MAJOR ARTICLE

Efficacy and Safety of Linezolid Compared with Vancomycin in a Randomized, Double-Blind Study of Febrile Neutropenic Patients with Cancer

Branimir Jaksic,[1] Giovanni Martinelli,[2] Jaime Perez-Oteyza,[3] Charlotte S. Hartman,[4] Linda B. Leonard,[4] and Kenneth J. Tack[4]

[1]Department of Medicine, Merkur University Hospital, Zagreb, Croatia; [2]Instituto Europeo Di Oncologia, Milan, Italy; [3]Hospital Ramon y Cajal, Madrid, Spain; and [4]Pfizer, Ann Arbor, Michigan

Background. Gram-positive pathogens can cause serious infections in neutropenic patients with cancer, and vancomycin therapy is often initiated empirically. Linezolid may offer an option for these patients.

Methods. To compare the safety and efficacy of linezolid and vancomycin in febrile, neutropenic patients with cancer, we conducted a double-blind, multicenter equivalence study. Eligible patients with proven or suspected infection due to a gram-positive pathogen were randomized to receive linezolid or vancomycin.

Results. Clinical success rates 7 days after completion of therapy (primary end point) were equivalent between groups in the intent-to-treat (ITT) analysis (linezolid, 219 [87.3%] of 251 patients; vancomycin, 202 [85.2%] of 237 patients; 95% CI, −4.1 to 8.1; $P = .52$), modified ITT analysis, clinically evaluable analysis, and microbiologically evaluable analysis, as well as between subsets analyzed by malignancy and infection type. Mean time to defervescence was shorter for linezolid than vancomycin in the modified ITT (6.6 vs. 8.5 days; $P = .04$) and microbiologically evaluable subsets (5.9 vs. 9.1 days; $P = .01$), although post hoc analyses revealed delayed recovery of absolute neutrophil counts for linezolid in these subsets ($P < .05$). There were no between-group differences in microbiologic success rates in the modified ITT subset (41 [57.7%] of 71 patients vs. 29 [50.0%] of 58 patients; $P = .38$) and microbiologically evaluable subsets, as well as in mortality rates in the ITT subset (17 [5.6%] of 304 patients vs. 23 [7.6%] of 301 patients; $P = .31$) and all subsets. Distribution of adverse events, including reported hematologic events, was similar between groups, except that linezolid was associated with fewer drug-related adverse events (52 [17.2%] of 303 patients vs. 72 [24.0%] of 300 patients; $P = .04$) and fewer cases of drug-related renal failure (1 [0.3%] of 303 patients vs. 7 [2.3%] of patients; $P = .04$).

Conclusions. Linezolid demonstrated efficacy and similar safety outcomes equivalent to those for vancomycin in febrile neutropenic patients with cancer.

Immediate empirical antibiotic therapy is the standard of care for patients with febrile neutropenia [1], but no single regimen is ideal. Vancomycin is an option for selected patients, such as those with serious catheter-related infections or colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) [1]. The rationale is based on the shift in causative pathogens, with gram-positive bacteria accounting for 60%–70% of bacterial pathogens isolated from febrile neutropenic patients [1, 2], and an increasing prevalence of MRSA. The role of vancomycin is debatable, because it has not been shown to reduce the overall mortality of patients with gram-positive bacterial infections, with the possible exception of viridans streptococcal infections [3, 4]. Additional disadvantages include vancomycin resistance [5, 6], enhanced aminoglycoside nephrotoxicity, and lack of orally bioavailable formulation.

Linezolid, a novel oxazolidinone antimicrobial agent, is an alternative because of its activity against gram-positive bacteria [7], including bactericidal activity against streptococci [8]. The clinical efficacy and safety of linezolid were comparable to those of vancomycin in randomized studies of nonneutropenic patients with gram-positive bacterial infections, including nosocomial pneumonia [9, 10], complicated skin and soft-tissue infections [11], and MRSA infections [12, 13].

Received 2 August 2005; accepted 26 October 2005; electronically published 25 January 2006.

Reprints or correspondence: Dr. Branimir Jaksic, Dept. of Medicine, Merkur University Hospital, Zajceva 19, 10000 Zagreb, Croatia (branimir.jaksic@zg.htnet.hr).

Clinical Infectious Diseases 2006; 42:597–607

1058-4838/2006/4205-0003$15.00

We hypothesized that linezolid would be as safe and effective as vancomycin in febrile neutropenic patients with cancer. To test this hypothesis, we conducted a randomized, double-blind, multicenter, phase 3 equivalence study involving patients eligible for vancomycin therapy because of proven or suspected gram-positive bacterial infection.

PATIENTS AND METHODS

Eligibility criteria. Hospitalized febrile adults (age, ⩾13 years; weight, >40 kg) with cancer were eligible for the study if they had proven or suspected gram-positive bacterial infection, as determined on the basis of suspected catheter infection, severe mucositis or dermatitis, colonization with methicillin-resistant staphylococci or drug-resistant *Streptococcus pneumoniae,* hypotension, or failure of empirical broad-spectrum antibiotic therapy within 72 h before enrollment. Fever was defined as a single oral temperature of >38.9°C or axillary temperature of >38.1°C, or as a temperature for ⩾1 h of ⩾38.6°C orally or ⩾37.8°C axillary. Patients were required to have chemotherapy-induced neutropenia (absolute neutrophil count, ⩽500 cells/mm^3) or expected to develop neutropenia within 48 h. Females of child-bearing potential were required to have a negative pregnancy test result, to take contraceptive precautions, and to refrain from breast-feeding. Exclusion criteria were pathogen resistance to the study drugs; fever of noninfectious etiology; neutropenia unassociated with high risk of bacterial infection; allogenic bone marrow transplantation ⩽4 weeks earlier; death likely to occur before posttherapy evaluation; clinical improvement ⩽72 h after commencement of broad-spectrum antibiotic; exposure to vancomycin therapy within 1 week before enrollment; endocarditis, osteomyelitis, or CNS infection; pheochromocytoma, carcinoid syndrome, uncontrolled hypertension, or untreated hyperthyroidism; or allergy to study drugs.

The study was approved by investigators' institutional review boards. Patients were required to provide valid written informed consent.

Interventions. Eligible patients were randomly assigned in a 1:1 ratio to receive linezolid (600 mg every 12 h) or vancomycin (1 g every 12 h), each administered intravenously for 10–28 days. To maintain blinding, a research pharmacist prepared study medications; an unblinded coinvestigator monitored vancomycin or serum creatinine levels in accordance with local practice.

