Effects of Teicoplanin and Those of Vancomycin in Initial Empirical Antibiotic Regimen for Febrile, Neutropenic Patients with Hematologic Malignancies

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The efficacy and toxicity of teicoplanin and vancomycin in the initial empirical antibiotic regimen in febrile, neutropenic patients with hematologic malignancies were compared in a prospective, randomized, unblinded, multicenter trial in the setting of 29 hematologic units in tertiary-care or university hospitals. A total of 635 consecutive febrile patients with hematologic malignancies and chemotherapy-induced neutropenia were randomly assigned to receive intravenously amikacin plus cefazidime plus either teicoplanin at 6 mg/kg of body weight once daily or vancomycin at 1 g twice daily. An efficacy analysis was done for 527 evaluable patients: 275 treated with teicoplanin and 252 treated with vancomycin. Overall, successful outcomes were recorded for 78% of patients who received teicoplanin and 75% of those who were randomized to vancomycin (difference, 3%; 95% confidence interval [CI], −10 to 4%; P = 0.33). A total of 102 patients presented with primary, single-agent, gram-positive bacteremia. Coagulase-negative staphylococci accounted for 42%, Staphylococcus aureus accounted for 27%, and streptococci accounted for 21% of all gram-positive blood isolates. The overall responses to therapy of gram-positive bacteremias were 92 and 87% for teicoplanin and vancomycin, respectively (difference, 5%; CI, −17 to 6%; P = 0.22). Side effects, mainly represented by skin rash, occurred in 3.2 and 8% of teicoplanin- and vancomycin-treated patients, respectively (difference, −4.8%; CI, 0.7 to 8%; P = 0.03); the rate of nephrotoxicity was 1.4 and 0.8% for the teicoplanin and vancomycin groups, respectively (difference, 0.6%; CI, −2 to 1%; P = 0.68). Further infections were caused by gram-positive organisms in two patients (0.7%) treated with teicoplanin and one patient (0.4%) who received vancomycin (difference, 0.3%; CI, −0.9 to 1.0%; P = 0.53). Overall mortalities were 8.5 and 11% for teicoplanin- and vancomycin-treated patients, respectively (difference, −2.5%; CI, −2 to 7%; P = 0.43); death was caused by primary gram-positive infections in three patients (1%) in each treatment group. When used for initial empirical antibiotic therapy in febrile, neutropenic patients, teicoplanin was at least as efficacious as vancomycin, but it was associated with fewer side effects.

The increasing prevalence of gram-positive infections noted in recent years in neutropenic cancer patients (5,9) suggests that an anti-gran-positive antibiotic might be included in empirical therapeutic regimens for febrile, neutropenic patients. There has been considerable debate about whether a glycopeptide antibiotic should be part of the initial empirical regimen (15). Although several randomized studies demonstrated no survival advantage when every patient with neutropenia was treated with a glycopeptide antibiotic (5, 18, 19), a better response in patients with gram-positive bacteremias was clearly documented (4, 5, 12, 22). The initial empirical use of a glycopeptide antibiotic can be restricted to centers with a high

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incidence of methicillin-resistant staphylococci. In the previous Gimeña Infection Program trial (9), among 619 neutropenic patients receiving fluoroquinolone prophylaxis, 61 (64%) of 95 single-agent bacteremias were caused by gram-positive cocci, with coagulase-negative staphylococci (27 of 61 [44%]) and streptococci (25 of 61 [41%]) representing the most frequently isolated pathogens. Because these microorganisms were poorly susceptible to ceftazidime and amikacin and only half of the staphylococci proved to be susceptible to methicillin, we decided that a glycopeptide antibiotic should be included in the initial empirical antibiotic regimen.

Vancomycin is considered the drug of choice when a glycopeptide antibiotic is to be used in neutropenic patients; it exerts a greater antibacterial activity against some strains of coagulase-negative staphylococci than teicoplanin (10) and there are more data on its routine clinical use, but there are some concerns related to its potential nephrotoxicity, especially when it is used in combination with aminoglycosides (20), and the induction of “red-man syndrome.” Teicoplanin, an antibiotic administered once daily with activity against strains of enterococci resistant to vancomycin, seems to be less toxic (13, 21) and is easier to administer. Both vancomycin (12, 22) and teicoplanin (4, 14, 16), when used in initial, combined therapy, have proved to be efficacious in the treatment of neutropenic patients with gram-positive bacteremias; however, comparative studies able to establish which glycopeptide antibiotic may be the better choice in febrile, neutropenic patients are lacking.

