MAJOR ARTICLE

Vancomycin versus Placebo for Treating Persistent Fever in Patients with Neutropenic Cancer Receiving Piperacillin-Tazobactam Monotherapy

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This prospective, double-blind trial assessed whether the addition of a glycopeptide would be able to reduce the time to defervescence in neutropenic patients with cancer who had persistent fever 48–60 h after the initiation of empirical piperacillin-tazobactam monotherapy. Of 763 eligible patients, 165 with persistent fever were randomized to receive piperacillin-tazobactam therapy plus either vancomycin therapy or placebo. Defervescence was observed in 82 (95%) of 86 patients in the vancomycin group and in 73 (92%) of 79 patients in the placebo group ($P = .52$). The distributions of the time to defervescence were not statistically significant between the 2 groups (estimated hazard ratio, 1.03; 95% confidence interval, 0.75–1.43; $P = .75$). The number of additional episodes of gram-positive bacteremia and the percentage of patients for whom amphotericin B was empirically added to their therapy regimen were also similar in both groups. This study failed to demonstrate that the empirical addition of vancomycin therapy to the treatment regimen is of benefit to persistently febrile neutropenic patients with cancer.

Therapeutic changes are a common clinical practice for granulocytopenic patients with cancer and persistent fever, despite the absence of clinical deterioration and/or documented infection with a microorganism resistant to the allocated regimen. In 3 large trials assessing the efficacy of meropenem or ceftazidime monotherapy, the most frequent treatment modification was the addition of a glycopeptide antibiotic (i.e., vancomycin or teicoplanin) after 3–4 days of empirical therapy, mainly for the treatment of persistent fever [1–3]. However, to date, no study has documented that this practice is of any benefit to such patients. In addition, the indiscriminate administration of glycopeptides is expensive and might lead to increased resistance among staphylococci and enterococci, which would in itself have major clinical implications [4].

Because the addition of vancomycin did not reduce mortality in any previous study and was primarily jus-

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tified by the presence of persistent fever, the primary objective of this prospective, randomized, multicenter, double-blind trial was to assess whether the addition of a glycopeptide would be able to reduce the time to defervescence in neutropenic patients who had persistent fever 48–60 h after the initiation of empirical piperacillin-tazobactam (P-T) monotherapy [5–7]. The choice of P-T as the initial monotherapy was based both on data that showed that administration of empirical monotherapy is feasible for febrile granulocytopenic patients and on results of in vitro susceptibility testing of bacteria, which caused bacteremia in neutropenic patients randomized in our previous trials, that showed that P-T has the potential to be effective in the management of these infections [1–3, 8–10].

PATIENTS AND METHODS

Eligibility criteria. This trial comprised patients from 34 centers of the International Antimicrobial Therapy Group of the European Organisation for Research on Treatment of Cancer (EORTC-IATG) located in Europe, the Middle East, and North America. Febrile granulocytopenic patients with cancer were enrolled in the trial if they met the following inclusion criteria: (1) a diagnosis of leukemia, lymphoma, or Hodgkin disease or receipt of a stem cell or bone marrow transplant (allogenic or autologous) for the treatment of neoplastic disease; (2) an absolute granulocyte count of $\leqslant$1000 cells/mm^3, which was anticipated to decrease to <500 cells/mm^3 within 24–48 h and was expected to remain at this level for >7 days after the onset of fever; (3) a fever (oral or axillary temperature, $\geqslant$38.5°C [101.3°F] once, or >38°C [100.4°F] on $\geqslant$2 occasions separated at least by 1 h during a 12-h period); and (4) had presumed bacterial infection. Exclusion criteria were as follows: age of <2 years; receipt of intravenous antibacterial agent within 4 days before the initiation of study; known allergy to any of the antibiotics used in this trial; previous inclusion in the study; renal failure requiring hemodialysis or peritoneal dialysis, serum creatinine level of >200 μmol/L or 2.25 mg/dL or estimated creatinine clearance of <40 mL/min in adult patients; high probability of death within 48 h; and documented catheter-related infection, presence of lung infiltrate, pregnancy, or known HIV infection.

