%] vs. 132 [50.2%] recipients; χ² = 5.536; P = .019). Only 4 infections—2 in each group—were considered to be fungal breakthrough infections. One piperacillin-tazobactam recipient developed candidemia. The remaining patients had oropharyngeal candidiasis.

The study agents were well tolerated. Adverse events with frequencies of ≥10% are listed in table 5. Skin rash (29.4% of piperacillin-tazobactam recipients vs. 22.1% of cefepime recipients; P = .059) and prolonged severe neutropenia (11.7 [± 8.0] days vs. 10.3 [± 6.5] days; P = .023) were more com-
Table 4. Logistic regression analysis of variables associated with treatment success without regimen modification.

| Variable | Univariate OR (95% CI) | Univariate P | Multivariate OR (95% CI) | Multivariate P |
|----------|-------------------------|--------------|--------------------------|---------------|
| Allocation of piperacillin-tazobactam vs. cefepime<sup>a</sup> | 1.42 (0.95–2.12) | .0914 | 1.65 (1.04–2.64) | .0354 |
| Male vs. female | 0.71 (0.48–1.07) | .1023 | ... | ... |
| Age, >65 vs. ≤65 years | 1.40 (0.85–2.29) | .1843 | ... | ... |
| Antibacterial prophylaxis, yes vs. no | 1.09 (0.73–1.64) | .6644 | ... | ... |
| ANC, ×10<sup>9</sup> cells/L | 1.13 (0.41–3.11) | .8117 | ... | ... |
| Baseline, >0.5 vs. ≤0.5 | 0.26 (0.11–0.62) | .0023 | 0.37 (0.15–0.94) | .0363 |
| HSCT, yes vs. no | 0.86 (0.58–1.29) | .4697 | ... | ... |
| Autologous HSCT, yes vs. no | 1.20 (0.79–1.82) | .3996 | ... | ... |
| Allogeneic HSCT, yes vs. no | 0.41 (0.21–0.83) | .0129 | 0.33 (0.16–0.70) | .0039 |
| BMT, yes vs. no | <0.001 (0.001 to >999) | .9844 | ... | ... |
| PBSCT, yes vs. no | 1.50 (0.99–2.28) | .559 | ... | ... |
| Central venous catheter, yes vs. no | 0.35 (0.20–0.62) | .004 | 0.32 (0.16–0.65) | .0014 |
| Hematological malignancy, yes vs. no | 1.94 (1.27–2.98) | .0024 | 1.58 (0.95–2.62) | .0793 |
| Acute leukemia, yes vs. no | 0.53 (0.34–0.82) | .045 | ... | ... |
| Lymphoma, yes vs. no | 1.81 (1.18–2.78) | .0066 | ... | ... |
| HGF administered prior to study entry | 1.47 (0.97–2.23) | .0713 | ... | ... |
| HGF administered concomitant with study entry | 0.50 (0.31–0.79) | .0198 | ... | ... |
| Region of residence | | | | |
| United States<sup>a</sup> | 0.47 (0.31–0.72) | .0005 | 0.54 (0.29–1.02) | .0567 |
| Canada<sup>a</sup> | 2.35 (1.55–3.56) | <0.001 | 1.72 (0.93–3.19) | .0835 |
| Australia | 0.93 (0.57–1.52) | .7612 | ... | ... |

NOTE. ANC, absolute neutrophil count; BMT, bone marrow transplant; BSI, bloodstream infection; CDI, clinically documented infection; HGF, hematopoietic growth factors; HSCT, hematopoietic stem cell transplant; MDI, microbiologically documented infection; PBSCT, peripheral blood stem cell transplant; UF, unexplained fever.

<sup>a</sup> Forced variables in the multivariate model.

mon among piperacillin-tazobactam recipients. Figure 1 shows that more cefepime patients discontinued taking the study agent (64 vs. 43 recipients; χ² = 5.371; P = .02); mostly this was because of adverse events (30 vs. 19 recipients; χ² = 2.815; P = .093). Acute leukemia (HR, 0.46; 95% CI, 0.38–0.57; P < .0001), glycopeptide administration (HR, 0.75; 95% CI, 0.59–0.94; P = .046), and use of fluoroquinolone antibiotics (HR, 0.71; 95% CI, 0.58–0.87; P = .0009), but not randomization to receive piperacillin-tazobactam (HR, 0.87; 95% CI, 0.71–1.06; P = .1555), were independently associated with prolonged time to neutrophil recovery in a Cox proportional hazards model. Acquisition of vancomycin-resistant enterococci and extended-spectrum β-lactamase–producing gram-negative bacilli were not observed during this trial. *Clostridium difficile*–associated diarrhea was observed more often among cefepime recipients than among piperacillin-tazobactam recipients (2.3% vs. 6.8%; OR, 0.32; 95% CI, 0.12–0.81; χ² = 6.381; P = .012).

