ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 1995, p. 445–452 Vol. 39, No. 2
0066-4804/95/$04.00+0

Piperacillin-Tazobactam plus Amikacin versus Ceftazidime plus Amikacin as Empiric Therapy for Fever in Granulocytopenic Patients with Cancer

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Received 11 August 1994/Returned for modification 13 October 1994/Accepted 6 December 1994

Gram-positive bacteria have become the predominant infecting organisms in granulocytopenic cancer patients. Empiric antibiotic regimens used in febrile neutropenic patients often include an extended-spectrum cephalosporin, but the response to therapy in gram-positive coccal bacteremia has been unsatisfactory. Thus, new antibiotics with better activity against gram-positive bacteria should be tested. The objective of this prospective randomized controlled study was to evaluate and compare the efficacy and tolerance of piperacillin-tazobactam plus amikacin with that of ceftazidime plus amikacin, the standard regimen of the International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer, in the empiric treatment of febrile granulocytopenic cancer patients. A total of 858 episodes were eligible for this study, and 706 episodes were assessable for efficacy. The antibiotic treatment was successful in 210 (61%) of 342 episodes in the piperacillin-tazobactam–amikacin group compared with 196 (54%) of 364 episodes treated with ceftazidime plus amikacin ($P = 0.05$). The time to defervescence was significantly shorter ($P = 0.01$) and the time to failure was significantly longer ($P = 0.02$) in the piperacillin-tazobactam–amikacin group. A significant difference in response to bacteremic infections between the two patient groups was found: piperacillin-tazobactam plus amikacin was successful in 40 of 80 episodes (50%), and ceftazidime plus amikacin was successful in 35 of 101 episodes (35%) ($P = 0.05$). A multivariate analysis showed that the probability of failure was significantly greater with ceftazidime plus amikacin than with piperacillin-tazobactam plus amikacin ($P = 0.02$). Toxicity was assessed in 854 episodes, and no significant difference in the overall occurrence of unwanted effects was found between the two treatment groups. However, rash or urticaria did occur more frequently in the piperacillin-tazobactam–amikacin group (12 of 421 episodes compared with 3 of 433 episodes in the ceftazidime-amikacin group; $P = 0.02$). This trial suggests that piperacillin-tazobactam plus amikacin is more effective than ceftazidime plus amikacin for the empiric treatment of fever and bacteremia in granulocytopenic cancer patients. Although cutaneous reaction was more frequently associated with piperacillin-tazobactam plus amikacin than with ceftazidime-amikacin, this unwanted effect was relatively mild and its incidence was comparable to that of other penicillin compounds.

In the past decade most centers have reported a relative increase in the number of infections caused by gram-positive cocci in granulocytopenic patients. In studies conducted by the International Antimicrobial Therapy Cooperative Group

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(IATCG) of the European Organization for Research and Treatment of Cancer (EORTC), these organisms, notably coagulase-negative staphylococci and viridans group streptococci, have increased in frequency as agents of single organism bacteremia from 29% in our first trial in 1974 to 1976 (6, 9) to over 65% in our trial of 1988 to 1990 (12). Although mortality from gram-positive coccal bacteremia in granulocytopenic patients is relatively low (three deaths among 135 patients in the trial of 1986 to 1988 [8]), the response to therapy with extended-spectrum cephalosporins such as ceftazidime or ceftriaxone in gram-positive bacteremic episodes has been unsatisfactory, usually less than 50% (12, 16). New antibiotics with better activity against gram-positive organisms should be tested, provided that they retain activity against gram-negative bacteria. Gram-negative bacteremic episodes still represent 30% of the bacteremic episodes in granulocytopenic cancer patients, and they are associated with higher mortality rates.

The extended-spectrum penicillins such as piperacillin, azlocillin, and ticarcillin have been used for the empiric treatment of fever in neutropenic patients (14). However, the dissemination of β-lactamase-producing organisms (5) has limited their use or required their combination with extended-spectrum cephalosporins (19). The addition of the β-lactamase inhibitor tazobactam improves the antibacterial activity of piperacillin. Recent in vitro studies testing piperacillin-tazobactam against 365 bacteremic isolates from granulocytopenic cancer patients in previous trials of the IATCG-EORTC (7) demonstrated activity comparable to that of ceftazidime against gram-negative bacteria and activity better than that of the extended-spectrum cephalosporin against gram-positive bacteria, especially viridans group streptococci and *Staphylococcus aureus.*

The objectives of the present trial were to evaluate and compare the safety, tolerance, and efficacy of piperacillin-tazobactam plus amikacin with that of ceftazidime plus amikacin for the empiric treatment of febrile granulocytopenic patients.

(This work has been presented in part at the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, La., 17 to 20 October 1993.)

MATERIALS AND METHODS

This protocol was designed in accordance with the guidelines published by the Immunocompromised Host Society (11).

Patient eligibility. In this trial, the IATCG-EORTC consisted of 29 centers located in Europe, the United States, and the Middle East. Eligible patients included those with cancer and those who had undergone bone marrow transplantation for neoplastic disease. Patients were eligible for randomization if they had fever (≥38.5°C on one occasion or ≥38°C on two or more occasions within 12 h), granulocytopenia (absolute granulocyte count, ≤1,000 cells per μl anticipated to fall below 500 cells per μl within 24 to 48 h), and a presumed infection (i.e., fever not likely to be due to a noninfectious cause such as drug or blood product administration, etc.). All patients were informed about the investigative nature of this study, and all patients provided informed consent. The trial was conducted in accordance with the Declaration of Helsinki and all applicable national and local ethical requirements. The protocol was also approved by the EORTC Protocol Review Committee (EORTC study number 46911) and by the Ethics Committee of each participating institution.