The aim of our study was to compare the safety and efficacy of teicoplanin and vancomycin in combination with amikacin and ceftazidime as an initial empirical antibiotic regimen in neutropenic patients with hematologic malignancies.

**MATERIALS AND METHODS**

**Patient eligibility.** Patients in any participating center of the Gimeña Infection Program were eligible for the present study if they had hematologic malignancies, neutropenia (neutrophil count, <1,000/mm³), and fever (>38°C on one occasion) in the absence of an obvious noninfectious cause and had not received parenteral antibiotics for >4 days before randomization. Patients were excluded before randomization if they were allergic to any of the trial antibiotics or if their serum creatinine level was >1.4 mg/ml.

**Study design, end points, and sample size.** The specific hypothesis tested in the present prospective, randomized, multicenter study was whether once-daily teicoplanin therapy was as effective as multiple-times-daily vancomycin therapy when both were combined with amikacin and ceftazidime for the empiric therapy of febrile, neutropenic patients with hematologic malignancies. To determine the sample size for the study we assumed that, among the evaluable patients, the overall response rate to the amikacin plus ceftazidime and vancomycin regimen would be 75%, as observed in a previous study (5), a difference in efficacy of less than 10% was necessary to conclude that both treatments had similar efficacies, and 85% of all randomized patients would be evaluable for response to treatment. To ensure a probability of 80% (that is, beta = 0.20) that the upper 95% confidence interval (CI) (that is, alpha = 0.05) for the true difference in response rates between the two treatment groups would not exceed 10%, 250 evaluable patients were needed in each study arm. Thus, assuming a 15% nonevaluable rate, 575 patient entries were required. On the basis of an estimated rate of 20% gram-positive bacteremia, 50 documented cases of gram-positive bacteremia could be expected in each treatment group. With an expected response rate of gram-positive bacteremias of 85%, a difference in response of greater than 15% could be demonstrated with a type 1 error of 5% (alpha = 0.05) and a power of 80% (two-sided test).

**Initial and follow-up patient evaluations.** Patients were evaluated before randomization and during follow-up as described previously (17).

**Randomization procedure and antibiotic treatment.** At the start of chemotherapy, all patients received oral prophylaxis with ciprofloxacin at 500 mg twice daily plus either fluconazole at 150 mg once daily or amphotericin B suspension at 500 mg four times daily. Antibacterial prophylaxis was stopped for patients who developed fever, and after informed consent was obtained, they were randomly allocated to one of the following two regimens by drawing consecutive sealed envelopes: amikacin plus ceftazidime plus either teicoplanin or vancomycin. The envelopes at each institution were stratified so that equal numbers of patients were randomized to each trial arm with every 10 patients entered into the study.

Amikacin was given at a dosage of 15 mg/kg of body weight per day divided into three equal doses (the average adult received 350 mg every 8 h). Ceftazidime was given at a dosage of 90 mg/kg divided in three equal doses (the average adult received 2 g every 8 h). Each antibiotic was dissolved in 100 ml of 0.9% saline and was administered intravenously over 15 to 30 min. Teicoplanin was given at a dosage of 6 mg/kg/day in a single daily dose (the average adult received 400 mg once daily) dissolved in 10 ml of sterile water and administered intravenously over 3 min, with an initial loading dose of 8 mg/kg (maximum initial dose, 600 mg). Vancomycin was given at a dosage of 30 mg/kg/day in two divided doses (the average adult received 1 g every 12 h) dissolved in 100 ml of 5% glucose in water and was administered intravenously over 60 min. Patients who responded to therapy were maintained on the trial antibiotics for at least 5 consecutive days after fever and all signs of infection had disappeared (not less than a total of 10 days). In patients with a persistent unexplained fever despite 4 to 6 days of the triple-drug antibiotic regimen, empirical intravenous amphotericin B therapy was started.

**Classification of febrile episodes.** Febrile episodes were classified as microbiologically documented infections subdivided into those with and those without bacteremia, clinically documented infections, and unexplained fevers according to previously published definitions (7, 9).

**Case review.** Every case report form was reviewed by the Data Review Committee, which was blinded to the allocated antimicrobial regimen, to ensure uniformity in case reviewing and to verify patient eligibility, the classification of the infection, and the evaluation of response according to protocol definitions.

