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Prospective Randomized Clinical Trial of Teicoplanin for Empiric Combined Antibiotic Therapy in Febrile, Granulocytopenic Acute Leukemia Patients

ALBANO DEL FAVERO,[1]* FRANCESCO MENICHETTI,[2] ROBERTO GUERCIOLINI,[1] GIAMPAOLO BUCANEVE,[1] FRANCO BALDELLI,[2] FRANCO AVERSA,[1] ADELMO TERENZI,[1] STEPHEN DAVIS,[1] AND SERGIO PAULUZZI[2]

Institutes of First Internal Medicine[1] and Infectious Diseases,[2] University of Perugia, 06100 Perugia, Italy

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The increasing prevalence of bacteremia caused by gram-positive bacteria in granulocytopenic acute leukemia patients prompted us to evaluate, in a prospective randomized trial, the role of teicoplanin, a new glycopeptide antibiotic, when it was added to amikacin plus ceftazidime, as an empiric therapy of fever in these patients. Of 47 evaluable episodes, 22 were treated with the teicoplanin regimen and 25 were treated with the combination of amikacin and ceftazidime. The overall response to therapy of patients treated with teicoplanin was slightly better (82% improvement) than that obtained with amikacin plus ceftazidime (52%). The response rate of patients with gram-positive bacteremias was 80% (4 of 5) to the regimen that included teicoplanin; 25% (1 of 4) of the patients treated with amikacin plus ceftazidime responded to treatment; and for patients with gram-negative bacteremias, the response rates were, respectively, 100% (4 of 4) and 70% (7 of 10). The better results obtained with amikacin-ceftazidime-teicoplanin treatment were most evident in patients with profound (<100/mm^3) and persistent neutropenia (83 versus 30% improvement). Furthermore, a good response rate of patients with gram-positive bacteremias (seven of eight; 87% improvement) was achieved in a small group of bone marrow transplant patients who were all treated with amikacin-ceftazidime-teicoplanin. No severe side effects were documented in any patient. Teicoplanin, as a drug administered as a single daily dose, seems to be a safe and useful anti-gram-positive agent when used in combination with amikacin-ceftazidime as an empiric therapy of febrile episodes in granulocytopenic acute leukemia patients.

Changes in the relative prevalence of bacterial pathogens among granulocytopenic cancer patients have been observed in many centers and in numerous large clinical trials. Not only has the frequency of gram-positive bacteremias increased in recent years, but the clinical and microbiological picture of gram-positive infections has changed as well (6, 8, 10, 12). The mortality rate for these infections has increased (6), and many staphylococcal strains have become resistant to beta-lactam antibiotics and the aminoglycosides. Therefore, the antimicrobial regimens designed for empiric therapy in granulocytopenic patients, such as the combination of a beta-lactam and an aminoglycoside (2), do not satisfactorily cover the spectrum of gram-positive infections, especially those caused by methicillin-resistant strains of staphylococci or enterococci.

A rational choice would be the addition of vancomycin or a similar drug to these regimens. Teicoplanin is a new glycopeptide antibiotic, chemically related to vancomycin (9). It is active against aerobic and anaerobic gram-positive bacteria only, including methicillin-resistant staphylococci, group D streptococci, *Clostridium difficile*, and group JK corynebacteria. Teicoplanin, therefore, has the same antibacterial spectrum that vancomycin has, with the added advantage of a long half-life, allowing once-a-day administration (1, 4; S. Pauluzzi, A. Del Favero, F. Menichetti, E. Baratta, M. V. Moretti, P. Di Filippo, M. B. Pasticci, R. Guerciolini, R. F. Frongillo, and L. Patoia, J. Antimicrob. Chemother., in press).

* Corresponding author.

The aim of this study was to evaluate the comparative efficacy and safety of a standard empiric antibiotic treatment (amikacin plus ceftazidime) with or without teicoplanin in granulocytopenic, febrile acute leukemia patients.