Patients were not to receive other potentially effective antibiotics with activity against gram-positive pathogens unless the study drug was ineffective. Concomitant therapy was allowed in accordance with the usual standard of care.

Assessment of response and safety. Patients were assessed at enrollment (baseline), during therapy, at the end of therapy, and at 7 days after completion of therapy (test of cure [TOC]). Temperature was measured daily; other vital signs were measured weekly. Blood samples were drawn for duplicate cultures at baseline; if the results were positive at baseline, samples were also obtained at 48 h and at the TOC examination; and if the results were positive at 48 h, samples were obtained at 96 h. Infection site cultures and bacterial susceptibility tests were performed at a central laboratory at baseline and, if possible, at the end of therapy and at the TOC assessment. Hematologic and serum chemistry studies were performed at baseline, at predetermined intervals during therapy, at the end of therapy, and at the TOC assessment. Urinalysis was performed at baseline and at the TOC assessment.

Patients were evaluated for response at the end of therapy and at the TOC assessment. Clinical success was defined as cure (defervescence and resolution of signs and symptoms of infection) or improvement (defervescence and improvement of signs and symptoms of infection). Defervescence was defined as maximum oral temperature of ⩽37.5°C or axillary temperature of ⩽36.7°C on 3 consecutive days. Failure was defined as persistence or progression of clinical signs and symptoms of infection or development of new findings. An indeterminate outcome was defined as an inability to make an assessment.

Microbiologic outcome was assessed as success (documented eradication, presumed eradication, or colonization), failure (documented persistence, presumed persistence, or superinfection), indeterminate, or missing. Data on gram-negative pathogens were not collected.

Investigators monitored patients for adverse events through the TOC assessment. Because of anticipated morbidity and mortality, an independent data-monitoring committee was established to prospectively assess safety data and the potential need for study modification.

Data analysis. Three hundred clinically evaluable patients (150 per group) were required to determine equivalence (15% margin) between groups based on a 2-sided test level of .05 and statistical power of 90%, assuming a clinical cure rate of 80% [14, 15]. The intent-to-treat (ITT) population comprised patients who received at least 1 dose of study drug. The modified ITT (MITT) subset comprised ITT patients infected with gram-positive pathogens at baseline. The clinically evaluable (CE) subset comprised ITT patients who received sufficient therapy (i.e., ⩾7 days for outcome of success or ⩾3 days for outcome of failure), received ⩾80% of intended therapy, and underwent postbaseline assessment; patients were nonevaluable if they received potentially effective antibiotics for intercurrent illness. The microbiologically evaluable (ME) subset comprised CE patients infected with baseline gram-positive pathogens susceptible to both study drugs.

Groups were compared for demographic characteristics using analysis of variance for continuous variables and the χ^2 test for 2-way contingency tables for categorical variables. The primary

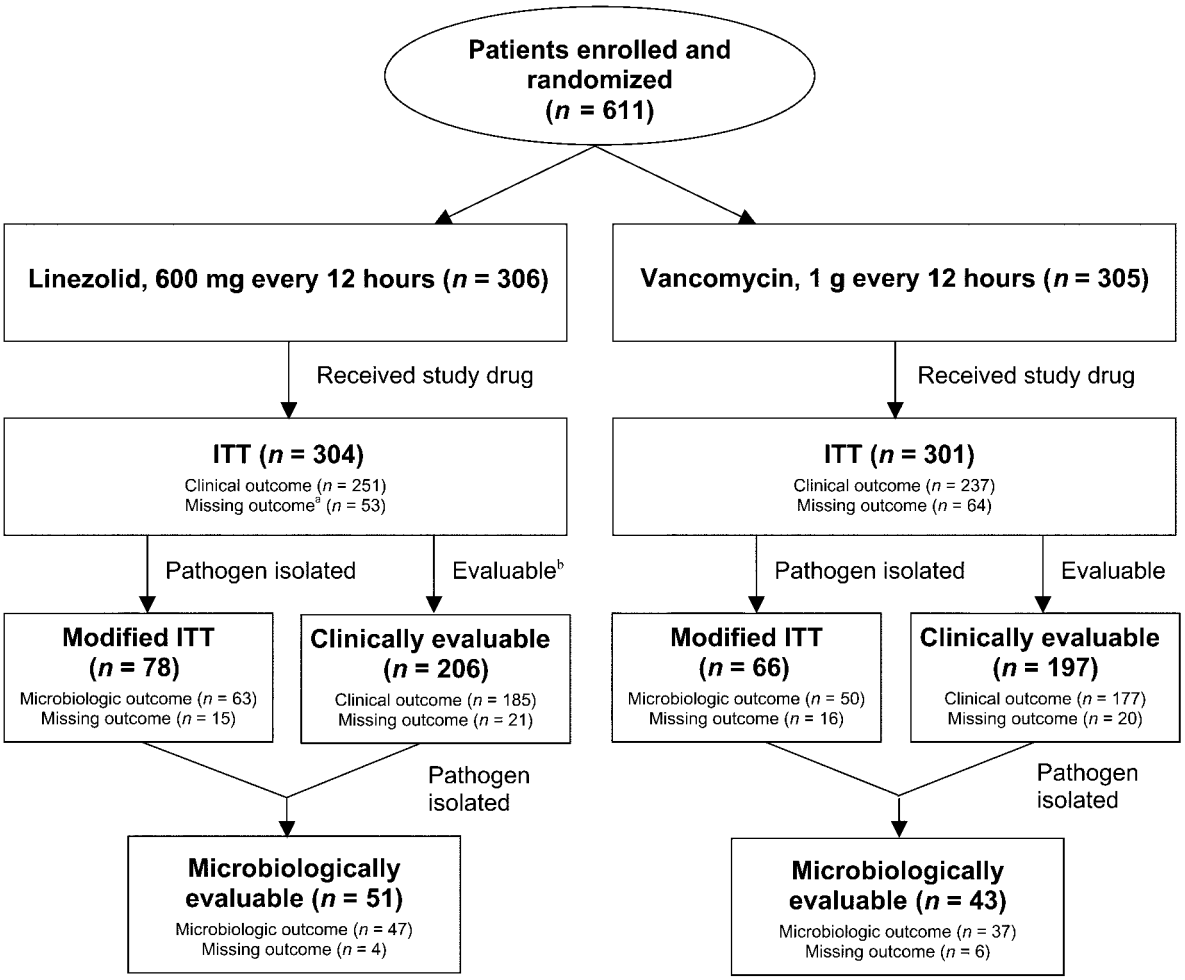

Figure 1. Flow diagram for the analysis population. [a]Missing or indeterminate outcome. [b]Evaluable patients received sufficient therapy (⩾7 days for outcome of success or ⩾3 days for outcome of failure), received ⩾80% of intended therapy, and completed a postbaseline assessment; patients were considered to be nonevaluable if they received a potentially effective antimicrobial for intercurrent illness. ITT, intent-to-treat.