**Evaluation of response.** The responses to the antibiotic regimens were classified as successes, failures, or not evaluable. Success was resolution of fever and clinical signs of infection and eradication of the infecting microorganism without a change in the allocated antibacterial therapy; the response had to be maintained for >4 days after the discontinuation of therapy. Failure was no response to empirical therapy; that is, the pathogen or fever persisted and the patient's clinical condition was not improving, requiring a change in antibacterial therapy, or the death of the patient as a result of the primary infection. Not evaluable was used if the patient had a fungal or viral infection or if a major protocol violations occurred. The central venous catheter (CVC) was promptly removed from patients with a CVC tunnel infection after 4 to 6 days of the triple-drug regimen if no clinical improvement was evident in patients with CVC exit-site infection, and after
no less than 4 days of empiric antibiotic therapy if blood cultures remained positive in patients with bacteremias and CVCs in place.

**Toxicity.** Antibiotic-related nephrotoxicity was defined as a rise in the serum creatinine level above the normal range when other causes of nephrotoxicity (hypotension, hypovolemia) or other nephrotic drugs had been excluded. Besides clinical evaluation, no audiometric studies were performed for ototoxicity evaluation.

**Further infections and death.** Secondary infections were classified as superinfection or subsequent infection. These were defined as any infection at the original site (superinfection) or at any other site (subsequent infection) caused by another organism not recognized as the initial infecting pathogen that occurred either during therapy or within the week after the discontinuation of protocol antibiotics. Death was attributed to infection when it occurred as a direct consequence of the presenting infection.

**Microbiology.** All bacterial isolates were identified by standard techniques, and their antimicrobial susceptibilities were tested by the Kirby-Bauer method (1). Pathogens were considered susceptible to amikacin if the zone diameter was >17 mm, to ceftazidime if the zone diameter was >18 mm, and to vancomycin and teicoplanin if the zone diameter was >14 mm.

**Statistical evaluation.** Statistical analysis was done at the Gimena Infection Program Data Center (University of Perugia) with the SAS package (SAS Institute, Inc., Cary, N.C.). Results for patients evaluable for the clinical efficacy analysis are presented here. The chi-square test with a correction for continuity or, where appropriate, the Fisher exact test was used to compare differences in proportions between the two groups. The Student unpaired t test was used to compare the means. CIs are given where appropriate.

**RESULTS**

From 1989 to 1991, 635 febrile patients entered into the trial. A total of 108 (17%) were excluded from the analysis (57 in the teicoplanin group and 51 in the vancomycin group) because of doubtful infections, fungal or viral infections, and protocol violation in 33 and 24, 9 and 17, and 15 and 10 patients in the teicoplanin and vancomycin groups, respectively.

Among the 527 evaluable patients, 275 were treated with teicoplanin and 252 were treated with vancomycin. The patients in the treatment groups were similar with regard to sex, age, underlying condition (most had acute leukemia), type of chemotherapy (the majority received induction chemotherapy), and severe neutropenia at the time of entry into the study (Table 1).

Infections were classified as unexplained fevers in 267 (51%) of 527 evaluable patients, clinically documented in 108 (20%) patients and microbiologically documented in 152 (29%) patients. Fevers in 129 patients in the latter group were associated with bacteremia caused by multiple organisms in 14 patients and single organisms in 115 patients. Gram-negative bacteria accounted for 13 (11%) of the episodes and gram-positive bacteria accounted for 102 (89%) of the episodes of single-organism bacteremia.

Overall, successful outcomes were recorded for 216 (78%) of 275 patients who were randomized to teicoplanin and 190 (75%) of 252 patients randomized to vancomycin (difference, 3%; CI, −10 to 4%; P = 0.33). For patients with unexplained fever, improvement was reported for 108 (79%) of 137 treated with teicoplanin and 95 (73%) of 130 patients treated with vancomycin (difference, 6%; CI, −16 to 4%; P = 0.21). The clinically documented infections in 43 (72%) of 60 patients treated with teicoplanin and 31 (65%) of 48 patients treated with vancomycin responded to therapy (difference, 7%; CI, −24 to 10%; P = 0.31). The microbiologically documented infections without bacteremia in 10 (71%) of 14 patients treated with teicoplanin and 7 (78%) of 9 patients treated with vancomycin responded to therapy (difference, −7%; CI, −29 to 42%; P = 0.88). Polymicrobial bacteremia improved in six (75%) of eight patients treated with teicoplanin and five (83%) of six patients treated with vancomycin (difference, −8%; CI, −34 to 50%; P = 0.77). Single gram-negative bacteria responded in three (50%) of six patients treated with teicoplanin and seven (100%) of seven patients treated with vancomycin (difference, −50%; CI, 9 to 90%; P = 0.07); *Pseudomonas aeruginosa* bacteremias in two (40%) of five patients who received teicoplanin and three (100%) of three patients treated with vancomycin responded to therapy (difference, −60%; CI, 17 to 100%; P = 0.17). The distributions of the gram-negative bacteremic isolates were similar in the two groups: *Pseudomonas* species accounted for 10 isolates (5 in the teicoplanin group and 5 in the vancomycin group), while other gram-negative bacilli were found in 1 patient in the teicoplanin group and 2 patients in the vancomycin group.