MATERIALS AND METHODS

Consecutive patients with acute leukemia admitted to the First Internal Medicine Institute of Perugia General Hospital were eligible for this study if they had an absolute granulocyte count below 1,000/mm^3 and an axillary temperature of 38°C or more in the absence of obvious noninfective causes of fever. Patients who had a history of an allergy to any of the three classes of antibiotics used or who in the previous 5 days had received systemic antibiotics were excluded from the study prior to randomization. Also excluded were patients having a creatinine level in serum above 2 mg/100 ml.

Random grouping of patients was achieved by using consecutive sealed envelopes assigning patients to regimens of either amikacin plus ceftazidime or these two drugs plus teicoplanin as determined by random permuted blocks. Amikacin was given at the dosage of 15 mg/kg per day divided in three equal doses (maximum daily dose, 1 g), which were subsequently adjusted to maintain optimal peak (15 to 25 mg/liter) and trough (<5 mg/liter) levels in serum (Abbott-TDX). Ceftazidime was given at the dosage of 90 mg/kg per day divided in three equal doses (maximum daily dose, 6 g). Each antibiotic was dissolved in 100 ml of 0.9% saline and administered intravenously over 15 to 30 min. Teicoplanin was given at the dosage of 5 mg/kg per day in a single daily dose (maximum daily dose, 400 mg) dissolved in

TABLE 1. Patient characteristics

Characteristic	Value for group on drug regimen[a]	
	AK/CAZ/TEICO	AK/CAZ
Febrile episodes (no. of patients)	33 (27)	33 (27)
Mean age (range) (yr)	39 (8–66)	39 (8–71)
Males/females (no.)	24/9	23/10
Pretherapy granulocyte count (per mm^3)		
<100	21	19
100–499	6	8
500–1,000	6	6
Mean duration of therapy (range) (days)	10 (1–31)	7 (2–18)

[a] AK, Amikacin; CAZ, ceftazidime; TEICO, teicoplanin.

10 ml of sterile water and administered intravenously in 3 min, with an initial loading dose of 8 mg/kg (maximum initial dose, 600 mg).

All bacterial isolates were identified by standard techniques, and antimicrobial susceptibility was tested by the Kirby-Bauer method. Pathogens were considered susceptible to teicoplanin if the zone diameter was 13 mm.

Blood cell counts and differential leukocyte counts, determinations of electrolytes and creatinine in serum, blood cultures, and culture specimens from infection sites were obtained every 3 days during the study and within 72 h after discontinuation of the drugs studied.

Febrile episodes were classified according to the definitions of the European Organization for Research on Treatment of Cancer (3). Response to therapy was evaluated 72 to 96 h after the beginning of empiric treatment, when the antimicrobial susceptibility data were generally available, and was classified as previously indicated (11). One or more of the investigators examined all protocol patients daily. Patients who responded to therapy remained on the study drugs for at least 5 days after all signs of infection had disappeared; a change in therapy was taken into consideration 72 to 96 h after randomization in patients evaluated as nonresponsive to the treatment. Teicoplanin was stopped in patients with documented bacteremia caused by gram-negative bacilli.

Antibiotic-related nephrotoxicity was defined as an increase in the creatinine level in serum of more than 0.4 mg/100 ml from normal base line when other causes of nephrotoxicity (hypotension or another nephrotoxic drug) were excluded. Besides clinical evaluation, no audiometric studies were performed for ototoxicity evaluation.

The Yates corrected chi-square test was used for comparing significant differences in proportion.

RESULTS

Over a 14-month period, 66 febrile episodes (54 patients) were randomly assigned to regimens as follows: 33 to the amikacin-ceftazidime-teicoplanin regimen and 33 to the amikacin-ceftazidime regimen. Patient characteristics are illustrated in Table 1 and are equally distributed in both groups.

Of all febrile episodes, 71% (47 of 66) were considered evaluable for analysis. Reasons for exclusion from analysis were as follows (amikacin-ceftazidime-teicoplanin/amikacin-ceftazidime groups): doubtful infections (7/7), nonbacterial infections (2/0), protocol violation (1/1), and length of therapy <24 h (1/0).