efficacy end point was clinical outcome at the TOC assessment. Secondary efficacy end points were defervescence rate, time to defervescence, resolution of neutropenia, time to resolution of neutropenia, microbiologic outcome, and mortality rate. Rates of efficacy outcomes and adverse events were compared between groups using the χ^2 test of homogeneity of proportions; 95% CIs were calculated for between-group differences in rates of efficacy end points and were based on the normal approximation to the binomial distribution. Kaplan-Meier estimates were obtained for time-to-event end points, and log-rank tests were used to compare time-to-event end points between groups. All statistical analyses were 2-tailed. *P* values ⩽.05 were considered to be statistically significant.

RESULTS

Six hundred eleven patients were enrolled from November 2000 through May 2002 by 58 investigators in Australia, Austria, Belgium, Croatia, France, Germany, Greece, Italy, Poland, Russia, Slovenia, South Africa, Spain, and Switzerland (figure 1). Six patients did not receive the study drug. Two hundred two patients were not clinically evaluable because they had fever of uncertain origin and received additional antiviral, antiparasitic, or antifungal drugs (56 subjects in the linezolid group and 57 subjects in the vancomycin group); received insufficient study drug (21 and 27 subjects, respectively); did not undergo a postbaseline assessment (18 and 26 subjects, respectively); received concomitant anti-infectives for intercurrent illness (10 and 12 subjects, respectively); did not comply with drug regimen (1 and 2 subjects, respectively); or were not eligible (1 and 0 subjects, respectively). Some patients were not evaluable for >1 reason.

Baseline characteristics were similar between groups (table 1). Most patients had hematologic malignancies (linezolid group, 95.4%; vancomycin, 93.7%) and absolute neutrophil counts of <100 cells/mm^3 (72.0% and 72.0%, respectively). The absolute neutrophil count was not reported in 123 patients,

Table 1. Baseline demographic and disease characteristics of the intent-to-treat population.

Characteristic	Linezolid recipients (n = 304)	Vancomycin recipients (n = 301)
Age, years		
Mean ± SD	47.2 ± 15.0	48.1 ± 15.7
Range	13–76	15–86
Sex		
Male	179 (58.9)	161 (53.5)
Female	125 (41.1)	140 (46.5)
Primary malignancy		
Leukemia	176 (57.9)	172 (57.1)
Lymphoma	86 (28.3)	79 (26.2)
Myeloma	28 (9.2)	31 (10.3)
Solid tumor or other	14 (4.6)	19 (6.3)
Disease status at baseline[a]		
Progression of disease	185 (61.3)	190 (64.2)
Remission	117 (38.7)	106 (35.8)
Not reported	2	5
Absolute neutrophil count[b]		
<100 cells/mm^3	172 (72.0)	175 (72.0)
100–500 cells/mm^3	59 (24.7)	63 (25.9)
>500 cells/mm^3	8 (3.3)	5 (2.1)
Not reported	65	58
Duration of neutropenia, days[c]		
Mean ± SD	9.3 ± 14.5	9.0 ± 12.0
Range	−1 to 159	1–168
Primary infection		
Fever of uncertain origin	89 (29.3)	94 (31.2)
Bacteremia	91 (29.9)	89 (29.6)
Vascular-catheter related	34 (11.2)	31 (10.3)
Pneumonia	27 (8.9)	23 (7.6)
Skin and soft tissue	27 (8.9)	20 (6.6)
Urinary tract	2 (0.7)	3 (1.0)
Other	34 (11.2)	41 (13.6)
Gram-positive pathogen[d]	78 (25.7)	66 (21.9)
Staphylococcus aureus	9 (3.0)	5 (1.7)
Methicillin-resistant *S. aureus*	5 (1.6)	4 (1.3)
Staphylococcus epidermidis	46 (15.1)	34 (11.3)
Staphylococcus hemolyticus	12 (3.9)	9 (3.0)
Other staphylococci	10 (3.3)	5 (1.7)
Streptococci	7 (2.3)	12 (4.0)
Enterococcus faecium	5 (1.6)	7 (2.3)
Enterococcus faecalis	6 (2.0)	4 (1.3)
Other enterococci	4 (1.3)	1 (0.3)
Corynebacteria	5 (1.6)	3 (1.0)
Other gram-positive bacteria	1 (0.3)	1 (0.3)

NOTE. Data are no. (%) of patients, unless otherwise indicated. P values were determined by χ^2 test for categorical variables and analysis of variance for continuous variables and were not significant.

[a] Disease status at baseline was reported for 302 patients in the linezolid group and 296 patients in the vancomycin group. Patients for whom data were not reported were excluded from calculation of percentages.

[b] Patients could be enrolled with an absolute neutrophil count ⩾500 cells/mm^3 if it was expected to decrease to <500 cells/mm^3 within 48 h. "Not reported" includes patients in whom the absolute neutrophil count may not have been determined because their WBC count was less than their institutions' limit for differentiation. Data were available for 239 patients in the linezolid group and 243 patients in the vancomycin group. Patients for whom data were not reported were excluded from calculation of percentages.

[c] Duration of neutropenia before receipt of the first dose was determined for 297 patients in the linezolid group and for 293 patients in the vancomycin group.

[d] Some patients were infected with >1 pathogen. The most common streptococci were *Streptococcus mitis* (2 patients in the linezolid group and 5 in the vancomycin group) and *Streptococcus oralis* (2 and 3 patients, respectively). The most common "other" staphylococci were *Staphylooccus hominis* (4 and 3 patients, respectively) and *Staphylococcus warneri* (3 and 1 patients, respectively).

principally because their WBC counts were so low that the institutions did not require or were not capable of performing differentiation. All but 2 patients, both in the vancomycin group, received anti-infective medication before enrollment or starting on day 1 (table 2). More than one-third of patients received a colony-stimulating factor before enrollment or starting on day 1 (40.5% of linezolid recipients and 37.5% of vancomycin recipients).

