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Double-Blind Comparison of Teicoplanin versus Vancomycin in Febrile Neutropenic Patients Receiving Concomitant Tobramycin and Piperacillin: Effect on Cyclosporin A-Associated Nephrotoxicity

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A prospective, randomized, and double-blind study comparing teicoplanin with vancomycin in the initial management of febrile neutropenic patients was conducted. Teicoplanin was administered at 6 mg per kg of body weight every 24 h (q24h) intravenously (i.v.) after initial loading at 6 mg/kg q12h for three doses. Vancomycin was administered at 15 mg/kg q12h i.v. Patients also received piperacillin (3 g q4h i.v.) and tobramycin (1.5 to 2.0 mg/kg q8h i.v.). Of 53 patients enrolled, 50 were judged to be evaluable. Among these, 25 received teicoplanin and 25 received vancomycin. At enrollment, both groups were comparable in age, sex, renal function, underlying hematologic condition, and concurrent therapy. Both groups had similar sites of infection and microbial pathogens. Empirical antimicrobial therapy resulted in the cure of or improvement in 23 (92%) teicoplanin patients and 21 (84%) vancomycin patients ($P = 0.67$). Failures occurred with two vancomycin patients but no teicoplanin patients. Clinical response was indeterminate for two patients in each group. Adverse reactions occurred significantly more often in the vancomycin group than in the teicoplanin group ($P = 0.01$), and these reactions required the termination of the study regimens of 6 vancomycin versus 0 teicoplanin patients ($P = 0.02$). Nephrotoxicity was observed more frequently in the vancomycin group (10 versus 2 patients; $P = 0.02$). Subgroup analysis revealed a significant deterioration of renal function when vancomycin and cyclosporin A, but not teicoplanin and cyclosporin A, were used concurrently ($P = 0.02$). Among patients who received vancomycin and amphotericin B or teicoplanin and amphotericin B concurrently, deterioration in renal function was equivalent in both groups. Teicoplanin in the dosage employed was tolerated better than vancomycin in the empirical treatment of fever and neutropenia in our patient population.

The initiation of use of broad-spectrum antibiotics as empirical therapy has significantly improved the outcomes of treatment of febrile neutropenic patients (27, 30). In recent years, there has been an increased frequency of infections caused by gram-positive organisms, a trend that has paralleled the increased use of Hickman catheters and bowel decontamination regimens (19, 22, 28, 29). Consequently, vancomycin is frequently included in the empirical antimicrobial regimens of this patient population.

Teicoplanin is a glycopeptide antibiotic with a mode of action and a spectrum of activity similar to those of vancomycin (2, 5, 11, 24). Like vancomycin, it is active against most gram-positive organisms (18, 20–22, 32), but it offers several potential advantages over vancomycin, including low toxicity, better tolerance after intravenous (i.v.) or intramuscular administration, and a longer elimination half-life (up to 15 times that of vancomycin) (2, 5, 16, 26). However, teicoplanin is highly protein bound (>90%), and drug resistance appears to develop more readily with it than with vancomycin (1, 3, 4, 6, 10). We conducted a double-blind, randomized, prospective study to compare the tolerances and efficacies of teicoplanin and vancomycin when each was used in combination with piperacillin and tobramycin in the empirical treatment of febrile neutropenic patients. This is the first double-blind comparison of the effects of teicoplanin and vancomycin in febrile neutropenic patients to be reported.

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MATERIALS AND METHODS

Patient selection. Patients were hospitalized in the Acute Leukemia and Bone Marrow Transplant Unit at the Vancouver General Hospital, Vancouver, British Columbia, Canada. The inclusion criteria for patients were that they be 18 years of age or older and that neutropenia and fever were anticipated as results of cytotoxic chemotherapy. Patients who had received antibiotics in the prior 72 h, with a serum creatinine concentration exceeding 220 mmol/liter (2.5 mg/dl), or who had a history of hypersensitivity to penicillins, aminoglycosides, or glycopeptides were excluded from the study. The study protocol was approved by the appropriate institutional ethics committees, and informed consent was obtained from each patient prior to enrollment.