The results of treatment are shown in Table 2. The overall response achieved with the regimen that included teicoplanin was good (82%; 18 of 22 showed improvement) and better than that found with the amikacin-ceftazidime regimen (56%; 14 of 25 showed improvement), although this difference is not statistically significant ($P = 0.1$). The improvement rates in microbiologically documented infection were 92% (11 of 12) in patients treated with the regimen that included teicoplanin and 60% (9 of 15) in patients treated with amikacin-ceftazidime. The types and sensitivities of isolated pathogens were similar in the two groups.

The response rate of patients with gram-positive bacteremias was higher to the teicoplanin regimen (4 of 5 versus 1 of 4), but equal benefit for gram-negative bacteremias was found (4 of 4 versus 7 of 10) (Table 3). The observed better response in patients treated with teicoplanin was most evident in those with profound (<100/mm^3) and persistent neutropenia (83 versus 30%) (Table 4). In this group of patients, both patients who had gram-positive bacteremias and the single patient with gram-negative bacteremia improved with the teicoplanin regimen, whereas in the group treated with only two drugs, both patients with gram-positive bacteremias and two of the three patients with gram-negative bacteremias failed to respond to treatment.

An analysis of treatment failures among patients with gram-positive infections showed that in the group of patients treated with amikacin-ceftazidime, two of three bacteremic patients (one with enterococci and one with *Staphylococcus aureus*) whose treatment failed were treated by adding teicoplanin, and one of these (bacteremia caused by enterococci) was cured. In the teicoplanin-treated group, one patient with bacteremia caused by *S. aureus* and associated pneumonia failed to respond to treatment; the *S. aureus* bacteremia was cleared, but the clinical response was judged as a failure owing to the progression of pneumonia, causing the death of this patient despite 2 weeks of amphotericin B treatment.

Further evidence of the good rate of improvement obtained by the combination of teicoplanin with amikacin and ceftazidime in gram-positive bacteremias is supplied by the results obtained in patients undergoing allogenic bone marrow transplantation. We treated 20 febrile episodes in 14 patients (mean age, 28 years) with this regimen. All were treated with selective decontamination with norfloxacin (400 mg twice a day) in laminar airflow rooms, and all received total parenteral nutrition through a Hickman-Broviac central venous catheter (CVC). The initial neutrophil count was <100/mm^3 in 18 of 20 episodes. Nine bacteremic infections were documented, and eight were caused by gram-positive cocci (methicillin-susceptible *S. aureus*, four; *Staphylococcus epidermidis*, one; enterococci, two; viridans group streptococci, one). All were considered CVC related. Cure was achieved in seven of eight gram-positive bacteremias, and only one patient (with an *S. aureus* tunnel infection)

TABLE 2. Overall response to therapy

Improvement	No. of improved patients/total (%) with drug regimen[a]	
	AK/CAZ/TEICO	AK/CAZ
Microbiologically documented		
With bacteremia	8/9 (88)	8/14 (57)
Without bacteremia	3/3 (100)	1/1 (100)
Clinically documented	4/4 (100)	3/6 (50)
Possible	3/6 (50)	2/4 (50)
Total response	18/22 (82)	14/25 (56)

[a] AK, Amikacin; CAZ, ceftazidime; TEICO, teicoplanin.

TABLE 3. Pathogens and response to therapy

Pathogen	No. of improved patients/total (%) with drug regimen[a]			
	AK/CAZ/TEICO		AK/CAZ	
	Total patients	Patients with bacteremia	Total patients	Patients with bacteremia
Gram-positive organisms				
Staphylococcus aureus	3/4	3/4	1/2	0/1
Viridans group streptococci	1/1	1/1	1/2[b]	1/2[b]
Enterococci			0/1	0/1
Total	4/5 (80)	4/5 (80)	2/5 (40)	1/4 (25)
Gram-negative bacilli				
Escherichia coli	4/4	3/3	5/6	5/6
Pseudomonas aeruginosa	1/1	1/1	1/2	1/2
Klebsiella sp.	2/2		1/2	1/2
Total	7/7 (100)	4/4 (100)	7/10 (70)	7/10 (70)
Grand total	11/12 (92)	8/9 (89)	9/15 (60)	8/14 (57)