The mean duration of treatment (±SD) was similar between groups in the ITT population (linezolid group, 11.4 ± 5.2 days; vancomycin group, 11.5 ± 5.0 days). Approximately three-fourths of patients (75.0% and 80.7% in the linezolid and vancomycin arms, respectively) started receiving other anti-infectives after day 1 (table 2).

Clinical efficacy. Clinical success rates were equivalent between groups (table 3). In the ITT population (excluding patients with missing or indeterminate outcomes), clinical success occurred in 219 (87.3%) of 251 linezolid-treated patients and 202 (85.2%) of 237 vancomycin-treated patients. Results for other study populations were similar to those for the ITT population. Stratification by primary malignancy or infection type yielded similar between-group clinical success rates in the ITT population (table 3) and its subsets (data not shown).

Mean times to defervescence (±SD) were equivalent between groups in the ITT population (linezolid group, 6.4 ± 4.6 days; vancomycin group, 6.7 ± 5.3 days; P = .54) and clinically evaluable subset (6.2 ± 4.5 and 6.5 ± 5.2 days, respectively; P = .49). Mean time to defervescence (±SD) was shorter with linezolid than vancomycin in the MITT subset (6.6 ± 4.5 and 8.5 ± 5.9 days, respectively; P = .04) and microbiologically evaluable subset (5.9 ± 4.5 and 9.1 ± 6.2 days, respectively; P = .01) (figure 2). Defervescence occurred within 3 days in 21 (30.9%) of 68 linezolid-treated patients and 9

Table 2. Anti-infective agents most frequently used in the intent-to-treat population.

Anti-infective	No. (%) of patients	
	Linezolid group (n = 304)	Vancomycin group (n = 301)
Treatment started on or before day 1 of the study		
Azoles and other antifungals	229 (75.3)	212 (70.4)
Cephalosporins	199 (65.5)	214 (71.1)
Aminoglycosides	204 (67.1)	185 (61.5)
Fluoroquinolones	162 (53.3)	164 (54.5)
Piperacillin/tazobactam and other penicillins	135 (44.4)	115 (38.2)
Amphotericin B	43 (14.1)	49 (16.3)
Imipenem or meropenem	39 (12.8)	35 (11.6)
Treatment started after day 1 of the study		
Amphotericin B	104 (34.2)	100 (33.2)
Azoles and other antifungals	61 (20.1)	83 (27.6)
Antivirals	61 (20.1)	66 (21.9)
Aminoglycosides	54 (17.8)	53 (17.6)
Fluoroquinolones	51 (16.8)	60 (19.9)
Cephalosporins	45 (14.8)	43 (14.3)
Piperacillin/tazobactam and other penicillins	35 (11.5)	33 (11.0)

(16.4%) of 55 vancomycin-treated patients in the MITT subset with available data, and in 18 (40.0%) of 45 linezolid-treated patients and 6 (16.2%) of 37 vancomycin-treated patients in the microbiologically evaluable subset.

Microbiology. No pathogens were resistant to study drugs at baseline. Microbiologic success rates were similar between groups in the MITT subset, excluding patients with missing or indeterminate outcomes (linezolid group, 41 [58%] of 71 patients; vancomycin group, 29 [50%] of 58 patients; $P = .38$) (table 4), and in the microbiologically evaluable subset (32

Table 3. Clinical outcome at 7 days after the completion of therapy (i.e., at the test of cure assessment).

Population, presentation	No. of successes/no. of patients assessed (%)[a]		95% CI, %[b]	P[c]
	Linezolid group	Vancomycin group		
ITT	219/251 (87.3)	202/237 (85.2)	−4.1 to 8.1	.52
Primary malignancy				
Leukemia	119/143 (83.2)	111/138 (80.4)	−6.2 to 11.8	.55
Lymphoma	63/71 (88.7)	56/62 (90.3)	−12.0 to 8.8	.77
Myeloma	24/24 (100)	23/24 (95.8)	−3.8 to 12.2	.31
Tumor	11/11 (100)	11/12 (91.7)	−7.3 to 24.0	.33
Other	2/2 (100)	1/1 (100.0)	Not calculable	
Type of infection				
Fever of uncertain origin	72/78 (92.3)	66/74 (89.2)	−6.1 to 12.3	.51
Bacteremia of unknown source	59/72 (81.9)	53/67 (79.1)	−10.3 to 16.0	.67
Vascular catheter–related infection	23/27 (85.2)	24/28 (85.7)	−19.2 to 18.1	.96
Skin and soft-tissue infection	19/21 (90.5)	14/17 (82.4)	−13.9 to 30.2	.46
Pneumonia	19/23 (82.6)	13/15 (86.7)	−27.2 to 19.1	.74
Urinary tract infection	2/2 (100)	2/3 (66.7)	−20.0 to 86.7	.36
Other	25/28 (89.3)	30/33 (90.9)	−16.7 to 13.5	.83
MITT	55/63 (87.3)	43/50 (86.0)	−11.4 to 14.0	.84
Clinically evaluable	171/185 (92.4)	158/177 (89.3)	−2.8 to 9.1	.30
Microbiologically evaluable	41/47 (87.2)	32/37 (86.5)	−13.8 to 15.3	.92

NOTE. ITT, intent to treat; MITT, modified ITT.

[a] Clinical success rates were based on the number of patients with success (cure or improvement) divided by the number with success or failure; patients with missing or indeterminate outcomes were excluded.

[b] Ninety-five percent CI for the difference in success rates based on normal approximation to the binomial distribution; 95% CI ± 15% is within equivalence margin.

[c] Determined by χ^2 test.