Study design. Eligible patients were randomized by a computer-generated schedule to receive either teicoplanin or vancomycin. Vancomycin was administered at a dosage of 15 mg per kg of body weight every 12 h (q12h) i.v. Teicoplanin was administered with a loading dosage of 6 mg/kg q12h i.v. for three doses, followed by a maintenance dosage of 6 mg/kg q24h. A placebo dosage of 5% glucose was interposed q24h with teicoplanin to maintain blinding. Each

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of these doses was infused over 1 h. Serum teicoplanin and vancomycin levels were monitored daily for the first 3 days prior to and at 1 and 3 h after the end of infusion, and they then were monitored every 3 to 7 days thereafter. Serum drug levels were determined by a *Bacillus subtilis* bioassay as described previously by us (16) and were adjusted by an unblinded investigator (P.J.J.) to maintain 1-h peak concentrations of 30 to 50 mg/liter and trough concentrations of 5 to 15 mg/liter for both teicoplanin and vancomycin. The vancomycin values obtained by this bioassay were determined to be approximately 20% higher than those obtained by the corresponding fluorescence polarization immunoassay method (TDX; Abbott Laboratories, North Chicago, Ill.) (16). In addition, each patient received piperacillin (3 g q4h i.v.) and tobramycin (1.5 to 2.0 mg/kg q8h i.v.) adjusted to maintain peak serum tobramycin concentrations (C_{max}) at between 5 and 10 mg/liter and trough serum tobramycin concentrations (C_{min}) at ≤2 mg/liter. Patients requiring antifungal therapy received amphotericin B (0.5 to 1 mg/kg i.v. per day).

Definitions and evaluations of response. Empirical triple-antibiotic therapy was initiated if the patient was neutropenic and febrile with an oral temperature of 38°C or higher or if infection was suspected on clinical grounds (i.e., hemodynamic changes, cellulitis, and Hickman line site induration, etc.). Neutropenia was defined as an absolute granulocyte count of <500/μl. All patients were assessed daily while on the study regimens for signs and symptoms of infection and adverse drug reactions. Blood, urine, and other appropriate specimens were obtained for culture prior to the initiation of antibiotic therapy and for 3 to 7 days thereafter while fever or other signs of infection persisted. All gram-positive aerobic isolates were tested by the Kirby-Bauer disk diffusion method to determine their in vitro susceptibilities to both vancomycin and teicoplanin. Daily hemograms, serum electrolyte measurements, and serum creatinine level determinations were obtained while the patients remained on the study regimens. Nephrotoxicity was defined as a rise in serum creatinine concentration from the normal range to >110 mmol/liter (1.1 mg/dl) for males and to >90 mmol/liter (1.0 mg/dl) for females. Creatinine clearance, estimated from the age and weight of the patient and from serum creatinine levels, was determined by the method of Cockcroft and Gault (7). The teicoplanin and vancomycin groups were also compared with respect to the percent change in estimated creatinine clearance during therapy (i.e., creatinine clearance at enrollment minus the lowest creatinine clearance while on the study regimen). The regimen was modified on the basis of culture results, clinical responses, and putative adverse effects. Antibiotics were continued until neutropenia was resolved and the patient had been free of signs and symptoms of infection for 5 days.

Responses to antibiotics were categorized as follows: "cured" if the patient had had a microbiologically or clinically documented infection that resolved while the patient was on the study regimen; "improved" if within 48 h of therapy, the patient's oral temperature decreased below 38°C, the patient was hemodynamically stable, and any other symptoms for which antibiotics had been started had partially resolved; "failure" if no improvement occurred; and "indeterminate" if there was no improvement but the causative agent (e.g., fungal, viral, or underlying disease) would not be expected to respond to the regimen. "Superinfection" was defined as infection with new organisms which emerged during the study regimen, and "colonization" was defined as the isolation of an organism during the study regimen in the absence of clinical signs and symptoms of infection. Investigators (A.K., M.R., and A.W.C.) assessed the clinical response and adverse effects in each patient while blinded to the specific antimicrobial regimen received.