In case of persistent fever (defined as an oral or axillary temperature of >38°C twice in the previous 12 h or of >38.5°C once), patients were randomized to receive either vancomycin therapy or placebo in addition to P-T therapy, provided that they had persistent neutropenia and had received a diagnosis of possible infection (fever of unknown origin), clinically documented infection, or microbiologically documented infection due to P-T–susceptible gram-positive bacteria (such as methicillin-susceptible staphylococci, streptococci, or enterococci). Patients were not randomized if they were no longer febrile or neutropenic or if they had persistent fever and 1 of the following conditions present at initial enrollment (i.e., onset of fever): microbiologically documented infection due to gram-negative bacteria; microbiologically documented infection due to P-T–resistant gram-positive bacteria (e.g., methicillin-resistant staphylococci or penicillin-resistant streptococci); microbiologically documented viral, fungal, or mixed infection; clinically documented catheter-related infection; or a documented lung infiltrate.

Enrollment and randomization procedures. All patients who fulfilled the inclusion criteria received P-T therapy. Then, between 48 and 60 h later, if the patient was persistently febrile and neutropenic, the investigator checked whether the patient was eligible for randomization into the vancomycin-placebo trial. Data for both initial enrollment and subsequent randomization were centralized at the EORTC-IATG Data Center in Brussels, as previously described [11]. Data for treatment allocation was computerized, and randomization was dynamically performed after the application of a randomization algorithm, which used the minimization technique of a global imbalances function between the 2 treatment arms, with the following 3 stratification variables: name and location of study center, infection documentation at randomization, and underlying disease (i.e., any cancer that required bone marrow transplantation, such as leukemia, lymphoma, or Hodgkin disease).

Hypotheses and statistical considerations. The primary objective of the trial was to compare the overall distribution of the time to defervescence between granulocytopenic patients with cancer and persistent fever who were initially treated with P-T and randomized to receive vancomycin therapy and those randomized to receive placebo. We estimated that the addition of vancomycin therapy should have decreased the febrile period by at least 36 h to be clinically meaningful. To determine the required sample size, we assumed that the ratio of the risks of defervescence (hazard ratio) did not change with time. We estimated that the study should be powered such as to reject the hypothesis that there was no significant difference in the time to defervescence between the 2 arms, given a hazard ratio of 1.6. This value of 1.6 was based on an expected median additional time to defervescence of 96 h in the placebo group (according to a previous trial [12]) and on a reduction in the additional time to defervescence of 36 h in the vancomycin group. Thus, using a 2-tailed log-rank test with the assumption of ~20% of censored data, we calculated that 113 assessable patients per arm would have been necessary (with an α error of 0.05 and a β error of 0.15) to show a decrease in the median time to defervescence from 96 to 60 h in the vancomycin arm. Thus, a total sample size of 226 assessable patients was required.

On the basis of our experience, we also estimated that the proportion of febrile and granulocytopenic patients with cancer who were suitable for randomization should have approached 45% of the total population of febrile neutropenic patients

enrolled in the trial [12]. Therefore, we planned to enroll ~500 patients to be able to randomize ~250 patients. However, during the study, it became clear that only 20% of the enrolled patients were actually eligible for randomization. For this reason, we first extended the study period from 24 to 30 months and then decided to close the study, but this decision was not driven by treatment-arm comparisons. On the basis of the number of cases of defervescences actually observed, the power to detect a hazard ratio of 1.6 (in other words, a decrease of 36 h in the median time to defervescence) decreased from 85% to 78%.

Statistical evaluation of treatment response. Definitions of febrile episodes and additional infections, clinical assessments, toxicity, and microbiological methods have been described previously [12]. Death was attributed to infection when it occurred as a direct consequence of either the presenting infection or an additional infection. All case reports were reviewed by the Data Review Committee of the EORTC-IATG for completeness, accuracy, eligibility criteria, and assessment of the outcome variables.

The primary end point of efficacy was the time to defervescence after randomization. Defervescence or resolution of fever was defined as a period of 3 complete days with a temperature of <38°C. Other end points were the number of patients who defervesced during receipt of the protocol regimen, the number of patients who remained febrile on day 6 after initiation of the protocol regimen, the number of patients who had additional episodes of gram-positive bacteremia, and the number of patients who received amphotericin B for persistent fever. The distribution of the time to defervescence in the 2 groups was estimated by the nonparametric Kaplan-Meier method. The 2 curves were then compared using a 2-tailed log-rank test; the 95% CIs for the median duration of fever before defervescence were calculated by the Brookmeyer-Crowley method. Comparisons between proportions were performed using χ^2 tests (with continuity correction) or Fisher's exact test (when required because of the sample size).