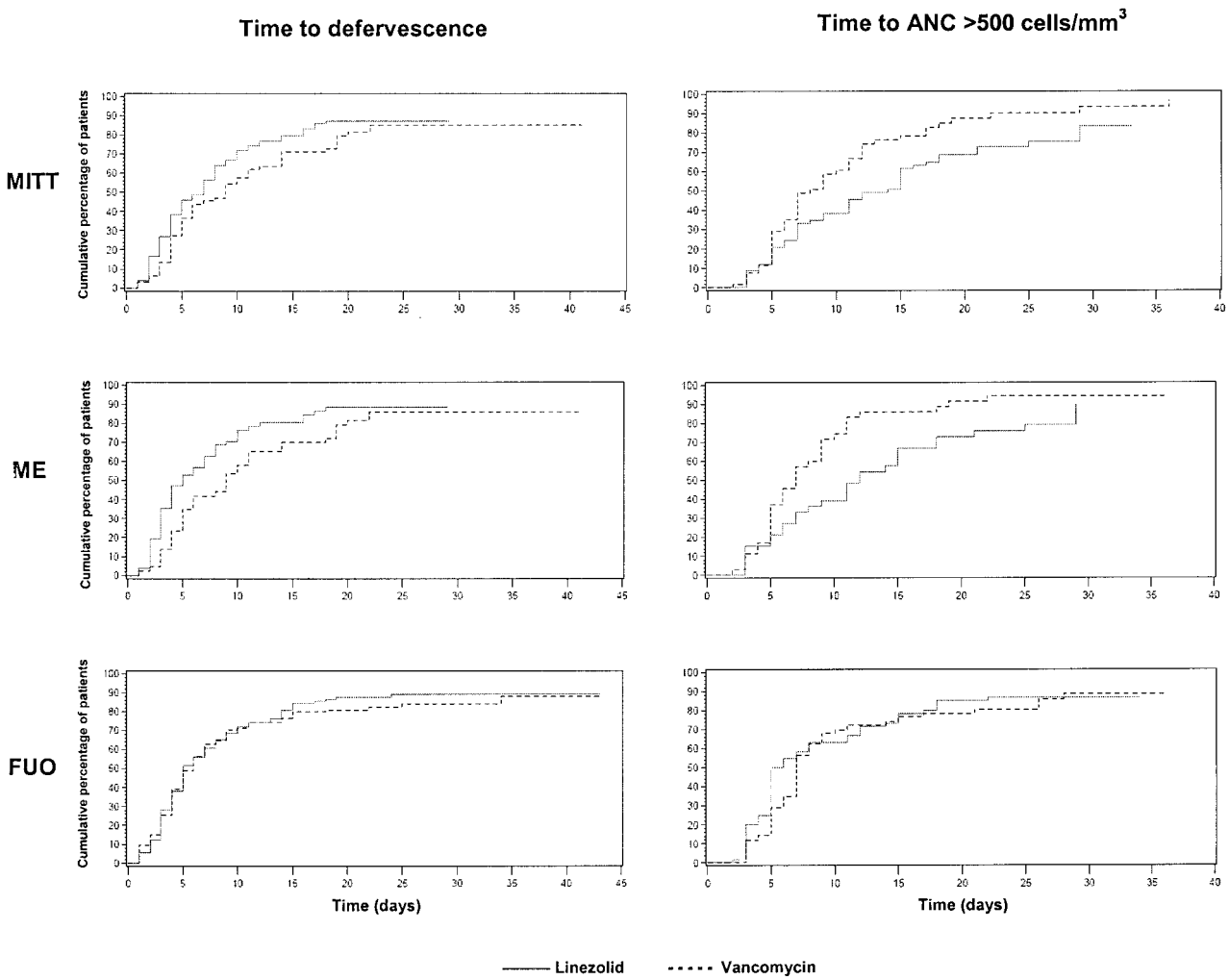

Figure 2. Kaplan-Meier analyses of time to defervescence and to neutrophil recovery in the modified intent-to-treat (MITT), microbiologically evaluable (ME), and fever of uncertain origin (FUO) populations. ANC, absolute neutrophil count.

[63%] of 51 and 24 [56%] of 43 patients, respectively; $P = .50$). There were no differences in eradication rates for individual pathogens, including MRSA, except for *Enterococcus faecium,* which was eradicated from 4 (100%) of 4 linezolid-treated patients and 2 (29%) of 7 vancomycin-treated patients ($P = .02$). A respiratory isolate of *E. faecalis* developed resistance to vancomycin during treatment, and vancomycin-resistant *E. faecium* was isolated from a blood sample from another vancomycin-treated patient who had negative baseline culture results. Linezolid resistance was not observed.

Mortality. Mortality rates at 16 days after completion of therapy were similar between groups in all study populations. In the ITT population, 17 (5.6%) of 304 linezolid-treated patients died, compared with 23 (7.6%) of 301 vancomycin-treated patients ($P = .31$). In the linezolid group, the most common causes of death were septic shock or sepsis (8 patients), pneumonia or respiratory failure (3 patients each), and cerebral hemorrhage or multiple-organ failure (2 patients each). In the vancomycin group, the most common causes were progression of malignancy (5 patients); pneumonia, septic shock or sepsis, and renal failure or increased serum creatinine level (4 patients each); respiratory failure or cardiopulmonary arrest (3 patients each); and dyspnea or multiple-organ failure (2 patients each). Some patients had >1 potential cause of death.

Safety. All patients were analyzed for adverse events, except for 1 in each group whose adverse events were not recorded. The distribution of all adverse events, including those unrelated to treatment, was similar between groups (table 5). Drug-related adverse events occurred more frequently in the vancomycin group (24.0% vs. 17.2%; $P = .04$). Renal failure occurred more frequently in the vancomycin group for drug-related episodes (2.3% vs. 0.3%; $P = .04$) and all-causality episodes (5.0% vs. 1.7%; $P = .02$).

Most drug-related adverse events were mild or moderate in

Table 4. Microbiologic outcome at 7 days after the completion of therapy (i.e., the test of cure assessment).

Variable	No. of successes/no. of patients assessed (%)[a]		95% CI, %[b]	P[c]
	Linezolid	Vancomycin		
Population				
MITT	41/71 (58)	29/58 (50)	−9.5 to 25.0	.38
Microbiologically evaluable	32/51 (63)	24/43 (56)	−13.0 to 26.8	.50
Gram-positive pathogen				
Staphylococcus aureus	5/9 (56)	1/3 (33)	−40.2 to 84.7	.51
Staphylococcus epidermidis	27/44 (61)	18/29 (62)	−23.5 to 22.1	.95
Staphylococcus hemolyticus	7/12 (58)	3/8 (38)	−22.8 to 64.5	.36
Viridans streptococci	3/6 (50)	4/8 (50)	−0.5 to 0.5	1.00[d]
Enterococcus faecium	4/4 (100)	2/7 (29)	38.0 to 100.0	.02
Enterococcus faecalis	5/6 (83)	1/4 (25)	6.5 to 100.0	.07

NOTE. MITT, modified intent to treat.

[a] For the study populations, microbiologic success rates were based on the number of patients with success (documented eradication, presumed eradication, or colonization) divided by the number with success or failure (documented persistence, presumed persistence, or superinfection); patients with missing or indeterminate outcomes were excluded. For the gram-positive pathogens, microbiologic success rates were based on the number of pathogens with documented or presumed eradication divided by the number with success or failure, displayed by pathogen for pathogens isolated from ⩾5 patients.