Patients were excluded from the trial if they had received any intravenous antibiotic during the granulocytopenic episode or during the preceding 96 h; had a known allergy to any of the protocol antibiotics; had been previously randomized to this protocol during the same episode of granulocytopenia; had renal failure requiring hemo- or peritoneal dialysis, a serum creatine level greater than 300 μmol/liter or 3.5 mg/dl, or an estimated creatine clearance below 20 ml/min for adults and 40 ml/min for patients <14 years of age; were less than 2 months of age; were pregnant; or had known human immunodeficiency virus infection. Pediatric patients were excluded from the trial if they had received treatment with any investigational drug within the 30 days preceding randomization.

Randomization procedure. Patients were randomized into two groups: those with leukemia or who had undergone bone marrow transplantation (for any reason) and those with lymphoma and solid tumors. Patients could be entered into the trial more than once during successive neutropenic episodes, but their subsequent assignments were independently randomized. By allowing these subsequent entries, the assumption that data from different neutropenic episodes in the same patient were observations of independent variables was made. The patients were randomized by opening consecutive sealed envelopes. Each center was provided with two sets of envelopes, one for each level of stratification. The correct balance between treatment arms was ensured by the use of random permuted blocks.

Hypothesis and sample size required for the analysis. The objectives of the trial were the assessment of the efficacy, safety, and tolerance of the piperacillin-tazobactam–amikacin regimen compared with those for the control regimen of ceftazidime-amikacin. The primary objective was to compare the overall response rates of the two regimens. According to previous experience (5, 8, 12), the expected response to ceftazidime-amikacin was 75% among all evaluable patients. An absolute increase of 10% for the overall response rate was considered clinically significant. To show such a difference by a two-tailed hypothesis test based on a chi-square distribution with a continuity correction (type I error level, 5%; power, 80%), the inclusion of 269 evaluable patients in each treatment arm was required. Assuming from previous IATCG-EORTC trials (5, 8, 12) that 80% of the eligible patients would be evaluable for response to therapy, a total of 673 eligible patients would be needed to reach the desired power. Special attention was given to the efficacy of the experimental regimen among pediatric patients, and at least 200 children were included in the study. Interim analyses for toxicity were planned after the inclusion of the first 200 and 400 episodes evaluable for adverse effects with delineated predetermined stopping rules in the event of an unacceptable difference in toxicity between the regimens (a minimum toxicity rate of 10% with an absolute increase of 10% was judged as unacceptable).

Clinical and laboratory evaluation. A complete history and physical examination as well as a complete battery of laboratory tests and two sets of blood cultures (from different venipunctures performed at 30-min intervals) were performed on all patients prior to administering study antibiotics. Other cultures were performed as clinically indicated, and a routine chest X-ray also was obtained.

Follow-up studies included repeat hematological analyses, coagulation studies, chemistries, and urinalyses as prescribed by protocol. Blood cultures were repeated daily in the face of persistent fever or if the patient was bacteremic, until cultures were negative.

Bacteria isolated from blood cultures were sent to the Microbiological Reference Center (Clinical Microbiology Laboratory, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland), where standardized bacterial identification and antibiotic susceptibility tests were performed (1, 13, 18). The evaluation of antimicrobial susceptibility was done with zone diameter interpretive standards and equivalent MICs recommended by the National Committee for Clinical Laboratory Standards; breakpoints for resistance included an inhibitory zone diameter of 17 mm or less for piperacillin-tazobactam and 14 mm or less for ceftazidime and amikacin or a MIC of 32 μg/ml or more for ceftazidime and amikacin. For the piperacillin-tazobactam resistance breakpoints, MICs were 64-4 μg/ml when testing *Pseudomonas* spp., 16-4 μg/ml when testing all other gram-negative microorganisms, and 8-4 μg/ml when testing staphylococci.

Classification of febrile episodes and evaluation of response. Primary febrile episodes were classified as (i) microbiologically documented infections with or without bacteremia, (ii) clinically documented infections, (iii) unexplained fever, or (iv) noninfectious fever (such as neoplastic, chemotherapy-induced, and transfusion-induced fevers) according to previously published definitions (8, 12). Patients were evaluated between 72 and 96 h after the initiation of empirical therapy (i.e., early evaluation) and at the completion of the therapeutic trial (i.e., overall evaluation).

A patient's trial was regarded as a success if fever and clinical signs of infection (whenever present) resolved and if the infecting microorganisms (whenever isolated) were eradicated without change of the allocated antibacterial therapy. The response had to be maintained for at least 4 days after the discontinuation of therapy to qualify as a treatment success. If the primary infection did not recur within 1 week after the discontinuation of protocol therapy, treatment was considered successful.

A patient's trial was regarded as a failure if (i) the patient died of the primary infection, (ii) bacteremia persisted beyond the first 24 h of therapy, (iii) breakthrough bacteremia was documented, (iv) the documented pathogen was resistant to the allocated beta-lactam regardless of the evolution of the patient's clinical condition, or (v) no response was seen following empiric therapy, which usually prompted a modification of or an addition to the protocol antibacterial therapy in an attempt to eradicate the primary infection. A premature modification of the allocated regimen was allowed and the trial was considered a failure under one or more of the following conditions: development of shock, acute respiratory distress syndrome, disseminated intravascular coagulation, or multiple organ failure; progression of the primary infection; and persistence of fever 48 h or more after the initiation of empirical therapy. For all gram-positive infections susceptible to the allocated beta-lactam, the persistence of fever in an otherwise stable patient was not considered a sufficient criterion for the modification of protocol therapy; if treatment was changed under such circumstances, the patient trial was considered a protocol violation.