Statistical analysis. The significance of difference arising between the two study groups was assessed by the two-tailed Wilcoxon rank sum test for continuous variables and by Fisher's exact and Yates' corrected chi-square tests for discrete variables.

RESULTS

Fifty-three patients, of whom 50 were evaluable, were enrolled in the study. Among these, 25 received teicoplanin and 25 received vancomycin. The three remaining patients were inevaluable because of premature discontinuation of study drugs 24 h after initiation of therapy. One patient from each group received teicoplanin or vancomycin in the absence of piperacillin and tobramycin for what were assessed to be localized infections caused by gram-positive organisms (cellulitis and Hickman line infection, respectively). Both treatments were judged to be cures, and no adverse effect was noted. One patient in the vancomycin group became febrile but did not become neutropenic. Efficacy was judged to be indeterminate for this patient. All three patients were felt to be evaluable for drug tolerance and were included in this analysis.

Patients evaluated were comparable in age, sex, underlying hematological condition, baseline renal function, and concurrent therapy (Table 1). All 50 patients had Hickman catheters in place. Steady-state levels in serum (mean ± standard deviation [SD]) at 1 and 3 h postinfusion and trough levels in serum were 42 ± 15, 22 ± 5, and 12 ± 3 mg/liter, respectively, for teicoplanin and were 37 ± 15, 20 ± 8, and 8 ± 4 mg/liter, respectively, for vancomycin. The pharmacokinetic data from this study have been fully described elsewhere (16). Mean (±SD) tobramycin levels (mg/liter) at steady state were comparable in both groups, with a C_{max} level of 6.7 ± 1.4 and a C_{min} level of 0.9 ± 0.4 for patients in the teicoplanin group and a C_{max} level of 7.0 ± 1.4 and a C_{min} level of 1.1 ± 0.5 for patients in the vancomycin group.

Treatment was successful in 23 (92%) teicoplanin patients, with 14 cures and 9 improvements, and in 21 (84%) vancomycin patients, with 12 cures and 9 improvements ($P = 0.67$) (Table 2). There were no failures in the teicoplanin group and two failures in the vancomycin group. One of them had clinically suspected sinusitis but died with pneumonia, and the postmortem lung culture grew vancomycin-susceptible *Streptococcus faecalis*; the other had extensive oral mucositis with no other identified site of infection, and all cultures were negative. Two patients in each group were considered to have indeterminate responses. One such patient in the teicoplanin group had rotavirus infection as well as *Clostridium difficile* colitis prior to antibiotic therapy; the other had extensive oral mucositis but died with unremitting acute myelogenous leukemia. Among the two patients in the vancomycin group, one presented with pneumonia, but open lung biopsy revealed bronchiolitis obliterans without specific microbial etiology; the other had extensive oral mucositis but died with severe graft-versus-host disease and multiple organ failure. The sites of infection in the two patient groups and their clinical responses to therapy are summarized in Table 3. In none of the six Hickman catheter-associated infections was removal of the device necessary. Among patients with microbiologically documented infections (13 in the teicoplanin group and 9 in the vancomycin group), the

TABLE 1. Demographic characteristics of patients with fever and neutropenia

Characteristic	Value for group	
	Teicoplanin (n = 25)	Vancomycin (n = 25)
Age (yr)		
Median	40	38
Range	19–68	20–76
Male/female	11/14	15/10
Diagnosis[a]		
AML/ALL	14	14
CML	10	8
Other	1	3
BMT[b]		
Allogeneic	13	11
Autologous/syngeneic	3	1
None	9	13
Baseline renal function (mean ± SD)		
Serum creatinine (mmol/liter)	70 ± 15	76 ± 18
Estimated creatinine clearance (ml/min/70 kg)	123 ± 31	117 ± 32
Concurrent cytotoxic therapy		
Ara-C	16	16
Cyclophosphamide	15	13
Cyclosporin A	13	10
Methotrexate	11	10
Etoposide (VP-16-213)	11	9
Mesna	6	1
Busulfan	9	8
Methylprednisolone sodium succinate	5	11
Daunorubicin	4	9
Hydroxyurea	4	4
Other adjunctive therapy		
Acyclovir	20	19
Amphotericin B	17	12
Allopurinol	16	17
Furosemide	4	1