[b] Ninety-five percent CI for the difference in success rates based on normal approximation to the binomial distribution; 95% CI ± 15% is within equivalence margin.

[c] Determined by χ^2 test.

[d] Results should be interpreted with caution because of the small number of pathogens.

severity; serious drug-related adverse events occurred in 3 linezolid-treated patients and 12 vancomycin-treated patients. The distribution of treatment discontinuations associated with drug-related adverse events was similar between groups (linezolid group, 3.6%; vancomycin group, 5.0%; $P = .41$). Death was probably or possibly related to study drug for 1 patient in each group. The causes of death were septic shock, dermatitis, and skin disorder in the linezolid-treated patient and anuria and acute renal failure in the vancomycin-treated patient.

There were no between-group differences in hematologic events in the ITT population. The incidence of any bleeding complication, including episodes unrelated to treatment, was similar between groups (linezolid group, 34 [11.2%] of 304 patients; vancomycin group, 38 [12.6%] of 301 patients). Individual events related to bleeding occurred in <1% of patients, except for epistaxis (10 [3.3%] of 304 patients and 15 [5.0%] of 301 patients, respectively; $P > .1$) and petechiae (5 [1.6%] of 304 patients and 3 [1.0%] of 301 patients; $P > .1$). No bleeding complications were considered to be related to study drugs.

There were no between-group differences in mean hematologic parameters, although analysis of mean WBC and neutrophil counts revealed trends favoring vancomycin (table 6). Post-hoc Kaplan-Meier analysis of time to absolute neutrophil count recovery favored vancomycin in the MITT subset ($P = .02$, by the log rank test) and the microbiologically evaluable subset ($P = .01$), but not for patients with fever of uncertain origin ($P = .45$; figure 2). Mean platelet counts remained nearly identical between groups throughout the study (table 6), as did time to recovery of the platelet count ($P = .80$; figure 3). Abnormal platelet counts (i.e., <75% of the lower limit of normal or, if low at baseline, <75% of the baseline value) occurred in 162 (53.5%) of 303 linezolid-treated patients and in 169 (56.5%) of 299 vancomycin-treated patients.

The between-group distribution was similar for abnormal hemoglobin values (linezolid group, 108 [35.6%] of 303 patients; vancomycin group, 114 [38.1%] of 299 patients) and WBC counts (74 [24.4%] of 303 patients and 78 [26.1%] of 299 patients, respectively). Finally, the distribution of biochemistry test results, including mean values, changes from baseline values, and abnormal values, was similar between groups (data not shown).

DISCUSSION

This randomized, double-blind, multicenter, equivalence study demonstrates that linezolid is associated with efficacy equivalent to that of vancomycin in febrile neutropenic patients. Results measured by the primary end point (clinical success) and secondary efficacy end points (microbiologic outcome and mortality rate) were similar in linezolid- and vancomycin-treated patients.

Others have reported that addition of an antistaphylococcal

Table 5. Adverse events observed in linezolid and vancomycin recipients.

Type of adverse event	No. (%) of adverse events		P[b]
	Linezolid group[a] (n = 303)	Vancomycin group[a] (n = 300)	
Adverse event			
Any	229 (75.6)	232 (77.3)	.61
Serious event	37 (12.2)	48 (16.0)	.18
Drug-related adverse event[c]			
Any	52 (17.2)	72 (24.0)	.04
Serious event	3 (1.0)	12 (4.0)	
Drug-related adverse event leading to discontinuation	11 (3.6)	15 (5.0)	.41
Drug-related adverse events occurring in ⩾5 patients/group			
Nausea	10 (3.3)	8 (2.7)	NS
Rash	6 (2.0)	10 (3.3)	NS
Vomiting	9 (3.0)	6 (2.0)	NS
Diarrhea	3 (1.0)	8 (2.7)	NS
Erythema	4 (1.3)	6 (2.0)	NS
Increased serum creatinine level	1 (0.3)	5 (1.7)	NS
Renal failure[d]	1 (0.3)	7 (2.3)	.04[e]

NOTE. NS, not significant.

[a] Adverse events not reported in 1 patient in each group.

[b] Determined by Pearson χ^2 test, unless otherwise indicated.

[c] Drug-related adverse event as reported by investigator or with relatedness not reported.

[d] Renal failure included the predefined coding terms "failure kidney acute" and "kidney failure" but not "creatinine serum increased."

[e] Determined by Fisher's exact test.

antibiotic to broad-spectrum therapy did not improve outcome in febrile neutropenic patients. Between-study similarities in methods and patients invite comparison, although some end points differed. Cometta et al. [16] reported that 165 patients randomly assigned to receive vancomycin or placebo had similar median times to defervescence (3.5 vs. 4.3 days; $P = .75$) and mortality rates (5% vs. 10%; $P = .23$). Ramphal et al. [17] reported that 127 patients randomly assigned to receive vancomycin or no vancomycin had similar defervescence rates at 96 h (61% vs. 56%) and mortality rates (11% vs. 10%). Erjavec et al. [18] reported that 114 patients randomly assigned to receive teicoplanin or placebo had similar defervescence rates at 72 h (45% vs. 47%) and mortality rates (11% vs. 7%). The major difference between these studies and our study was sample size. Although the first and largest study did not meet its target sample size of 226 assessable patients, Cometta et al. [16] predicted that vancomycin was unlikely to cause a clinically meaningful reduction in time to defervescence, which was defined as 1.5 days. On the other hand, the between-group difference in mortality rate might have become statistically significant if more patients had been enrolled.

We met our target enrollment. Clinical success rates in the ITT population (linezolid group, 87%; vancomycin group, 85%) were not less than the 80% cure rate assumed for our power calculation. Times to and rates of defervescence appeared to be better in other studies [16–18], possibly because we defined defervescence as a temperature of ⩽37.5°C, not <38.0°C, for 3 days and reported mean, not median, values. Median time to defervescence was 5.0 days in our ITT analysis of both groups, which more closely approximated the values reported by Cometta et al. [16] than did our mean values. Importantly, mortality rates (5.6% and 7.6% for linezolid and vancomycin, respectively) were similar to those in other studies (5%–10%) [16–18].