Since in vitro susceptibility to the beta-lactam drug has been shown to be significantly related to the outcome in gram-negative bacteremic episodes (5, 14) as well as in gram-positive bacteremic episodes (6), the isolation of a pathogen

resistant to the allocated beta-lactam was added as a new criterion for failure. Also, the addition of a nonbacterial antimicrobial agent (e.g., antiviral or antifungal) in patients with possible infections who did not defervesce on protocol antibacterial therapy led to the classification of the episode as a failure.

A patient's trial was classified as nonevaluable for response to protocol antibacterial therapy if the primary infection was viral, fungal, or mixed (bacterial-fungal and bacterial-viral); if the febrile episode was not related to infection; or if the treatment had to be stopped because of toxicity.

Therapeutic regimens. Patients received either intravenous piperacillin-tazobactam (4 g/500 mg every 6 h for adults and 80 mg-10 mg/kg of body weight every 6 h for children ≤50 kg) plus a single daily dose of amikacin not to exceed 20 mg/kg/day or ceftazidime (2 g every 8 h for adults and 35 mg/kg every 8 h for children) plus amikacin at 20 mg/kg/day. Amikacin was given in a single daily dose in both groups. Twice-weekly monitoring of the concentrations of amikacin in sera was recommended. An adjustment of doses should be made in order to achieve a predose level in serum of ≤10 mg/liter (12). The beta-lactam antibiotic was first administered over 15 to 30 min; this step was followed by the infusion of amikacin over 60 min. Monitoring of the levels of the beta-lactam antibiotics in sera was not required.

Duration of protocol therapy. Successful response to therapy in patients with microbiologically or clinically documented infections and in those with possible infections required that they receive antibiotics for a minimum of 7 days, 4 of which were consecutive without fever. Antibiotics were discontinued in patients classified as having fever not related to infection. Patients with possible infection but with no microbiological documentation (unexplained fever) had amikacin discontinued on the 4th day, and therapy was continued with the beta-lactam alone for a total of 7 days, 4 of which were consecutive without fever.

Toxicity. Nephrotoxicity was defined as an increase in serum creatinine of 50% or greater from baseline or a rise in serum creatinine (adults only) of greater than 45 μmol/liter. Ototoxicity was defined as a decline in inner ear function, either auditory (a 20-decibel-or-greater decrease of auditory activity at any frequency in one or both ears) or vestibular (nystagmus, vertigo with nausea and vomiting, gait disturbances, or instability), without discernible physical causes. Hepatotoxicity was defined as a rise in the level of transaminases, bilirubin, or alkaline phosphatase 1.5 times above the baseline value and normal range. Hypokalemia was defined as a drop of 1.0 mmol/liter or more (without a concomitant supply of potassium) or 0.5 mmol/liter or more (with a concomitant supply of potassium) in the serum potassium level from the baseline. Adverse effects were recorded in the case report form and judged to be definitely, probably, possibly, unlikely to be, or definitely not related to the study drug(s).

Further infections and death. Further infections (i.e., secondary infections) were defined as those caused by a new organism not recognized as the initial pathogen and which occurred either during therapy or within a week after the discontinuation of protocol antibiotics. Further infections were classified as microbiologically documented infections with or without bacteremia, clinically documented infections, or unexplained fever.

Death was attributed to infection when it occurred as a direct consequence of either the presenting infection or a further infection.

Analysis. All case report forms were reviewed by the Data Review Committee for completeness, accuracy, eligibility criteria, and assessment of the outcome variables. The committee was blinded to the assigned regimen. All data were entered into a computerized data base and analyzed with SPSS programs or BMDP procedures (3, 15). Demographic data and response to therapy were analyzed for all febrile episodes.

Inferential analyses included contingency analyses by hypothesis tests based on an asymptotic chi-square distribution (with a continuity correction in the case of dichotomous variables) or by Fisher's exact tests for small samples where necessary. Mann-Whitney tests were used for the comparison of continuous variables. Distributions of time-to-event variables were estimated by the nonparametric method of Kaplan-Meier and were compared by the logrank test. Inferential multivariable analysis included use of the logistic regression model to estimate the probability distribution of a dichotomous variable (with a stepwise forward method for the selection of the covariates). The covariates tested were all assessable at the time of randomization, and each of them was treated as a categorical variable represented with I-1 indicator variables, where I referred to its number of levels. All significance probabilities were calculated for the two-tailed tests. Confidence intervals also were constructed.

RESULTS

From August 1991 to October 1992, 858 febrile episodes occurring in 696 patients were eligible for the study, of which 152 were not assessable for response to therapy (piperacillin-tazobactam plus amikacin and ceftazidime plus amikacin, respectively) for the following reasons: treatment changed without adequate reason (20 episodes compared with 21), incorrect regimen administration (8 episodes compared with 14), fever not related to infections (13 episodes compared with 6), documented nonbacterial infections (7 episodes [1 viral, 4 fungal, and 2 mixed infections] compared with 10 [3 viral, 6 fungal, and 1 mixed infections]), discontinuation of treatment because of toxicity (12 episodes compared with 3), continuation of antibacterial prophylaxis (7 episodes compared with 6), clinical course precluding evaluation (6 episodes compared with 4), missing data or patient's withdrawal from treatment (5 episodes compared with 4), early discontinuation of protocol therapy (5 episodes compared with 0), and coadministration of a nonprotocol antibiotic (0 episodes compared with 1).