**Gram-positive bacteremia. (i) Microbiology data.** A total of 102 patients presented with primary, single-agent, gram-positive bacteremia. Of these, 50 were treated with teicoplanin and 52 were randomized to receive vancomycin (Table 2). Most of these infections (65%) were caused by staphylococci. Coagulase-negative staphylococci accounted for 42% of all gram-positive blood isolates, and 51% of these strains were methicillin resistant. *Staphylococcus aureus* accounted for 27% of all gram-positive blood isolates, and 43% of these strains were methicillin resistant. Streptococci represented 21% of gram-positive blood isolates. The distributions of the responsible pathogens were not homogeneous among patients in the two treatment groups because coagulase-negative staphylococci were isolated from 32% of the patients who received teicoplanin and 52% of those treated with vancomycin (difference, −20%; CI, 1 to 38%; P = 0.06), and streptococci were documented in 26% of patients who received teicoplanin and

<table>
<thead>
<tr>
<th>TABLE 1. Patient characteristics</th>
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<tr>
<td>Characteristic</td>
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<tr>
<td>Febrile patients (no.)</td>
</tr>
<tr>
<td>Men:women (no.)</td>
</tr>
<tr>
<td>Mean age (yr [range])</td>
</tr>
<tr>
<td>Acute leukemia (no. [%])</td>
</tr>
<tr>
<td>Bone marrow transplantation (no. [%])</td>
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<tr>
<td>Other hematologic malignancy (no. [%])</td>
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<tr>
<td>Induction chemotherapy (no. [%])</td>
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<td>Protective environment (no. [%])</td>
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<tr>
<td>CVC (no. [%])</td>
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<tr>
<td>Initial neutrophil count (no. [%])</td>
</tr>
<tr>
<td>&lt;100/mm³</td>
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<tr>
<td>100-499/mm³</td>
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<tr>
<td>&gt;500/mm³</td>
</tr>
<tr>
<td>Risk factor (no. [%])</td>
</tr>
<tr>
<td>Mean days (range) of antibiotic therapy</td>
</tr>
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</table>
TABLE 2. Organisms isolated from patients with single gram-positive bacteremias

<table>
<thead>
<tr>
<th>Organism</th>
<th>No. (%) of patients</th>
<th>Teicoplanin</th>
<th>Vancomycin</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulate-negative staphylococci</td>
<td>16 (32)</td>
<td>27 (52)</td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Methicillin-resistant strains</td>
<td>10 (20)</td>
<td>12 (23)</td>
<td></td>
<td>0.8</td>
</tr>
<tr>
<td>S. aureus</td>
<td>15 (30)</td>
<td>13 (25)</td>
<td></td>
<td>0.7</td>
</tr>
<tr>
<td>Methicillin-resistant strains</td>
<td>7 (14)</td>
<td>5 (10)</td>
<td></td>
<td>0.7</td>
</tr>
<tr>
<td>Streptococci</td>
<td>13 (26)</td>
<td>8 (15)</td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>Pneumococci</td>
<td>2 (4)</td>
<td>1 (2)</td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>Enterococci</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>Others</td>
<td>4 (8)</td>
<td>2 (4)</td>
<td></td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>50</strong></td>
<td><strong>52</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

15% of those treated with vancomycin (difference, 11%; CI, -26 to 5%; P = 0.2).

(ii) **Antibiotic susceptibility.** All 102 gram-positive cocci which were isolated from blood proved to be susceptible to both glycopeptides, whereas 46% of these were resistant to ceftazidime and 35% were resistant to amikacin. In particular, 48% of coagulate-negative staphylococci proved to be resistant to ceftazidime and 29% were resistant to amikacin; 50% of the S. aureus isolates were shown to be resistant to ceftazidime and 46% were resistant to amikacin. Forty-one percent of the streptococci were resistant to ceftazidime and 29% were resistant to amikacin. Because of this susceptibility pattern, glycopeptide antibiotics were the only antibiotics administered that were active against the infecting strain in vitro for 23% of all gram-positive bacteremias.