Although the overall microbiologic success rate by patient was similar between groups, the eradication rate favored linezolid for enterococci (9 [90%] of 10 patients vs. 3 [23%] of 11 patients) and became significant for *E. faecium* ($P = .02$). In addition, vancomycin-resistant enterococci were isolated during therapy in 2 vancomycin-treated patients. Linezolid resistance was not observed. These findings should be interpreted with caution because of the small number of pathogens.

Our study demonstrated faster defervescence for linezolid than for vancomycin in patients infected with demonstrated gram-positive pathogens, accompanied by a transiently delayed absolute neutrophil count recovery that did not affect the mean duration of treatment. Although linezolid was reported to be associated with neutropenia in case reports [19–21], drug ther-

Table 6. Hematologic variables before and after treatment.

Hematologic variable, treatment group	Baseline		End of treatment		7 Days after completion of therapy	
	Mean ± SD	P^a	Mean ± SD	P^a	Mean ± SD	P^a
Hemoglobin, g/dL						
Linezolid	8.8 ± 1.6		9.4 ± 1.5		10.0 ± 1.6	
Vancomycin	8.8 ± 1.6	.58	9.3 ± 1.5	.43	10.0 ± 1.7	.80
Platelet count, × 10^3 cells/mm^3						
Linezolid	28.2 ± 30.5		74.7 ± 115.8		141.0 ± 148.4	
Vancomycin	31.5 ± 53.6	.36	75.2 ± 98.6	.96	149.9 ± 165.3	.52
WBC count, × 10^3 cells/mm^3						
Linezolid	0.77 ± 2.43		3.85 ± 5.16		4.79 ± 5.16	
Vancomycin	1.18 ± 9.04	.44	4.39 ± 5.54	.22	5.12 ± 6.45	.51
ANC, cells/mm^3						
Linezolid	118 ± 341		2480 ± 4136		2991 ± 4412	
Vancomycin	107 ± 290	.71	2788 ± 4365	.41	2935 ± 3592	.88

NOTE. ANC, absolute neutrophil count.

[a] Determined by analysis of variance.

apy did not appear to be responsible for the time-dependent associations in figure 2, because times to defervescence and absolute neutrophil count recovery were similar between groups for patients with fever of uncertain origin.

The paradox of faster defervescence with delayed absolute neutrophil count recovery may be attributable to physiological processes during recovery from acute bacterial infection. During the early convalescent phase, neutrophil egress from bone marrow decreases [22]. In addition, leukocytes integrate chemoattractant signals while rolling along the vascular endothelial surface, until they reach a critical activation level and then adhere at the inflammation site [23]. Therefore, decreased peripheral absolute neutrophil count may reflect delivery to the infection site, where neutrophils perform host defense activities. Collectively, these processes could explain why delayed absolute neutrophil count recovery in the linezolid group did not interfere with recovery from bacterial infection. In fact, one could postulate enhanced chemoattraction to the infection site, thereby accounting for transient peripheral neutropenia in patients with documented bacterial infection.

Laboratory findings confirmed profound myelosuppression at enrollment and gradual improvement during treatment, but there were no between-group differences in platelet count or in other hematologic variables except for the aforementioned transient absolute neutrophil count effects. In a dedicated analysis of hematologic effects [24], linezolid did not affect mean platelet counts, absolute or cumulative incidence of low counts, changes from baseline levels, or bleeding complications in randomized comparisons with vancomycin in patients with nosocomial pneumonia.

Both linezolid and vancomycin appeared to be well tolerated, as determined on the basis of the low incidence of treatment

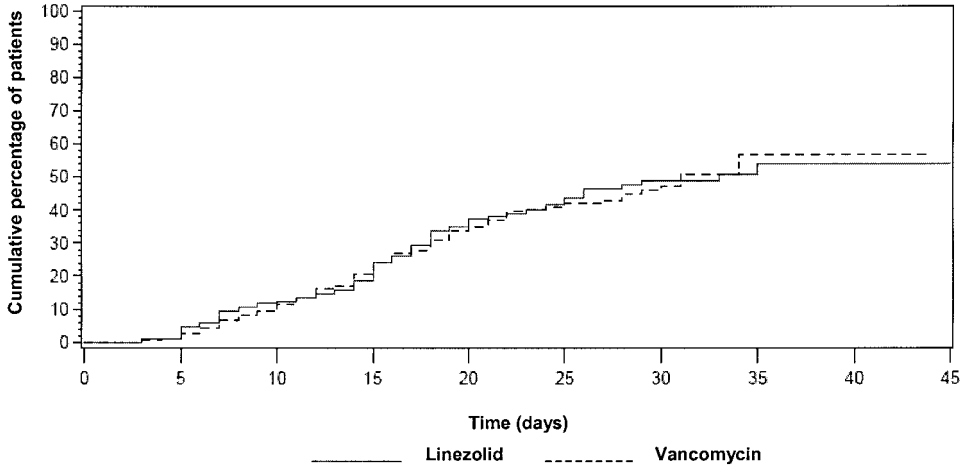

Figure 3. Kaplan-Meier analysis of time to recovery of the platelet count to >100 × 10^3 platelets/mm^3 in the intent-to-treat population

discontinuations associated with adverse events. Adverse events were similar to those in the phase III program [25]. Linezolid appeared to have a safety advantage based on the incidence of drug-related adverse events, drug-related episodes of renal failure, and all-causality episodes of renal failure.

We did not control use of antibiotics with activity against gram-negative bacteria, fungi, or viruses, but we confirmed absence of between-group differences. Furthermore, clinical success rates were similar after we excluded patients who received potentially effective antibiotics for intercurrent illness or who received antifungal or antiviral drugs (data not shown).

In conclusion, there is no clear gold standard for treatment of febrile neutropenic patients with cancer and gram-positive bacterial infections. In this study, efficacy was generally similar in linezolid- and vancomycin-treated patients. The defervescence advantage in the MITT and microbiologically evaluable subsets, coupled with transiently delayed absolute neutrophil count recovery, merits further analysis, to determine the kinetics and mechanism of linezolid's effect in patients with bacterial infection. Linezolid was well tolerated, with safety in these patients similar to that in other populations, and treatment did not appear to have negative effects on platelet recovery, a concern in this high-risk population. Linezolid appears to offer a useful option for febrile neutropenic patients with cancer who are candidates for vancomycin therapy, especially if resistance is suspected or documented.

Acknowledgments

We thank the investigators for enrolling and monitoring their patients, Sue K. Cammarata for closing the study and analyzing the data, Zhengquing Li for critically reviewing the manuscript, and Cindy W. Hamilton for assisting with manuscript preparation.