[a] AML, acute myelogenous leukemia; ALL, acute lymphocytic leukemia; CML, chronic myelogenous leukemia.
[b] BMT, bone marrow transplant.

initial organisms isolated and the responses to treatment were similar in the two groups. Polymicrobial infections occurred in three teicoplanin and five vancomycin patients. There were seven episodes of infections caused by gram-positive organisms (two staphylococcus, one streptococcus, one enterococcus, and three *C. difficile*) in the teicoplanin group, of which three were associated with bacteremia (two coagulase-negative staphylococcus and one viridans group streptococcus). In the vancomycin group, there were eight episodes of infections caused by gram-positive organisms (two staphylococcus, four streptococcus, three enterococcus, and one *C. difficile*), of which five were associated with bacteremia (one *Staphylococcus aureus*, one coagulase-negative staphylococcus, and four viridans group streptococcus) (some infections were caused by multiple organisms). No gram-positive organism resistant to either teicoplanin or vancomycin was encountered. All infections caused by gram-positive organisms resulted in cures except for those of one patient in the teicoplanin group with *C. difficile* and rotavirus infections who had an indeterminate response (described above). There were six episodes of infections caused by gram-negative organisms in the teicoplanin group (three *Escherichia coli*, one *Klebsiella pneumoniae*, one mixed coliform, and one mixed anaerobe), of which one was associated with bacteremia (*E. coli*). In the vancomycin group, there were four episodes of infections caused by gram-negative organisms (two *E. coli*, two *K. pneumoniae*, and one *Moraxella catarrhalis*), of which three were associated with bacteremia (one *E. coli*, two *K. pneumoniae*, and one *M. catarrhalis*). All of these infections were cured by the study regimens.

Adverse reactions occurred significantly more often in the group receiving vancomycin than in the group receiving teicoplanin (11 of 25 versus 2 of 25, respectively; $P = 0.01$) and required discontinuation of the study regimens for 10 patients in the vancomycin group and 2 patients in the teicoplanin group ($P = 0.02$) (Table 4). Nephrotoxicity (as defined in Materials and Methods) was observed in 6 patients in the vancomycin group and 0 patients in the teicoplanin group ($P = 0.02$). The decrease in creatinine clearance during treatment was significantly greater in the group receiving vancomycin than in the group receiving teicoplanin (Fig. 1). Because the study patients received various other agents known to be nephrotoxic, a subgroup analysis of change in creatinine clearance among the patients who had received amphotericin B or cyclosporin A concurrently was performed (Table 5). An equivalent number of patients in both groups had received cyclosporin A. Patients receiving

TABLE 2. Responses to treatment by category of infection

Type of infection or symptom	Total no. treated		No. cured or improved		No. of failures		No. of indeterminate responses	
	Teicoplanin	Vancomycin	Teicoplanin	Vancomycin	Teicoplanin	Vancomycin	Teicoplanin	Vancomycin
Microbiologically documented infection	13	9	12	9				
With bacteremia	4	6	4	6				
Without bacteremia	9	3	8	3			1	
Clinically documented infection	10	15	9	11		2	1	2
Unexplained fever	2	1	2	1				
Total	25	25	23 (92%)	21 (84%)	0	2	2	2

TABLE 3. Responses to treatment by site of infection

Site of infection	Total no. treated		No. cured or improved		No. of failures		No. of indeterminate responses	
	Teicoplanin	Vancomycin	Teicoplanin	Vancomycin	Teicoplanin	Vancomycin	Teicoplanin	Vancomycin
Oropulmonary	7 (1)[a]	11 (2)	6 (1)	7 (2)		2	1	2
Gastrointestinal	6	6	5	6			1	
Urogenital	6 (1)	4 (2)	6 (1)	4 (2)				
Hickman site and skin	4 (2)	2 (1)	4 (2)	2 (1)				
Primary bacteremia		1 (1)		1 (1)				
Undetermined	2	1	2	1				
Total	25 (4)	25 (6)	23 (4)	21 (6)	0	2	2	2