Thus, 706 episodes (82% of the eligible cases) were evaluable for response to antibacterial therapy, 342 in the piperacillin-tazobactam–amikacin group and 364 in the ceftazidime-amikacin group.

At randomization, there were no significant differences between the two treatment groups in any characteristics of the patients evaluable for response to therapy (Table 1). In particular, the groups were well balanced with respect to stratification by category of underlying disease.

Response rates. A successful outcome occurred in 210 (61%) of 342 episodes in the piperacillin-tazobactam–amikacin group compared with 196 (54%) of 364 episodes treated with ceftazidime plus amikacin ($P = 0.05$) (Table 2). The distribution of the time to defervescence was estimated for each treatment group, and the two groups were compared by the logrank test (Fig. 1), with a duration significantly shorter in the piperacillin-tazobactam–amikacin group ($P = 0.01$). Similarly, the time to failure of the treatment regimen was significantly shorter ($P = 0.02$) in the ceftazidime-amikacin group (Fig. 2).

The causes of failure in 132 episodes treated with piperacillin-tazobactam–amikacin and 168 episodes treated with ceftazidime-amikacin included, respectively, clinical deterioration in 49 and 66 episodes, relapsing fever in 53 and 51 episodes, isolation of a resistant organism in 23 and 39 episodes, relapse of infection in 3 and 5 episodes, breakthrough bacteremia in 3 and 5 episodes, and persistence of bacteremia in 1 and 2 episodes. The distributions of the causes of failure were not shown to be statistically different between the treatment groups (Table 2).

The success rate was analyzed according to the documentation of infection (Table 3). Microbiologically documented infections occurred in 205 episodes (29%), of which 181 (25.6% of the total) were bacteremias. These bacteremias were due to multiple organisms in 20 episodes and to single organisms in 161 episodes. Of the latter, 108 (67%) were caused by gram-positive bacteria and 53 (33%) were caused by gram-negative bacteria. Coagulase-negative staphylococci were isolated most frequently, followed in order by viridans group streptococci, *Escherichia coli*, *S. aureus*, and *Pseudomonas aeruginosa*. There were no statistically significant differences in the distributions of these organisms between the two groups. A significant difference in the responses to bacteremic infections was found between the two patient groups, with piperacillin-tazobactam plus amikacin resulting in 50% success and ceftazidime plus amikacin resulting in 35% success ($P = 0.05$). Significant differences were not found for subgroups of bacteremias or by specific organisms.

The initial regimen was stopped because of the documentation of an organism resistant to the allocated beta-lactam in 23 of 93 (25%) microbiologically documented episodes treated with piperacillin-tazobactam plus amikacin and 39 of 112 (35%) microbiologically documented episodes treated with ceftazidime plus amikacin ($P = 0.15$). The following causative gram-positive microorganisms were resistant to the allocated beta-lactam: coagulase-negative staphylococcus (18 in episodes treated with piperacillin-tazobactam and 26 in episodes treated with ceftazidime-amikacin); an *Enterococcus* sp. (1 and 4); a

TABLE 1. Characteristics of the 706 episodes evaluable for response to therapy

Characteristic	Value	
	Piperacillin-tazobactam + amikacin	Ceftazidime + amikacin
No. (%) of episodes		
Total	342	364
in Adults	256 (75)	265 (73)
in Children	86 (25)	99 (27)
Mean age (range) (yr)	31 (1–77)	35 (1–80)
No. of episodes in males/females	199/143	205/159
Mean wt (range) (kg)	60.5 (5–120)	59 (5.6–117)
No. (%) of episodes with underlying cancer		
Acute leukemia	193 (57)	207 (57)
Hodgkin's disease and lymphoma	69 (20)	65 (18)
Solid tumor	55 (16)	66 (18)
Myelodysplasic syndrome	10 (3)	8 (2)
Other	15 (4)	18 (5)
Median days of granulocytopenia ($\leq$1,000 cells/mm^3) (range)		
At study entry	4 (0–690)	4 (0–60)
Total	18 (1–720)	17 (2–88)
Median granulocyte count at entry (range) (cells/mm^3)	0 (0–999)	20 (0–986)
No. of episodes with $<$100 cells/mm^3 at entry	244 (71)	255 (70)
No. (%) of trial days with granulocytes (per mm^3) at:		
$\leq$100	1,662 (60.3)	1,660 (61.8)
100–500	620 (22.5)	580 (21.6)
501–1,000	237 (8.6)	237 (8.8)
$>$1,000	238 (8.6)	210 (7.8)
No. (%) of episodes with:		
Oral antibacterial prophylaxis	195 (57)[a]	219 (60)[b]
Quinolones	139	138
Cotrimoxazole	54	61
Penicillin	19	29
Nonabsorbable	10	14
Oral antifungal prophylaxis	212 (62)	212 (58)
Oral antiviral prophylaxis	72 (21)	75 (21)
No. (%) of episodes with:		
Intravenous catheter in situ	278 (81)	292 (80)
Shock	5	1

[a] Twenty-seven patients were given two antibiotics.
[b] Twenty-three patients were given two antibiotics.

viridans group streptococcus (0 and 2); *Corynebacterium jeikeium* (1 and 3); *S. aureus* (1 and 1); a *Clostridium* sp. (1 and 1); a *Bacillus* sp. (0 and 1), a *Listeria* sp., a *Micrococcus* sp. (0 and 1), and *Corynebacterium* non-*jeikeium* (0 and 1). In addition, *P. aeruginosa* was resistant to the allocated beta-lactam in three episodes, one in the piperacillin-tazobactam–amikacin group and two in the ceftazidime-amikacin group.