Therapeutic regimens. P-T therapy was administered at a dosage of 4.5 g q6h intravenously to adults and to children who weighed >50 kg. In smaller children, P-T was administered at a dosage of 80 mg/10 mg/kg q6h. Vancomycin was administered at a dosage of 15 mg/kg q12h (maximum daily dose, 2 g). The placebo was composed of a saccharose solution. Vancomycin and placebo were both stored in amber-colored bottles and administered via amber-colored syringes. Infusion time of either preparation was at least 1 h.

Randomized patients received P-T therapy plus vancomycin therapy or placebo for complete resolution of fever and/or of infection for a minimum of 4 consecutive days. If the patient was persistently febrile 4 full days after randomization (day 6 after enrollment), the protocol treatment regimen was stopped and the patient was treated at the discretion of the investigator. Patients enrolled in the trial were followed-up during the duration of their stay in the hospital. Blinding was maintained until all case report forms had been reviewed by the Data Review Committee of the EORTC. The study was approved by the Protocol Review Committee of the EORTC and by the ethical committees at each participating institution. Informed consent was provided by all patients who fulfilled the inclusion criteria.

RESULTS

A flowchart describing the whole study is provided in figure 1. Briefly, from December 1997 through June 2000, 859 febrile neutropenic patients with cancer were enrolled in the study to receive P-T monotherapy. Of these patients, 96 were ineligible for several reasons, including having an expected short course of neutropenia or no neutropenia ($n = 65$), no cancer ($n = 10$), or no fever ($n = 6$); previous inclusion in the trial ($n = 5$); presence of a lung infiltrate ($n = 5$); and other reasons ($n = 5$). Between hours 48 and 60 after the initiation of P-T monotherapy, we determined that, of the remaining 763 patients, 598 were not eligible for randomization in the double-blind study. Of these 598 patients, 422 were no longer febrile, 129 had documented infections incompatible with randomization (gram-negative bacteremias in 90 [13], P-T resistant gram-positive bacteremias in 17, catheter-related infections in 10, lung infiltrates in 9, viral infections in 2, fungal infection in 1), and 47 had other exclusion criteria (modification of the antibiotic regimen for 25 patients, neutropenia clearance in 12, dropout toxicity for 5, and other criteria for 5).

After 48–60 h of P-T monotherapy, 165 eligible patients were randomized to receive either vancomycin therapy ($n = 86$) or placebo ($n = 79$), in addition to P-T therapy. The median interval between the initiation of empirical P-T therapy and the first infusion of vancomycin therapy or placebo was 58 h in both groups. There were no significant differences between the groups in any demographic characteristics (table 1). In particular, the 2 groups were well balanced with respect to underlying disease, duration of neutropenia, and documentation of infection. Fevers of unknown origin accounted for the majority of febrile episodes (62 patients in the vancomycin group and 58 patients in the placebo group). Clinically documented infections (14 in the vancomycin group and 13 in the placebo group) included mucositis (8 in the vancomycin group and 6 in the placebo group), gastrointestinal infection (1 in the vancomycin group and 4 in the placebo group), respiratory tract infection (1 in the vancomycin group and 3 in the placebo group), perianal infection (3 in the vancomycin group), and skin and soft tissue infection (1 in the vancomycin group). Most of the cases of bacteremia were due to viridans streptococci susceptible to