[a] Numbers of patients with bacteremia shown in parentheses.

vancomycin and cyclosporin A had significantly more renal impairment (as determined by the percent change in creatinine clearance) than did patients receiving teicoplanin and cyclosporin A ($P = 0.02$). In addition, patients receiving vancomycin and cyclosporin A appeared to have a significantly higher mortality rate ($P = 0.02$). In this analysis, no differences in renal function between the teicoplanin and vancomycin groups were observed when patients who were not given cyclosporin were compared. Among patients who had received amphotericin B concurrently, equivalent deteriorations of renal function occurred in both the teicoplanin and the vancomycin groups after the introduction of antifungal therapy. However, among the subgroups that had not received amphotericin B, significant worsening of renal function was observed for the vancomycin group compared with the teicoplanin group ($P < 0.005$).

To study these findings further, an analysis to determine the three-way interaction among teicoplanin or vancomycin, cyclosporin A, and amphotericin B was performed. In order to do this, patients were divided into four groups and treated with antibiotics as follows: group A, neither cyclosporin A nor amphotericin B; group B, cyclosporin A but not amphotericin B; group C, amphotericin B but not cyclosporin A; and group D, both cyclosporin A and amphotericin B. We were able to partially overcome the problem of small sample sizes among these subgroups by adopting the following strategy of analysis. Since cyclosporin A, if administered, was usually given early, following bone marrow transplantation, while amphotericin B, if administered, was given later in the course, generally 5 to 10 days after the initiation of broad-spectrum antibiotics, the effect of concurrent therapy with these agents could be assessed separately and sequentially for each patient. Thus, for a patient who had received amphotericin B but not cyclosporin A, the period before amphotericin B was introduced could be included as data for group A. Likewise, for a patient who had received both amphotericin B and cyclosporin A, there was a period of several days when the patient was receiving only cyclosporin A and not amphotericin B. The data from this period could be included in the results for group B. The results of this analysis are shown in Table 6. When neither cyclosporin A nor amphotericin B was used, the vancomycin group had significantly more deterioration in renal function than did the teicoplanin group ($P = 0.01$). When cyclosporin A was used without amphotericin B, the vancomycin group still had renal function significantly worse than that of the teicoplanin group ($P = 0.01$). When only amphotericin B was used, both the vancomycin and the teicoplanin groups had equivalent changes in renal function. Lastly, when both cyclosporin A and amphotericin B were used, the vancomycin group again had more deterioration in renal function than did the teicoplanin group ($P < 0.05$). Unfortunately, because of the small sample size, a similar subgroup analysis could not be performed for other cytotoxic or nephrotoxic agents which were administered concurrently with teicoplanin or vancomycin.

The overall outcomes (seven deaths in the vancomycin group and two deaths in the teicoplanin group) were not statistically different for the two study groups (Table 7). Patients who received vancomycin were on the study regi-

TABLE 4. Adverse reactions related to study regimens

Adverse reaction	No. of reactions[a]		P^b
	Teicoplanin group ($n = 25$)	Vancomycin group ($n = 25$)	
Nephrotoxicity[c]	2 (0)	10 (5)	0.02 (0.05)
Red man syndrome	0	1 (1)	NS[d]
Total no. of patients with adverse reactions	2 (0)	11 (6)	0.01 (0.02)

[a] All values in parentheses express numbers of patients requiring termination of study.
[b] All values in parentheses refer to results for patients requiring termination of study.
[c] As defined in Materials and Methods.
[d] NS, difference not significant by Fisher's exact test.