Financial support. The study was supported by a grant from Pfizer. The authors had complete access to all data and had final control over the content, review, and submission of the manuscript.

Potential conflicts of interest (authors). B.J., G.M., and J.P.-O. received research grants from Pfizer. C.S.H., L.B.L, and K.J.T. are employed by Pfizer.

Potential conflicts of interest (acknowledged contributors). S.K.C. was employed by Pharmacia (now part of Pfizer) at the time of the study and is now employed by Novartis; Z.L. is employed by Pfizer; and C. W. H. is a consultant for Pfizer.

References

1. Hughes WT, Armstrong D, Bodey GP, et al. 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis **2002**; 34:730–51.
2. Gibson J, Johnson L, Snowdon L, et al. Trends in bacterial infections in febrile neutropenic patients: 1986–1992. Aust N Z J Med **1994**; 24: 374–7.
3. Elting LS, Rubenstein EB, Rolston KV, Bodey GP. Outcomes of bacteremia in patients with cancer and neutropenia: observations from two decades of epidemiological and clinical trials. Clin Infect Dis **1997**; 25:247–59.
4. Shenep JL, Hughes WT, Roberson PK, et al. Vancomycin, ticarcillin, and amikacin compared with ticarcillin-clavulanate and amikacin in the empirical treatment of febrile, neutropenic children with cancer. N Engl J Med **1988**; 319:1053–8.
5. Hiramatsu K, Hanaki H, Ino T, Yabuta K, Oguri T, Tenover FC. Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility. J Antimicrob Chemother **1997**; 40:135–6.
6. Smith TL, Pearson ML, Wilcox KR, et al. Emergence of vancomycin resistance in *Staphylococcus aureus*. Glycopeptide-Intermediate *Staphylococcus aureus* Working Group. N Engl J Med **1999**; 340:493–501.
7. Brickner SJ, Hutchinson DK, Barbachyn MR, et al. Synthesis and antibacterial activity of U-100592 and U-100766, two oxazolidinone antibacterial agents for the potential treatment of multidrug-resistant gram-positive bacterial infections. J Med Chem **1996**; 39:673–9.
8. Zurenko GE, Yagi BH, Schaadt RD, et al. In vitro activities of U-100592 and U-100766, novel oxazolidinone antibacterial agents. Antimicrob Agents Chemother **1996**; 40:839–45.
9. Rubinstein E, Cammarata S, Oliphant T, Wunderink R. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. Clin Infect Dis **2001**; 32:402–12.
10. Wunderink RG, Cammarata SK, Oliphant TH, Kollef MH. Continuation of a randomized, double-blind, multicenter study of linezolid versus vancomycin in the treatment of patients with nosocomial pneumonia. Clin Ther **2003**; 25:980–92.
11. Weigelt JA, Itani KM, Lau WK, Somero MS. Linezolid vs vancomycin in the treatment of complicated skin and soft tissue infections (CSSTI): clinically significant outcome differences [abstract 314]. In: Program and abstracts of the 40th Annual Meeting of the Infectious Disease Society of America (San Diego). Alexandria, VA: Infectious Diseases Society of America, **2003**:87.
12. Stevens DL, Herr D, Lampiris H, Hunt JL, Batts DH, Hafkin B. Linezolid versus vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* infections. Clin Infect Dis **2002**; 34:1481–90.
13. Stevens DL, Harrison M, Graham DR, Glick HA, Birmingham MC. Linezolid (LZD) IV/PO vs. Vancomycin (Vanco) IV for the treatment of suspected or proven methicillin-resistant staphylococcus spp. (MRSS) infections: a second randomized, open-label, clinical trial [abstract 181]. In: Program and abstracts of the 40th Annual Meeting of the Infectious Disease Society of America (Chicago). Alexandria, VA: Infectious Diseases Society of America, **2002**:76.
14. Makuch R, Simon R. Sample size requirements for evaluating a conservative therapy. Cancer Treat Rep **1978**; 62:1037–40.
15. Blackwelder WC. "Proving the null hypothesis" in clinical trials. Control Clin Trials **1982**; 3:345–53.
16. Cometta A, Kern WV, De Bock R, et al. Vancomycin versus placebo for treating persistent fever in patients with neutropenic cancer receiving piperacillin-tazobactam monotherapy. Clin Infect Dis **2003**; 37: 382–9.
17. Ramphal R, Bolger M, Oblon DJ, et al. Vancomycin is not an essential component of the initial empiric treatment regimen for febrile neutropenic patients receiving ceftazidime: a randomized prospective study. Antimicrob Agents Chemother **1992**; 36:1062–7.
18. Erjavec Z, de Vries-Hospers HG, Laseur M, Halie RM, Daenen S. A prospective, randomized, double-blinded, placebo-controlled trial of empirical teicoplanin in febrile neutropenia with persistent fever after imipenem monotherapy. J Antimicrob Chemother **2000**; 45:843–9.
19. Hachem RY, Hicks K, Huen A, Raad I. Myelosuppression and serotonin syndrome associated with concurrent use of linezolid and selective serotonin reuptake inhibitors in bone marrow transplant recipients. Clin Infect Dis **2003**; 37:e8–11.
20. Halpern M. Linezolid-induced pancytopenia. Clin Infect Dis **2002**; 35: 347–8.
21. Nimeiri HS, Nemiary DS. Challenges with linezolid therapy and reversible pancytopenia. Ann Hematol **2003**; 82:533.
22. Hansen NE, Karle H, Valerius NH. Neutrophil kinetics in acute bacterial infection: a clinical study. Acta Med Scand **1978**; 204:407–12.
23. Jung U, Norman KE, Scharffetter-Kochanek K, Beaudet AL, Ley K.

Transit time of leukocytes rolling through venules controls cytokine-induced inflammatory cell recruitment in vivo. J Clin Invest **1998**; 102: 1526–33.

24. Nasraway SA, Shorr AF, Kuter DJ, O'Grady N, Le VH, Cammarata SK. Linezolid does not increase the risk of thrombocytopenia in patients with nosocomial pneumonia: comparative analysis of linezolid and vancomycin use. Clin Infect Dis **2003**; 37:1609–16.
25. Rubinstein E, Isturiz R, Standiford HC, et al. Worldwide assessment of linezolid's clinical safety and tolerability: comparator-controlled phase III studies. Antimicrob Agents Chemother **2003**; 47:1824–31.