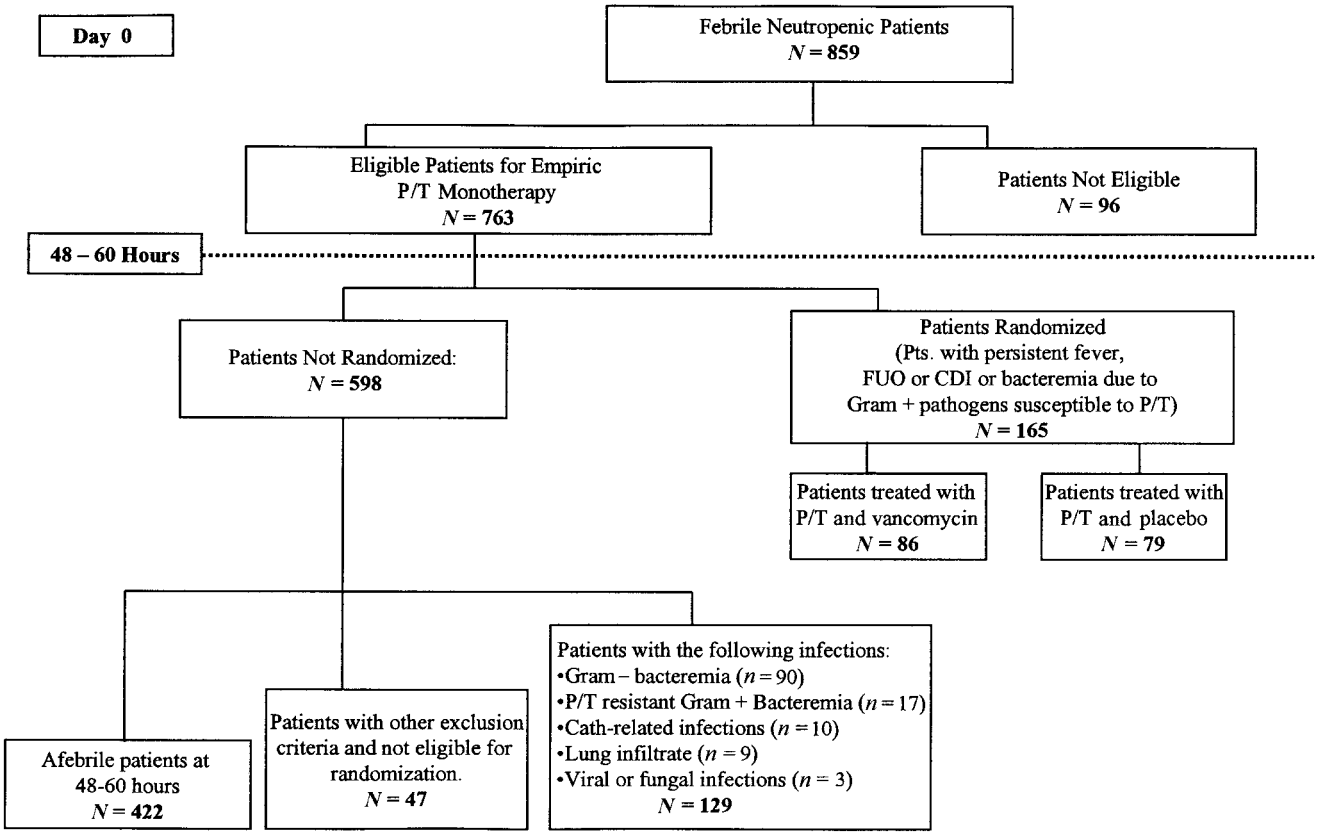

Figure 1. Flowchart illustrating the study design. CDI, clinically documented infection; FUO, fever of unknown origin; P/T, piperacillin-tazobactam; +, positive; −, negative.

P-T and vancomycin (9 of 10 patients and 6 of 8 patients in the vancomycin and placebo groups, respectively). Other gram-positive bacteria susceptible to P-T and vancomycin that were recovered from bacteremic patients were coagulase-negative staphylococci ($n = 3$), *Enterococcus faecalis* ($n = 2$), and *Micrococcus* species ($n = 1$) (3 of whom had polymicrobial gram-positive bacteremia).