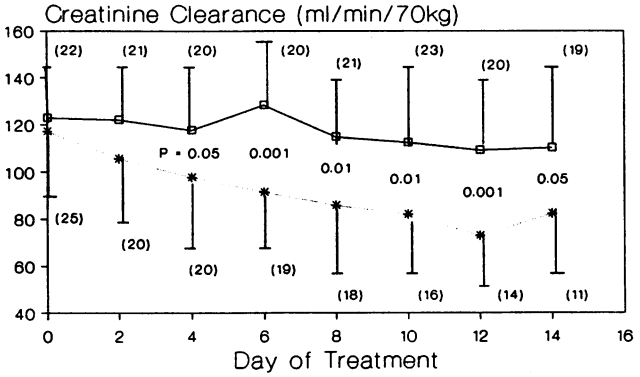

FIG. 1. Estimated creatinine clearance (mean ± SD) among patients receiving teicoplanin or vancomycin during the first 14 days of treatment. The number of observations at each interval is shown in parentheses. Significant differences ($P < 0.05$; Wilcoxon rank sum test) between the two groups were observed from day 4 of treatment onwards. □, teicoplanin; *, vancomycin.

TABLE 5. Decreases in creatinine clearance from baseline in different patient groups

Type of patient and parameter	Value for group[a]		P
	T (n = 25)	V (n = 25)	
All			
Baseline creatinine clearance (ml/min/70 kg)	123 ± 31[b]	117 ± 32	NS[c]
Lowest creatinine clearance during treatment	84 ± 26	67 ± 30	0.04
Receiving concurrent cyclosporin A	13	10	NS
Total days on cyclosporin A	32.5 ± 12.3	26.3 ± 10.8	NS
Days with concurrent T or V	15.0 ± 5.1	13.8 ± 8.3	NS
% Decrease in creatinine clearance	33 ± 17	53 ± 25	0.02
No. of deaths	1	6	0.02
Not receiving cyclosporin A	12	15	NS
% Decrease in creatinine clearance	25 ± 22	31 ± 17	NS
Receiving concurrent amphotericin B	17	12	NS
Cumulative dose (mg/kg)	7.7 ± 7.1	6.8 ± 4.7	NS
Days with concurrent T or V	14 ± 10	13 ± 12	NS
% Decrease in creatinine clearance	36 ± 19	44 ± 23	NS
No. of deaths	2	3	NS
Not receiving amphotericin B	8	13	NS
% Decrease in creatinine clearance	10 ± 12	30 ± 23	0.005

[a] T, teicoplanin; V, vancomycin.
[b] All values are mean ± SD.
[c] NS, difference not significant by Fisher's exact, Yates' corrected chi-square, or Wilcoxon rank sum test (two-tailed).

TABLE 6. Decrease in creatinine clearance from baseline by subgroup analysis

Group (drug received)[a] and parameter	Value for group		P
	Teicoplanin	Vancomycin	
A (neither AmB nor CsA)			
No. receiving drug	12	15	
% Decrease in creatinine clearance	5.8 ± 7.3[b]	21.8 ± 19.7	0.01
B (CsA but not AmB)			
No. receiving drug	13	10	
% Decrease in creatinine clearance	14.6 ± 14.6	41.7 ± 26.5	0.01
C (AmB but not CsA)			
No. receiving drug	9	7	
% Decrease in creatinine clearance	31.9 ± 20.5	34.7 ± 10.3	NS[c]
D (both CsA and AmB)			
No. receiving drugs	8	5	
% Decrease in creatinine clearance	40.0 ± 16.6	66.6 ± 16.0	<0.05

[a] AmB, amphotericin B; CsA, cyclosporin A.
[b] All ± values are mean ± SD.
[c] NS, difference not significant by Wilcoxon rank sum test (two-tailed).

DISCUSSION

Gram-positive organisms such as staphylococci and enterococci are increasingly important causes of nosocomial infections in the neutropenic patient population (12, 31). Vancomycin has been the antibiotic most frequently used for such infections. This glycopeptide is unique in that, despite 30 years of clinical use, emergence of resistance has been relatively rare (13, 17, 23). However, vancomycin has several disadvantages, including nephrotoxicity and poor tolerance by i.v. administration. Although nephrotoxicity occurs