There were 8 deaths (3%) during the course of treatment in the piperacillin-tazobactam group and 15 (5.7%) in the cefepime group (OR, 0.51; 95% CI, 0.21–1.24; χ² = 2.283; P = .131). The causes of death among piperacillin-tazobactam recipients included pneumonia and respiratory failure in 4, multiorgan system failure in 1, sepsis syndrome in 1, intracranial hemorrhage in 1, and cardiac failure in 1. The causes of death in the cefepime group included pneumonia and respiratory failure in 9, shock in 2, sepsis syndrome in 1 myocardial infarction in 1, pulmonary hemorrhage in 1, and cardiac failure in 1.

**DISCUSSION**

This study achieved its primary objective of demonstrating noninferiority of piperacillin-tazobactam, compared with cefepime, for the empirical treatment of high-risk febrile neutropenic patients with cancer. Furthermore, randomization to receive piperacillin-tazobactam was an independent predictor of treatment success and defervescence in multivariate analyses, which is consistent with the results of recent systematic reviews [46].

The multivariate analyses identified a treatment effect for piperacillin-tazobactam that was not observed in the primary analysis, but was consistent with previous reports from the
European Organization for Research and Treatment of Cancer [47]. This was likely obscured in our study by other variables. Furthermore, our analyses confirmed previously reported relationships between outcome and neutrophil recovery, presence of indwelling central venous catheters, underlying diagnosis, and HSCT. The analyses also identified some unexpected relationships. First, the parallel use of hematopoietic growth factors with empirical antibacterial therapy was associated with a lower likelihood of treatment success (OR, 0.53; 95% CI, 0.31–0.91; P < .02). Although this may represent a selection for a subgroup of subjects with more-severe infection, it may also be a surrogate, given our study design, for physicians more inclined to prescribe additional interventions in the circumstance of persistent fever, despite current guidelines [48–51]. Second, we noted that US subjects had a lower likelihood of earlier defervescence (HR, 0.65; 95% CI, 0.53–0.78; P < .0001), which suggests that either there may have been more patients at higher risk of nonresponse enrolled in US centers or, alternatively, US physicians may have been more likely to initiate salvage treatments for perceived nonresponse due to persistent fever.

Gram-positive bacteria was the predominant cause of microbiologically documented infections, causing two-thirds of the bloodstream infections. Piperacillin-tazobactam and cefepime both have a spectrum of activity that is well suited for the management of patients at risk for gram-positive infections. Despite this, we noted that second-line administration of glycopeptides for persistent fever was a common phenomenon with a regional time-to-prescription effect. Canadian investigators tended to prescribe glycopeptides later than either their US or Australian counterparts, suggesting a differential tolerance for persistent fever. Moreover, more than three-quarters of the subjects who experienced treatment failure received glycopeptides as empirical second-line therapy after a median of only 3 days of initial therapy, whereas defervescence among responders was observed after a median of 5 days of initial therapy, suggesting that modification prior to 5 days may have been unnecessary in many patients, as reported previously [37, 52, 53]. Furthermore, we noted a relationship between prolonged neutropenia and glycopeptide administration not here-tofore reported, except in anecdotal reports [37, 54–58]. These and other observations [14, 59, 60] suggest that in the interest of reducing excess glycopeptide-related adverse events and emergence of resistant pathogens, continued observation of empirical piperacillin-tazobactam monotherapy recipients without regimen modification in hemodynamically stable patients with persistent but unexplained fever for >5 days should be considered.

We noted a differential median time to response of 9 days in the piperacillin-tazobactam group and 14 days in the cefepime group among patients classified as experiencing treatment

**Figure 2.** A, Time to defervescence for all patients in the modified intent-to-treat analysis. Median times were 7 days and 10 days for the piperacillin-tazobactam and cefepime groups, respectively (P = .1058). B, Time to defervescence for modified intent-to-treat patients classified as experiencing treatment success without modification. Median times were 5 days in both groups (P = .9649). C, Time to defervescence for modified intent-to-treat patients classified as experiencing treatment failure. The median times were 9 days and 14 days for the piperacillin-tazobactam and cefepime groups, respectively (P = .0202).
Table 5. Common adverse events observed.