(iii) **Response to therapy.** The overall response of gram-positive bacteremias to therapy were similar in the two treatment groups; 92% of patients treated with teicoplanin and 87% of those treated with vancomycin improved (difference, 5%; CI, -17 to 6%; P = 0.22). No difference in response to therapy was found between the two treatment groups with respect to different blood isolates (Table 3). CVC-related gram-positive bacteremias were documented in 11 patients in the teicoplanin group and 27 patients in the vancomycin group; improvements without catheter removal were obtained in 10 (91%) and 22 (81%) patients, respectively (difference, 10%; CI, -13 to 31%; P = 0.81). All 11 patients who failed therapy (4 in the teicoplanin group and 7 in the vancomycin group) had persisting staphylococcal bacteremias mainly caused by coagulase-negative strains (3 in the teicoplanin group and 5 in the vancomycin group); many of these bacteremias were CVC related (1 of 4 in the teicoplanin group and 5 of 7 in the vancomycin group) and required catheter removal. Gram-positive infections caused the deaths of three patients in each treatment group, among the patients who received teicoplanin, the deaths were represented by one bacteremia and one CVC-related infection caused by coagulate-negative staphylococci and one bacteremia caused by S. aureus, and among vancomycin-treated patients the deaths were represented by two bacteremias and one CVC-related infection caused by S. aureus. One death occurred among the patients with gram-positive bacteremia when the glycopeptide was the only antibiotic administered that was active against the infecting strain in vitro; this patient, who received teicoplanin, was affected by bacteremia caused by methicillin-resistant S. aureus.

**Antibiotic-related toxicity.** Side effects occurred in 9 (3.2%) of 275 patients treated with teicoplanin and 20 (8%) of 252 patients treated with vancomycin (difference, -4.8%; CI, 0.7 to 8%; P = 0.03). Skin rash occurred in 4 (1.4%) of 275 patients who received teicoplanin and 15 (6%) of 252 patients treated with vancomycin (difference, -4.6%; CI, 1 to 7%; P < 0.01). No significant difference was shown between the two groups with respect to the occurrence of nephrotoxicity; a reversible rise in the serum creatinine level above the normal range was documented in four (1.4%) patients treated with teicoplanin and two (0.8%) patients who received vancomycin (difference, 0.6%; CI, -2 to 1%; P = 0.68). One case of transient hearing loss was documented in each treatment group; one case of fever and one case of hypotension were reported in vancomycin-treated patients (Table 4).

**Empirical use of intravenous amphotericin B.** Empirical intravenous amphotericin B was added to the initial antibiotic regimen for 27% of the patients in each treatment group: 74 of 275 patients treated with teicoplanin and 68 of 252 patients treated with vancomycin.

**Further infections.** Overall, further infections were documented in 37 (14%) of 275 patients who received teicoplanin and 29 (12%) of 252 patients treated with vancomycin (difference, 2%; CI, -3.6 to 7.5%; P = 0.58). Among the superinfections, which occurred in 5 (1.8%) patients treated with teicoplanin and 2 (0.8%) of those who received vancomycin (difference, 1%; CI, -2 to 0.9%; P = 0.45), no case of gram-positive infection was documented. Subsequent infections occurred in 32 (12%) teicoplanin-treated patients and 27 (11%) vancomycin-treated patients (difference, 1%; CI, -6 to 4%; P = 0.67), and in only 3 patients was a gram-positive etiology documented; in teicoplanin-treated patients they were represented by two infections caused by coagulase-negative staphylococci, one with bacteremia, and in vancomycin-treated patients they were represented by a urinary tract infection caused by enterococci.

**Mortality.** Deaths occurred in 23 (8.5%) of 275 teicoplanin-treated patients and 27 (11%) of 252 vancomycin-treated patients (difference, -2.5%; CI, -2 to 7%; P = 0.43). Death
from infection occurred in 15 (5.5%) patients who received teicoplanin and 17 (7%) patients treated with vancomycin (difference, −1.5%; CI, −5.3 to 2.8%; \( P = 0.66 \)).