men for fewer days, and their mean hospital stay was shorter than that of patients who received teicoplanin. However, these differences could be explained by the higher frequency of adverse effects requiring the discontinuation of vancomycin and by the higher mortality in the vancomycin group accounting for a shorter duration of treatment or hospital stay. Patients in the teicoplanin group had longer durations of neutropenia, but the subgroup that successfully completed therapy had shorter durations of neutropenia than the corresponding vancomycin group. This discrepancy could again be related to a higher mortality in the vancomycin group. Superinfections, veno-occlusive disease, and graft-versus-host disease occurred with equal frequency in the two groups (Table 7). However, the prevalence of superinfection due to *Candida* species was significantly higher in the vancomycin group ($P < 0.05$) than in the teicoplanin group (Table 8). This association of candidal superinfection did not appear to be related to the disproportionate concurrent administration of methylprednisolone sodium succinate (Solu-Medrol) to the vancomycin group (Table 1), since only 3 of 11 patients who received methylprednisolone sodium succinate developed candidal superinfection, compared with 4 of 14 who did not.

TABLE 7. Outcomes of treatment[a]

Characteristic	Value for group		P
	T (n = 25)	V (n = 25)	
No. of days of:			
T or V treatment	22.4 ± 9.5[b]	16.4 ± 9.6	0.01
Hospital stay	57.2 ± 22.8	44.4 ± 19.3	0.01
Neutropenia after T or V treatment			
All patients	19.0 ± 9.0	13.4 ± 9.7	0.01
Patients completing study	9.4 ± 8.9	16.9 ± 10.0	0.01
Fever	3.7 ± 4.1	3.2 ± 2.9	NS[c]
No. of patients who:			
Died during hospitalization	2	7	NS
Died with infection	1	3	NS
Had superinfection	7	11	NS
Had veno-occlusive disease	4	8	NS
Had graft-vs-host disease	4	7	NS

[a] T, teicoplanin; V, vancomycin.
[b] All ± values are mean ± SD.
[c] NS, difference not significant by Fisher's exact, Yates' corrected chi-square, or Wilcoxon rank sum test (two-tailed).

TABLE 8. Superinfections associated with study regimens

Characteristic of superinfection	No. of occurrences		P
	Teicoplanin group (n = 25)	Vancomycin group (n = 25)	
Pathogens			
Candida sp.	1	7 (3)[a]	0.05
Aspergillus sp.	1	0	NS[b]
CMV or HSV[c]	1	3	NS
E. coli	0	3 (2)	NS
Bacteroides or *Fusobacterium* sp.	0	2	NS
Staphylococcus	1 (1)	2 (1)	NS
Enterococcus	0	1	NS
C. difficile	2	1	NS
Other	1	0	NS
Sites			
Oropulmonary	2	5 (1)	NS
Gastrointestinal	3	3 (2)	NS
Urogenital	0	3 (1)	NS
Skin, Hickman site	2 (1)	2 (1)	NS
Total	7 (1)	11 (3)	NS

[a] Numbers of patients with positive blood cultures are shown in parentheses.
[b] NS, difference not significant by Fisher's exact test.
[c] CMV, cytomegalovirus; HSV, herpes simplex virus.

infrequently when vancomycin is used alone, this complication may be so common that it occurs in 35% of patients with concurrent administration of aminoglycosides (9). Teicoplanin has several potential advantages, including low toxicity (29), good tolerance when administered by i.v. and intramuscular routes (26), and a half-life that is up to 15 times longer than that of vancomycin (2, 5, 16). However, teicoplanin has a high degree of protein binding (>90%), which makes it more difficult to predict the in vivo clinical response on the basis of in vitro antimicrobial activity alone (4, 6). In addition, treatment failure with teicoplanin due to emergence of resistance against staphylococci has already been reported (1, 3, 13, 14).

In this randomized, double-blind comparison of teicoplanin and vancomycin during the empirical treatment of febrile neutropenic patients, fewer than 50% of our patients had microbiologically defined infections, as has been the experience of other investigators (8). Similar to the results of other reports, 68% of our patients with microbiologically documented infections were infected with gram-positive organisms. Thus, the inclusion of a glycopeptide antibiotic in the initial empirical therapy of our patients appears justified. However, in view of the small sample size of our study, no meaningful comparison in efficacies could be determined for the teicoplanin and vancomycin groups. Assuming that standard regimens currently available have a favorable response rate of 80%, a sample size of 114 patients in each arm of the study will be required to demonstrate a difference of 15%, given the probability of an alpha error of 0.05 and a beta error of 0.1 (power of 90%).