After randomization, resolution of fever was observed in 82 (95%) of 86 patients and 73 (92%) of 79 patients in the vancomycin and placebo groups, respectively ($P = .52$) (table 2). This occurred without any modification to the therapy administered to 42 patients (49%) who received vancomycin therapy and to 36 patients (46%) who received placebo ($P = .79$). The most frequent modification was the addition of a glycopeptide after the administration of vancomycin therapy or placebo was stopped: indeed, open-label vancomycin or teicoplanin therapy was added to the treatment regimen for 36 patients (42%) in the vancomycin group and for 34 patients (43%) in the placebo group ($P = 1$). The median time to defervescence after the addition of vancomycin therapy or placebo was 3.5 days (95% CI, 2.7–4.4) in the vancomycin group and 4.3 days (95% CI, 3.5–5.1) in the placebo group, with a difference that was not statistically significant ($P = .75$; figure 2). Using data for the placebo arm as a reference, we estimated the hazard ratio between the 2 distributions to be 1.03 (95% CI, 0.75–1.43).

Likewise, there was no significant difference between the 2 treatment groups when the analysis was restricted to 142 patients (76 in the vancomycin group and 66 in the placebo group) who received the allocated regimen for 4 full days after randomization. The median time to defervescence was 3.1 days (95% CI, 2.3–4.0) and 4.0 days (95% CI, 3.3–4.7) in the vancomycin and placebo groups, respectively ($P = .91$). Additional episodes of gram-positive bacteremia occurred in 7 patients, 3 of which were caused by *Staphylococcus aureus, Enterococcus* species, and *Corynebacterium* species in the vancomycin group and 4 of which were caused by coagulase-negative staphylococci (in 3 patients) and *S. aureus* (in 1 patient) in the placebo group; all gram-positive bacteria were susceptible to vancomycin. Finally, the rate of addition of amphotericin B to the therapeutic regimen was similar in both groups: 31 (36%) of 86 patients and 30 (38%) of 79 patients received amphotericin B in the vancomycin and placebo groups, respectively.

Overall mortality rates did not differ significantly between the 2 groups ($P = .23$). Death was reported for 12 (7%) of 165 randomized patients. Four (5%) of 86 patients who received

Table 1. Demographic and clinical characteristics of neutropenic patients with cancer and persistent fever who were randomized in the vancomycin-placebo study.

Characteristic	Patients who received piperacillin-tazobactam therapy plus	
	Vancomycin therapy (n = 86)	Placebo (n = 79)
Adults	81	75
Age, median years (range)	42 (4–76)	42 (4–78)
Underlying disease		
Acute leukemia	53 (62)	48 (61)
Lymphoma or Hodgkin disease	31 (36)	26 (33)
Other	2 (2)	5 (6)
Transplantation-associated		
Stem cell or autologous	20 (23)	20 (25)
Allogenic	4 (5)	5 (6)
Neutropenia		
Duration, mean days ± SD (range)	18 ± 1.6 (5–74)	18 ± 1.7 (5–69)
Neutrophil count,[a] median cells/mm^3 (range)	20 (0–816)	30 (0–620)
Oral prophylaxis received		
Fluoroquinolone	26 (30)	26 (33)
Cotrimoxazole	6 (7)	5 (6)
Antifungal	34 (40)	35 (44)
Antiviral	23 (27)	20 (25)
Documentation of febrile episode		
Gram-positive bacteremia	10 (12)	8 (10)
Clinically documented infection	14 (16)	13 (16)
Fever of unknown origin	62 (72)	58 (73)
Type of iv line received before onset of fever	66 (77)	65 (82)
Peripheral	16	18
Central	32	28
Port-a-Cath or Hickman	18	19

NOTE. Data are no. or no. (%) of patients, unless otherwise indicated.

[a] At the time of enrollment in the study.

vancomycin therapy died between days 14 and 31 after study entry; death was due to infection in 1 (gram-negative bacteremia [death occurred on day 14]), to extensive cancer in 2, and to hemorrhage in 1. Eight (10%) of 79 placebo-treated patients died between days 7 and 35; death was due to infection in 2 (gram-negative bacteremia complicated by acute respiratory distress syndrome [death on day 15] and diffuse peritonitis with pseudomembranous colitis complicated by acute respiratory distress syndrome [death on day 35]). The other causes of death were hemorrhage and extensive cancer in 3 patients each.

In the vancomycin group, adverse events definitely or probably associated with antibiotics were reported in 9 (10%) of 86 patients: rash occurred in 3 patients, pruritus in 2, nephrotoxicity in 2, swelling of the lips in 1, and red man syndrome in 1. In the placebo group, adverse events definitely or probably associated with antibiotics were reported in 3 (4%) of 79 patients and included pseudomembranous colitis, diarrhea, and rash. The difference in the occurrence of adverse events was not statistically significant between the 2 groups (P = .14).