**DISCUSSION**

Our study documented a growing rate of bacteremia caused by gram-positive cocci with poor antibiotic susceptibility, confirming the data reported from many centers and clinical trials. Gram-positive bacteremias represented 89% of all single-agent bacteremias, a figure higher than the 64% observed in our previous trial (9); coagulase-negative staphylococci remain the most frequently isolated organisms from blood, but a resurgence in the proportion of \( S.\) aureus was noted, rising from 8% in the previous trial to 27% in the present study. The concurrent increase in the rate of resistance of \( S.\) aureus to prophylactic ciprofloxacin from the previous 31% to the present 68% might explain this phenomenon at least in part. The decrease in the proportion of streptococcal bacteremias from 41% in the previous trial to the present 21% is difficult to explain and does not seem to be related only to the decrease in oral cavity infections from 9.4% in the previous trial to 6.7% in the present trial.

The efficacy of teicoplanin in combined, empirical antibiotic therapy in febrile, neutropenic patients was reported previously (4, 18), but a randomized, prospective comparison with vancomycin, the "gold standard" for glycopeptide antibiotic therapy, has not been performed. Our study clearly shows that teicoplanin is at least as efficacious as vancomycin for the combined, empirical antibiotic therapy for febrile, neutropenic patients with hematologic malignancies. The failure of teicoplanin monotherapy in treating some cases of staphylococcal bacteremias has been reported, raising some concern about its efficacy (2, 3, 6, 8); however, in our study the response of gram-positive bacteremias to the teicoplanin-containing regimen was excellent and similar to that for regimens that included vancomycin; the few patients who failed therapy with both drug regimens had persisting, CVC-related, coagulase-negative staphylococcal bacteremias which were cured only after removal of the catheter.

The differences in the responses of gram-negative bacteremias to the two drug regimens was related to the different responses of \( P.\) aeruginosa bacteremias; this could have been due to the poor susceptibilities to amikacin and ceftazidime of the \( P.\) aeruginosa strains isolated from patients treated with teicoplanin; among five strains, three were resistant to amikacin and four were resistant to ceftazidime. The three patients with \( P.\) aeruginosa bacteremias who failed to respond to teicoplanin received no antibiotic that was active in vitro against the infecting pathogen.

Unexpectedly, in our trial there was no difference in the nephrotoxicities between the two drug regimens. Our data do not confirm either the higher rate of nephrotoxicity (6%) attributable to vancomycin previously reported in neutropenic patients receiving an empirical antibiotic regimen (5) or the less nephrotoxic potential suggested for teicoplanin when both glycopeptide antibiotics were combined with tobramycin and piperacillin in neutropenic patients (13). However, it is worthy of note that in the small study by Kureishi et al. (13) teicoplanin was less nephrotoxic than vancomycin, especially in the subgroup of patients who concurrently received cyclosporin A; this was not the case for our patients. The very low rate of nephrotoxicity documented in our patients might be related to inadequate concentrations of aminoglycosides in serum, because an assay of serum for the recommended peak and trough levels was not routinely performed.

A significantly greater incidence of skin rashes occurred in patients who received the vancomycin regimen. However, the skin reactions noted in our neutropenic patients cannot be definitely attributed to the glycopeptide in the combination antibiotic therapy, nor can it be strictly classified as the red-man syndrome.

In our trial, precise guidelines about the time for starting intravenous amphotericin B therapy were given, removing an important variable which may influence this particular outcome measure. The low rate of empirical use of intravenous amphotericin B observed in our patients (27% in each treatment group) compared favorably with other series and seems to confirm the data suggesting that the initial use of a glycopeptide antibiotic reduces the need for empirical amphotericin B therapy (12).

Overall, further infections occurred in 14% of patients who received teicoplanin and 12% of those treated with vancomycin, a figure similar to the 13% rate recently reported for neutropenic patients empirically treated with regimens that do not include a glycopeptide antibiotic (11). However, it is noteworthy that a gram-positive etiology was documented in only 3 (5%) of 66 of our patients with further infections but compared 33 (35%) of 93 in patients who received an initial empirical regimen that did not include a glycopeptide antibiotic (11).

In the last decade, gram-positive bacteria have become the predominant causes of bacteremia in neutropenic patients with hematologic malignancies. Our study shows that, in a setting of a high incidence of staphylococcal infections caused by strains frequently resistant to methicillin, empiric antibiotic regimens that initially include teicoplanin or vancomycin are equally effective for the treatment of febrile episodes in neutropenic patients, especially those with gram-positive bacteremia.

Teicoplanin may be considered a valuable alternative to vancomycin because it is as efficacious as vancomycin, can be administered once daily, and has fewer side effects.

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