[a] AK, Amikacin; CAZ, ceftazidime; TEICO, teicoplanin.
[b] One patient with bacteremia caused by viridans group streptococci and a *Bacillus* sp. failed to respond to treatment; one patient with bacteremia caused by viridans group streptococci and *Pseudomonas aeruginosa* showed improvement.

required CVC removal. The only treatment failure was represented by a patient with a bacteremia caused by enterococci. In this patient, the bacteremia was cleared, but owing to the persistence of fever, antibiotic therapy was changed.

Side effects were minor and did not require the interruption of treatment in any patient. In patients treated with three drugs versus those treated with two drugs, hypokalemia (six versus three) and drug fever (zero versus one) were the only side effects observed. In particular, no "red man" syndrome and no clinical evidence of ototoxicity or nephrotoxicity were documented, and no differences in evolution of neutropenia were found between the two groups. Severe hypocalcemia was observed in one patient treated for 2 weeks concomitantly with teicoplanin-amikacin-ceftazidime and amphotericin B.

DISCUSSION

Our study shows that the empiric treatment of febrile episodes in granulocytopenic acute leukemia patients by a three-drug combination that included the new glycopeptide antibiotic teicoplanin is characterized by a very high success rate (82% overall improvement). These results tend to be better than those obtained with the standard two-drug combination (56% overall improvement), although this difference is not statistically significant owing to the small number of patients enrolled in the study.

TABLE 4. Evolution of granulocytopenia and response to therapy

No. of neutrophils/mm^3 before/after treatment	No. of improved patients/total (%) with drug regimen[a]	
	AK/CAZ/TEICO	AK/CAZ
<100/<100	5/6 (83)	3/10 (30)
<100/>100	6/6 (100)	4/5 (80)
>100/>100	5/7 (71)	7/9 (78)
>100/<100	2/3 (67)	0/1 (0)
Total	18/22 (82)	14/25 (56)

[a] AK, Amikacin; CAZ, ceftazidime; TEICO, teicoplanin.

The higher response rate of the regimen that included teicoplanin was most evident in the treatment of infections caused by gram-positive organisms. The cure rates of gram-positive bacteremias were in fact 80% (four of five) in teicoplanin-treated patients but only 25% (one of four) in patients treated with amikacin-ceftazidime. On the other hand, the response rate of patients with bacteremias caused by gram-negative bacilli was as good with the three-drug treatment (4 of 4) as it was with the two-drug treatment (7 of 10). This slightly greater response rate, even for patients with gram-negative bacteremias, achieved by the regimen that included teicoplanin cannot be owing to the direct effect of teicoplanin on gram-negative bacilli but is probably casual, owing to the smaller number of patients with gram-negative bacteremias included in the teicoplanin-treated group (4 versus 10).

The good results obtained in the three-drug treatment of gram-positive bacteremias in the acute leukemia patients are confirmed by our experience in bone marrow transplant patients: seven of eight gram-positive, CVC-related bacteremias were cleared and only one required catheter removal.

It is also noteworthy that the patients showing the greatest advantage from the regimen that included teicoplanin were those with profound (<100/mm^3) and persistent neutropenia (83% improvement versus 30% for the patients treated with only two drugs).

Tolerance of the teicoplanin regimen was also very good. Side effects of the three-drug regimen were minor and comparable to those found with the two drugs. It should be noted, however, that no formal evaluation of ototoxicity was carried out. No difference in evolution of neutropenia between the two groups was found, and this is important in view of those rare cases of reversible leucopenia probably related to teicoplanin that have been reported (G. Buniva, data on file at Lepetit-Merrel Dow, Milan, Italy). Recent data (5, 7) suggest the advantage of using a triple-drug combination including an antistaphylococcal drug in the treatment of gram-positive bacteremias in acute leukemia patients. Our results show that

teicoplanin can be successfully used in combination with amikacin and ceftazidime in these patients.

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