DISCUSSION

The empirical modification, merely on the basis of persistent fever, of the antibacterial therapy regimen for neutropenic patients has become very popular in hematological centers. The most frequent modification is the addition of a glycopeptide. For example, in a previous EORTC-IATG trial, 28% of the patients received a glycopeptide on the basis of persistent fever [3]. In 2 other studies, the percentage of patients who received empirical addition of vancomycin therapy were 26% [1] and 31% [14]. This broad administration of glycopeptides is of concern, given the emergence of vancomycin-resistant gram-

Table 2. Resolution of fever and time to defervescence in randomized neutropenic patients with cancer and persistent fever (intent-to-treat population).

Variable	Patients who received piperacillin-tazobactam therapy plus	
	Vancomycin therapy (n = 86)	Placebo (n = 79)
Fever resolved[a]	82 (95)	73 (92)
Fever resolved during receipt of protocol therapy[a]	42 (49)	36 (46)
Fever resolved after change of protocol therapy[a]	40 (47)	37 (47)
Fever did not resolve	4 (5)	6 (8)
Fever present[b]	38 (44)	41 (52)
Time to defervescence, median days (95% CI)[a]	3.5 (2.7–4.4)	4.3 (3.5–5.1)

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] $P > .5$.

[b] At day 6 after initiation of protocol therapy (with or without change of antibiotic treatment).

positive cocci [15]. No study has ever documented the benefit of this practice, and we decided to implement a prospective, randomized, clinical trial comparing the efficacy of vancomycin therapy with that of placebo for treating persistently febrile neutropenic patients. Given that, in a retrospective analysis of a previous trial, the median additional time to defervescence among patients still febrile after 2 days of empirical therapy was 4 days, we estimated that a constant hazard reduction of 1.6, corresponding to a reduction of at least 1.5 days, would have been necessary to justify the addition of vancomycin [12].

In the present study, the addition of vancomycin to the treatment regimen resulted in an estimated hazard ratio of 1.03 and a 95% CI of 0.75–1.43. A constant hazard ratio of 1.43 corresponds to a decrease in the median time to defervescence in the vancomycin arm of ~30 h. This means that a decrease of 1.5 days, which is a priori considered to be a clinically meaningful reduction, is unlikely to occur. In the absence of a benefit to the main end point of efficacy, these data suggest that, despite the reduced size of the expected sample size and the consecutive reduction of the power of the trial from 85% to 78%, the empirical addition of vancomycin therapy to the treatment regimen for persistently febrile patients is not justified. This conclusion is also supported by the fact that the proportions of patients who defervesced during receipt of protocol therapy were similar in the 2 arms and the fact that there was no reduction in the number of additional episodes of gram-positive bacteremia and the percentage of patients for whom amphotericin B was empirically added to their treatment regimen.

In contrast to our previous experience, only 20% of patients enrolled in the P-T monotherapy study were eligible for inclusion in the double-blind part of the study, resulting in a lower-than-expected randomization rate [12]. This was likely due to the narrow window of time (between the 48th and the 60th hour after the onset of fever) allowed for randomization. Prolonging the time window for randomization (to the 72nd or 96th hour) would have prevented physicians from empirically adding amphotericin B to the regimen within a reasonable time frame, an option that was considered unacceptable by the majority of the participating institutions.

A recent smaller study assessed the efficacy of the addition of a glycopeptide to the treatment regimen for neutropenic patients with persistent fever [16]. After 72–96 h of imipenem monotherapy, 114 patients were randomized to receive either teicoplanin or placebo. The number of patients who defervesced within 72 h after randomization was similar in both groups (44.6% in the teicoplanin group vs. 46.6% in the placebo group), but the time to defervescence was not reported.