Susceptibilities to piperacillin-tazobactam, ceftazidime, and amikacin, respectively, were 52, 28, and 79% for coagulase-negative staphylococci; 93, 93, and 66% for viridans group streptococci; 85, 96, and 89% for *E. coli*; and 73, 82, and 100% for *P. aeruginosa*.

Two hundred and ten febrile episodes were clinically documented infections, 105 in each treatment group. The observed response rate was higher with piperacillin-tazobactam plus amikacin (62 versus 51% for ceftazidime plus amikacin), but this difference was not significant ($P = 0.16$). The most frequent clinically documented infections were severe mucositis ($n = 62$), lower respiratory tract infections ($n = 53$), and cutaneous infections ($n = 38$). While there was no significant difference in efficacy either in severe mucositis (success in 25 of 36 episodes in the piperacillin-tazobactam–amikacin group and in 13 of 13 episodes in the ceftazidime-amikacin group; $P = 0.19$) or in cutaneous infections (success in 10 of 17 episodes in the piperacillin-tazobactam–amikacin group and in 12 of 21

TABLE 2. Outcome of therapy

Characteristic	Value	
	Piperacillin-tazobactam + amikacin	Ceftazidime + amikacin
Median days of therapy (range)	8 (1–31)	7 (1–30)
No. (%) of episodes		
Success	210 (61)	196 (54)
Failure	132 (39)	168 (46)
No. of episodes with[a]:		
Deterioration	49	66
Relapsing fever	53	51
Resistant pathogen[b]	23	39
Breakthrough bacteremia	3	5
Relapsing of local symptoms	2	3
Persistence of bacteremia	1	2
Relapsing infection	1	2

[a] Conditions resulting in failure of empiric antibiotic treatment.
[b] The following pathogens were resistant to the allocated beta-lactam (23 resistant pathogens in the piperacillin-tazobactam–amikacin group and 43 in the ceftazidine-amikacin group): methicillin-resistant coagulase-negative staphylococcus (18 in the piperacillin-tazobactam–amikacin group and 26 in the ceftazidime-amikacin group; an *Enterococcus* sp. (1 and 4); *Corynebacterium jeikeium* (1 and 3); *S. aureus* (1 and 1); a *Clostridium* sp. (1 and 1); *P. aeruginosa* (1 and 2); viridans group streptococcus (2 in the ceftazidime-amikacin group); and a *Bacillus* sp., *Listeria* sp., *Corynebacterium* sp., and *Micrococcus* sp. (1 in the ceftazidime-amikacin group).

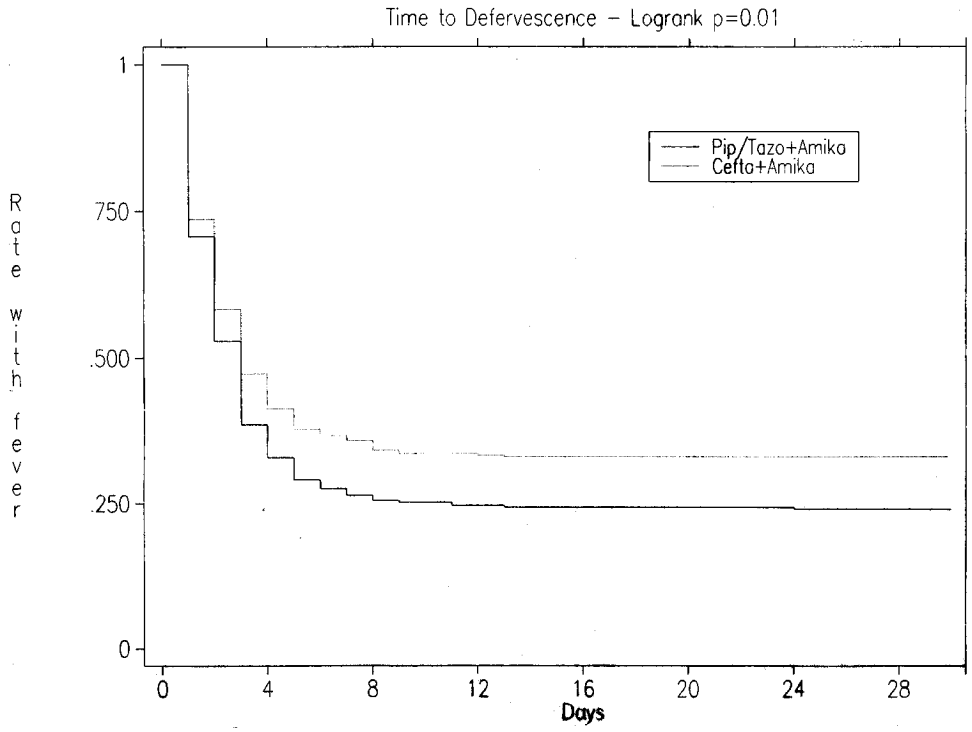

FIG. 1. Distributions of time to defervescence for patient groups treated with piperacillin-tazobactam plus amikacin and ceftazidime plus amikacin.

episodes in the ceftazidime-amikacin group; $P = 0.9$), there was a trend favoring piperacillin-tazobactam plus amikacin in patients with lower respiratory tract infections (success, 19 episodes of 29 versus 9 of 24; $P = 0.07$). Two hundred and ninety-one febrile episodes were classified as unexplained fever. No significant difference in response rate was observed between the two groups.