However, by using a prospective, randomized, double-blind experimental design, our study clearly demonstrated that teicoplanin in the dosage employed was significantly less nephrotoxic than vancomycin in our patient population (P = 0.02), especially in the subgroup of patients who had not received amphotericin B concurrently (P < 0.005) or who did receive cyclosporin A concurrently (P = 0.02). When the possible interactions with these concurrent medications were separately analyzed, vancomycin remained more nephrotoxic than teicoplanin (P = 0.01) in the subgroup of patients who had received neither amphotericin B nor cyclosporin A. Interestingly, a strong interaction between vancomycin and cyclosporin A was noted, and patients who had received both vancomycin and cyclosporin A had significantly worse outcomes than patients who had received teicoplanin and cyclosporin A (P = 0.02). Serum cyclosporin A levels were routinely monitored for dosage adjustment in our patients and were comparable in the two study groups. The reason for this apparent increase in nephrotoxicity during concurrent administration of vancomycin and cyclosporin A is unclear at present. Furthermore, our data must be interpreted with caution, since multiple other medications were concurrently administered to our patients, and a definitive statement of any causal relationship cannot be made at this time. However, the randomized, double-blind study design should have greatly minimized the possibility of any observer bias and enhanced the validity of our observations. If confirmed, the association of increased nephrotoxicity with concurrent administration of vancomycin and cyclosporin A has important therapeutic implications in view of the current controversy concerning the routine inclusion of vancomycin in the treatment of febrile patients with neutropenia (8, 15, 25, 27, 28). Proponents of early treatment with vancomycin have suggested that this approach may result in more rapid resolution of the first fever, a decrease in the frequency of breakthrough bacteremia with gram-positive organisms, and a reduction of the use of amphotericin B (15, 27). Opponents of routine administration of vancomycin have emphasized that mortality is not increased by withholding this agent from the initial regimen, while treatment costs and antibiotic-associated toxicity can be further reduced (8, 24, 25). The European Organization for Research and Treatment of Cancer recently published its findings, which also do not support the empirical addition of vancomycin to initial antibiotic therapy of cancer patients with fever and neutropenia (8). In a prospective, randomized, but unblinded comparison of ceftazidime plus amikacin with or without vancomycin as the initial empirical therapy, it was found that, although the vancomycin group had a significantly higher overall response rate (76 versus 63%; P < 0.001), particularly among patients with bacteremia caused by gram-positive organisms (72 versus 43%; P < 0.001), a similar proportion of patients had persistent fevers on each treatment day during the two regimens. Moreover, no patient with bacteremia caused by gram-positive organisms died during the first three days of true empirical therapy. Importantly, antibiotic-associated nephrotoxicity was more frequent in patients treated with vancomycin (6 versus 2%; P = 0.02) than in those not treated with it. These investigators concluded that successful treatment of infections caused by gram-positive organisms can be easily obtained without excess mortality when specific therapy is added after identification of the pathogen. They suggest that vancomycin should be included in initial empirical regimens only in centers where most bloodstream infections are caused by gram-positive bacteria. Our observations of markedly increased nephrotoxicity during concurrent administration of vancomycin and cyclosporin A lend further support to this view. Vancomycin should probably be avoided for patients who are receiving cyclosporin A and aminoglycosides. Teicoplanin may prove to be a valuable alternative for

the empirical treatment of such patients if its efficacy and reduced toxicity can be further documented.

Our study reported here was not designed to address the question of whether teicoplanin should be used routinely in the empirical treatment of febrile neutropenic patients. However, it should be considered that increased use of antimicrobial agents is associated with the emergence of resistant pathogens and with the possibility of a cumulative increase in adverse effects due to concurrent administration of multiple medications in this patient population.

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