| Adverse event                  | Piperacillin-tazobactam recipients (n = 265) | Cefepime recipients (n = 263) | P*   |
|-------------------------------|---------------------------------------------|-----------------------------|------|
| Any adverse event             | 257 (97.0)                                  | 257 (97.7)                  | .788 |
| Laboratory abnormalities      |                                             |                             |      |
| Hypokalemia                   | 65 (24.5)                                   | 66 (25.1)                   | .920 |
| Hypomagnesemia                | 32 (12.1)                                   | 32 (12.2)                   | 1.000|
| Hypophosphatemia              | 31 (11.7)                                   | 42 (16.0)                   | .167 |
| Duration of neutropenia, mean days ± SDb | 11.7 ± 8.0                                  | 10.3 ± 6.5                  | .023c|
| Clinical abnormalities        |                                             |                             |      |
| Skin/mucous membranes         |                                             |                             |      |
| Rash                          | 78 (29.4)                                   | 58 (22.1)                   | .059 |
| Stomatitis                    | 58 (21.9)                                   | 56 (21.3)                   | .369 |
| Infusion site reaction        | 53 (21.9)                                   | 56 (21.3)                   | .916 |
| Epistaxis                     | 35 (13.2)                                   | 24 (9.1)                    | .167 |
| Cardiorespiratory system      |                                             |                             |      |
| Cough                         | 29 (10.9)                                   | 50 (19.0)                   | .010 |
| Dyspnea                       | 18 (6.8)                                    | 33 (12.5)                   | .027 |
| Tachycardia                   | 17 (6.4)                                    | 30 (11.4)                   | .048 |
| Gastrointestinal system       |                                             |                             |      |
| Abdominal pain                | 58 (21.9)                                   | 61 (23.2)                   | .755 |
| Nausea                        | 33 (12.5)                                   | 38 (14.4)                   | .526 |
| Vomiting                      | 33 (12.5)                                   | 39 (14.8)                   | .449 |
| Diarrhea                      | 91 (34.3)                                   | 80 (30.4)                   | .353 |
| Anorexia                      | 17 (6.4)                                    | 31 (11.8)                   | .035 |
| CNS                           |                                             |                             |      |
| Headache                      | 40 (15.1)                                   | 36 (13.7)                   | .710 |
| Somnolence                    | 21 (7.9)                                    | 27 (10.3)                   | .367 |

NOTE. Data are no. (%) of patients, unless otherwise indicated. A common adverse event is defined as an event with an incidence of ≥10%.

* By Fisher’s exact test.
* Neutropenia defined as an absolute neutrophil count <0.5 x 10^9 cells/L.
* By Student’s t test.

failure (P = .02). The distributions of second-line antibiotic modifications, breakthrough infections, or empirical antifungal therapy by allocation did not account for this difference. Whether this represents a function of a heretofore undetected delayed primary treatment effect cannot be discerned from the present data; however, this observation, to our knowledge, appears to be unique and should be explored further in future studies.

The study regimens were well tolerated in both arms of the trial. Rashes and diarrhea were reported relatively frequently, 26% and 33%, respectively, compared with other trials [34, 47] and may have been a function of the high proportion of patients (53%) who underwent HSCT. Consistent with previous studies [61–63], we noted a reduced risk for *C. difficile*-associated diarrheaa among piperacillin-tazobactam recipients (OR, 0.32; 95% CI, 0.12–0.81), an observation with important economic implications [64]. Although piperacillin-related myelosuppression has been reported previously [65, 66], the prolonged neutropenia observed among piperacillin-tazobactam recipients in our study was associated with other factors, including underlying disease and use of other potentially myelosuppressive agents, such as glycopeptides [54–58]. The all-cause mortality among cefepime recipients was nonsignificantly higher in our study (3% in the piperacillin-tazobactam group vs. 5.7% in the cefepime group), a finding that is in keeping with a recent systematic review [46].

This study has several limitations. First, the study design would have been enhanced by double-blinding. The differing schedules of drug administration, however, made this logistically difficult. Second, like previous studies [67], early modification of the primary empirical antibacterial regimen with a glycopeptide was at the discretion of the investigator and may have impaired our ability to recognize a treatment effect. Third, our rates of treatment success were low but consistent with previous reports, which reflects higher-risk patient populations with similar rigorous definitions of treatment success and fail-
ure [34, 37, 47]. Fourth, a treatment success difference of 20% between the 2 treatment regimen arms may be too large to be clinically acceptable. Because the piperacillin-tazobactam arm achieved response rates that were as good as or, in some instances, better than the cefepime arm, this a priori requirement had no impact on the analysis. Finally, the advantages for piperacillin-tazobactam over cefepime were observed only after controlling for other variables in the multivariate analyses, which suggests that the entry criteria permitted enrollment of a study population too heterogeneous to detect the treatment effect in the primary analysis. This not withstanding, the study achieved its primary objective of noninferiority.

This trial, taken together with other large clinical trials, firmly establishes the safety and efficacy of piperacillin-tazobactam monotherapy for the empirical treatment of the febrile neutropenic patients with cancer. Based on our observations and in consideration of the Spanish [1] and German [3] guidelines, it seems appropriate to revise the North American guidelines [2, 4] to include piperacillin-tazobactam as an acceptable monotherapeutic option in the higher-risk febrile neutropenic population.

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