Since previous trials have shown that extended-spectrum

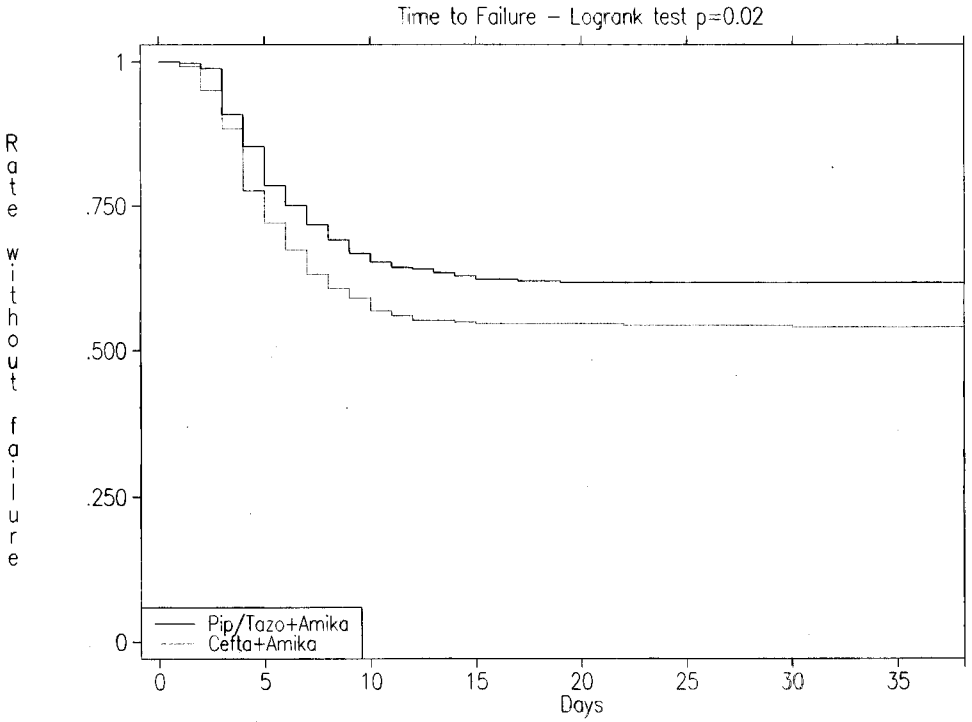

FIG. 2. Times to failure for patient groups treated with piperacillin-tazobactam plus amikacin and ceftazidime plus amikacin.

TABLE 3. Success rates by type of infection and infecting organism

Infection or pathogen	No. (%) of successful outcomes/total treated		*P*
	Piperacillin-tazobactam + amikacin	Ceftazidime + amikacin	
Overall rate	210/342 (61)	196/364 (54)	0.05
Microbiologically documented infections	49/93 (53)	43/112 (38)	0.04
Bacteremia	40/80 (50)	35/101 (35)	0.05
Single gram-positive bacteremia	20/52 (38)	14/56 (25)	0.19
Coagulase-negative staphylococci	3/24 (13)	3/28 (10)	
S. aureus	3/6	1/4	
Streptococci	13/20 (65)	10/20 (50)	
Other gram-positive bacteria	1/2	0/4	
Single gram-negative bacteremia	18/24 (75)	18/29 (62)	0.38
E. coli	9/10 (90)	8/12 (67)	
Klebsiella and/or *Enterobacter* spp.	3/6	4/5	
P. aeruginosa	3/4	2/6	
Other gram-negative bacteria	3/4	4/6	
Polymicrobial infections	2/4	3/16 (19)	
Nonbacteremic infections	9/13 (69)	8/11 (73)	
Clinically documented infections	65/105 (62)	54/105 (51)	0.16
Unexplained fever	96/144 (67)	99/147 (67)	1.0

TABLE 5. Intent-to-treat analysis

Parameter	No. (%) of episodes	
	Piperacillin-tazobactam + amikacin	Ceftazidime + amikacin
Episodes		
Randomized	425	433
Not evaluable	26 (5.5)	29 (6.2)
Treatment changed without adequate reason[a]	20	21
With fever not related to infection[b]	13	6
Treatment stopped because of toxicity[a]	12	3
With viral, fungal or mixed infections[a]	7	10
With too short therapy[b]	5	0
Evaluable episodes	399 (94.5)	404 (93.8)
Episodes with response to treatment:		
Success[c]	228 (57)	202 (50)
Failure	171 (43)	202 (50)

[a] Assessed as failures.
[b] Assessed as successes.
[c] $P = 0.051$.

cephalosporins lack efficacy in gram-positive infections, the effects of the addition of a glycopeptide were compared for the two groups; overall, vancomycin or teicoplanin was added significantly more frequently in episodes treated with ceftazidime plus amikacin (in 128 of 364 [35%] episodes versus 83 of 342 [24%] episodes treated with piperacillin-tazobactam plus amikacin; $P = 0.002$). The need for empirical antifungal therapy did not differ between the two groups (17% in both groups).