In view of data supporting the association between vancomycin use and the increase of vancomycin-resistant enterococci in US hospitals, the Hospital Infection Control Practice Advisory Committee has developed recommendations for prudent glycopeptide administration by clinicians [17–19]. In particular, this committee has published a list of situations in which the prescription of vancomycin should be discouraged. Thus, the data provided by these 2 trials are sufficient to add to this list the empirical addition of glycopeptides to the treatment course for persistently febrile patients without documented gram-positive infection. After the description of the first clinical isolate of *S. aureus* fully resistant to vancomycin, restricted use of glycopeptides is urgently required [15].

In conclusion, with a statistical power of 78% to detect a difference between the 2 study arms, the present study failed to demonstrate that the empirical addition of vancomycin therapy is of benefit to persistently febrile and granulocytopenic patients with cancer and without lung infiltrates, septic shock, clinically documented infections likely due to gram-positive bacteria (catheter-related or skin and soft-tissue infections), and documentation of gram-positive bacterial infections resistant

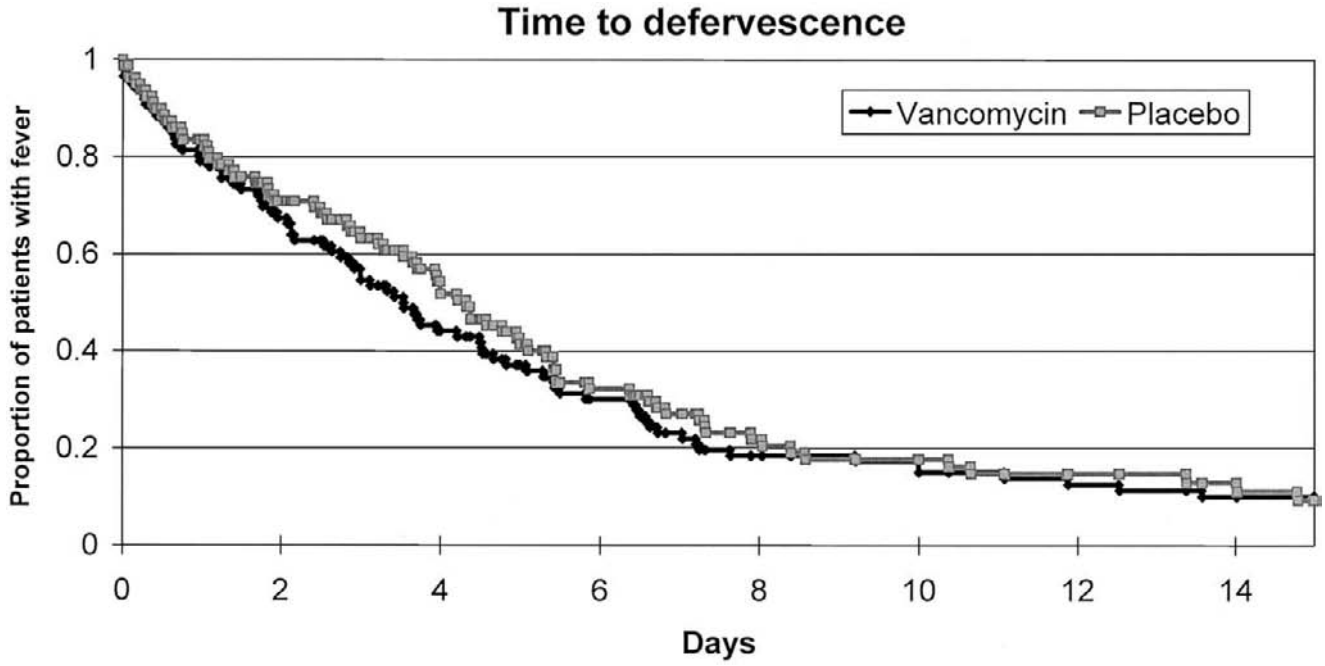

Figure 2. Time to defervescence in patients randomized to receive vancomycin therapy or placebo. The observation was censored for all patients who did not defervesce (4 in the vancomycin group and 6 in the placebo group). Time 0 indicates the date of administration of vancomycin therapy or placebo.

to P-T. Because healthy persons can be colonized by vancomycin-resistant enterococci, the indiscriminate administration of glycopeptides might exert selective pressure on the intestinal flora [20]. Therefore, appropriate administration of glycopeptides should help to decrease the emergence of glycopeptide-resistant gram-positive bacteria [21].

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