Multivariate (logistic regression) analyses were performed for 702 evaluable episodes (4 had missing data) to estimate the probability of failure. Among the tested covariates (treatment arm; stratification factor; age; gender; use of growth factors; antimicrobial, antiviral or antifungal agents before trial; granulocyte count; and duration of granulocytopenia at entry into the trial), three variables were significant predictors of outcome: the stratification factor (leukemia and bone marrow transplantation versus solid tumor), gender, and the treatment regimen. The probability of failure was significantly greater with ceftazidime plus amikacin than with piperacillin-tazobactam plus amikacin ($P = 0.02$). After inclusion of these three variables, the best-fit model with the estimated odds ratio was applied to the data; the model is presented in Table 4. These analyses were repeated for the 463 patients having a granulocyte count of less than 100 cells per μl at randomization, and similar results were obtained.

TABLE 4. Logistic regression model estimating the probability of treatment failure

Variable	C[a]	SE	*P*	Exp C[b]	95% CI[c]
Stratification factor[d]	−1.08	0.19	<0.0001	0.34	0.24–0.49
Gender[e]	−0.45	0.16	0.005	0.64	0.46–0.87
Treatment arm[f]	0.36	0.16	0.02	1.43	1.05–1.95

[a] C, coefficient. A negative coefficient means a higher probability of failure for patients belonging to reference group.
[b] Exp C, exponential coefficient.
[c] 95% CI, confidence interval at 95%.
[d] 0 = leukemia and bone marrow transplantation (reference value); 1 = solid tumor.
[e] 0 = male (reference value); 1 = female.
[f] 0 = piperacillin-taxobactam plus amikacin (reference value); 1 = ceftazidime plus amikacin.

In addition, an intent-to-treat analysis (Table 5) included all patients assessed as evaluable plus the following nonevaluable patients: those with viral, fungal, or mixed infections; those with toxicity; those with treatment changed without reason (assessed as failures); those with fever not related to infections; and those with short-course therapy (assessed as successes). This analysis also showed a benefit for piperacillin-tazobactam plus amikacin with 228 of 399 episodes (57%) treated successfully compared with 202 of 404 episodes (50%) in the ceftazidime-amikacin group ($P = 0.05$). Multivariate analyses were repeated on 800 evaluable patients. Similarly, the same three variables entered the model: the stratification factor, gender, and the treatment regimen (the probability of failure was significantly greater with ceftazidime-amikacin; $P = 0.02$).

Further infections. Further infections occurred in 56 of 342 (16%) episodes in the piperacillin-tazobactam–amikacin group and in 61 of 364 (17%) episodes treated with ceftazidime plus amikacin. Bacteremic infections subsequent to the initial infection developed more frequently in patients treated with ceftazidime plus amikacin than in those receiving piperacillin-tazobactam plus amikacin (19 of 364 episodes [5%] versus 6 of 342 episodes [1.7%], respectively; $P = 0.02$). Of the 19 bacteremic further infections in the ceftazidime-amikacin group, 12 were due to single gram-positive organisms, 2 were due to gram-negative rods, and 5 were polymicrobial: among the 24 strains isolated from blood cultures, 15 were resistant to ceftazidime. In the piperacillin-tazobactam–amikacin group, three bacteremic further infections were due to gram-positive cocci and three were due to gram-negative bacilli: among the 6 strains isolated from blood cultures, one was resistant to piperacillin-tazobactam. There was no difference between the treatment groups with respect to the number of days to development of a further infection (median, 9 days after random-

ization in both groups) or the number of patients with granulocyte counts less than 100 cells per μl at the time of documentation of further infection (31 of 56 patients in the piperacillin-tazobactam–amikacin group versus 43 of 61 patients in the ceftazidime-amikacin group).

Mortality. The overall mortality rate was 8% in both groups (32 cases in both groups). Death occurred at a median of 28.5 days (range, 7 to 45 days) after entry in the piperacillin-tazobactam–amikacin group and at 21 days (range, 1 to 56 days) after entry in the ceftazidime-amikacin group. Mortality due to the presenting or further infection was relatively uncommon. Only seven patients died from their presenting infection (three who received piperacillin-tazobactam plus amikacin and four who received ceftazidime plus amikacin). Eight patients in the ceftazidime-amikacin group died from a further infection compared with two patients in the piperacillin-tazobactam–amikacin group (not statistically significant). Other causes of death included extensive cancer (20 cases in the piperacillin-tazobactam–amikacin group and 12 cases in the ceftazidime group, with infection in 11 and 7 cases, respectively), hemorrhage (2 and 5 cases, with infection in 1 and 4 cases, respectively), and other causes (5 and 3 cases, respectively).

Adverse events. A total of 854 episodes were evaluable for adverse events: four episodes in the piperacillin-tazobactam–amikacin group were not assessed for toxicity, three episodes did not receive the regimen, and one episode had missing data. There was no significant difference in the overall occurrence of side effects between the two treatment groups (92 of 421 patients (22%) for the piperacillin-tazobactam–amikacin group and 76 of 433 patients (18%) for the ceftazidime-amikacin group; $P = 0.14$). Rash or urticaria did occur more frequently in the piperacillin-tazobactam–amikacin group: 12 of 431 patients (leading to discontinuation of the regimen in 9) compared with 3 of 433 patients (1 discontinued the regimen) in the ceftazidime-amikacin group ($P = 0.02$). Moderate to severe nephrotoxicity probably attributable to the study regimen developed in four patients in the piperacillin-tazobactam–amikacin group and in one patient in the ceftazidime-amikacin group. Hepatic toxicity probably related to regimen was reported for two patients in the piperacillin-tazobactam–amikacin group and in three patients receiving ceftazidime plus amikacin; hypokalemia related to regimen was reported for eight and five patients in the piperacillin-tazobactam–amikacin and ceftazidime-amikacin groups, respectively; and gastrointestinal intolerance was reported for two patients in each group.

DISCUSSION

Although gram-positive bacteria have become the predominant bacteremic isolates in granulocytopenic cancer patients, the need to administer a glycopeptide at the onset of empiric therapy for fever has not been clearly demonstrated (8, 17). However, the poor response rate of gram-positive bacteremic episodes to ceftazidime plus amikacin in previous trials prompted us to test new compounds with better activity against these organisms. The present trial compared an extended-spectrum penicillin (piperacillin) combined with a new β-lactamase inhibitor (tazobactam) to the extended-spectrum cephalosporin (ceftazidime) for the empiric treatment of fever in granulocytopenic cancer patients. Both regimens included amikacin in a single daily dose (12). Overall, febrile episodes in neutropenic patients responded significantly better to piperacillin-tazobactam–amikacin than to ceftazidime plus amikacin. This difference was also statistically significant for the subgroup of bacteremic episodes but not when the analysis was limited to single-organism gram-positive bacteremic infections. The lack of significant difference in the latter subgroup is certainly related to the high proportion of methicillin-resistant coagulase-negative staphylococci that caused 36% of the single gram-positive bacteremic episodes assessed as failures.

The better efficacy associated with piperacillin-tazobactam plus amikacin, also demonstrated with an intent-to-treat analysis, could not be attributed to a single factor but may be explained by the following factors. First, the number of resistant pathogens requiring discontinuation of the allocated regimen was lower in patients treated with piperacillin-tazobactam plus amikacin. Second, a better clinical response was observed in non-coagulase-negative gram-positive infections. Third, a similar trend was seen in clinically documented infections and especially in pneumonia. In addition, bacteremic further infections were more frequent in patients treated with ceftazidime plus amikacin than in patients treated with piperacillin-tazobactam plus amikacin.

Since differences in antimicrobial susceptibility did not explain the better outcome in patients treated with piperacillin-tazobactam plus amikacin, other hypotheses should be considered. Ceftazidime was administered every 8 h, and piperacillin-tazobactam was administered every 6 h. This resulted in shorter periods of time without residual beta-lactam activity in the piperacillin-tazobactam-treated patients. It has been postulated that the activity of a beta-lactam drug depends on the aggregate time the serum drug level stays above the MIC (2). Also, in *P. aeruginosa* thigh infections in a neutropenic mouse model, the fractionated dosing of beta-lactams was superior to bolus injections (10). This pharmacokinetic difference might have influenced the present results, especially in bacteremic patients. Another difference between the treatment arms in this study might relate to differential synergism with the aminoglycoside and the two beta-lactams (4).

The overall response rate, which is relatively low in both groups, is certainly due to the more stringent definitions of failure of empiric treatment used in this trial. However, this high failure rate was not associated with high mortality, since deaths due to the presenting infection were reported in only seven patients. Compared with the previous trial of the IATCG-EORTC, this study showed a 20% reduction in the overall response rate for patients treated with ceftazidime plus amikacin (from 74 to 54%). This was observed in all subcategories of infection: from 57 to 38% in microbiologically documented infections, from 76 to 51% in clinically documented infections, and from 85 to 67% in unexplained febrile episodes (12). Given the ceftazidime and amikacin susceptibilities for the most frequent bacteremic isolates, the decreased response rate to ceftazidime plus amikacin was not attributed to the emergence of resistance. Although the definition for failure has been modified in this trial (see Materials and Methods), these changes could explain a reduction of efficacy only in microbiologically documented infections and in some patients with possible infections. Some differences in the patients' characteristics suggest that patients randomized into this trial were at a higher risk of infectious complications than those randomized into the previous study. A higher proportion of patients with bone marrow transplantation (17% in this trial compared with 8% in the previous trial) as well as patients with less than 100 granulocytes/mm^3 at entry (71 versus 64%, respectively) were included in the present trial. However, multivariate analyses did not suggest that these factors or others such as age, granulocyte count at randomization, stratification factor, disease status, or antibacterial prophylaxis might explain the reduced efficacy of ceftazidime plus amikacin.

Toxicities and side effects found with the two regimens were mild, and overall, there were no statistically significant differ-

ences in the occurrence of adverse events definitely or probably attributed to antibiotics by regimen. However, rash and urticaria leading to the discontinuation of a regimen were significantly more frequent in the piperacillin-tazobactam–amikacin group. As in previous studies (8, 12), the rates of nephrotoxicity probably related to trial drugs were extremely low in both groups (less than 1%).

In summary, this trial suggests that piperacillin-tazobactam plus amikacin is more effective than ceftazidime plus amikacin for the empiric treatment of fever and bacteremia in granulocytopenic patients with cancer. Although cutaneous reaction was more frequently associated with piperacillin-tazobactam plus amikacin than with ceftazidime plus amikacin, this unwanted effect was relatively mild and its incidence was comparable to that of other penicillin compounds.

ACKNOWLEDGMENTS

This work was supported by a grant from Lederle International, American Cyanamid Company, Wayne, N.J.

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