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Feasibility, efficacy, and adverse effects of outpatient antibacterial prophylaxis in children with acute myeloid leukemia

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Abstract

BACKGROUND—Intensive chemotherapy for pediatric acute myeloid leukemia (AML) incurs the risk of infectious complications, but the benefits of antibiotic prophylaxis remain unclear.

METHODS—In 103 children treated on the AML02 protocol between October 2002 and October 2008 at St. Jude Children's Research Hospital, we retrospectively assessed the effect of antibiotic prophylaxis on the frequency of febrile neutropenia, clinically or microbiologically confirmed infections (including bacteremia), and antibiotic resistance, and on the results of nasal and rectal surveillance cultures. Initially, patients received no prophylaxis or oral cephalosporin (Group A). Then the protocol was amended to give intravenous cefepime alone or intravenous vancomycin plus either oral cephalosporin, oral ciprofloxacin, or intravenous cefepime (Group B).

RESULTS—There were 334 infectious episodes. Group A had a significantly greater frequency of documented infections and bacteremia (both $P < .0001$) (including gram-positive and gram-negative bacteremia, $P = .0003$ and .001, respectively) than Group B, especially viridans streptococcal bacteremia ($P = .001$). The incidence of febrile neutropenia without documented infection was not different between the two groups. Five cases of bacteremia with vancomycin-resistant enterococci (VRE) occurred in group B (vs. none in Group A), without related mortality. Two of these cases were preceded by positive VRE rectal surveillance cultures.

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CONCLUSIONS—Outpatient intravenous antibiotic prophylaxis is feasible in children with AML and reduces the frequency of documented infection but not of febrile neutropenia. Despite emergence of VRE bacteremia, the benefits favor antibiotic prophylaxis. Creative approaches to shorten the duration of prophylaxis and thereby minimize resistance should be explored.

Keywords

acute myeloid leukemia; antibiotics; children; infection; prophylaxis

INTRODUCTION

Although long-term survival has increased in children with acute myeloid leukemia (AML),[1, 2] the highly myelosuppressive treatment frequently causes infection.[3–5] For example, more than 60% of patients in the Children's Cancer Group 2961 trial experienced at least one microbiologically documented infection during therapy, and the cumulative infectious mortality rate was 11%.[3] Viridans-group streptococci were frequently isolated.[3–7]

In adults with cancer and neutropenia, antibiotic prophylaxis reduced the frequency of febrile neutropenic episodes, clinically or microbiologically documented bacterial infection, and mortality.[8–10] These findings prompted amendment of the ongoing St. Jude Children's Research Hospital (St. Jude) AML02 protocol to include outpatient antibiotic prophylaxis with intravenous (IV) cefepime or with IV vancomycin plus oral cephalosporin/ciprofloxacin or IV cefepime.[7] In a preliminary analysis (n = 78), these regimens significantly reduced the incidence of bacterial infection, especially viridans streptococcal infection, and the duration of hospital stay.[7] In the Children's Oncology Group AAML0531 study, antibacterial prophylaxis significantly reduced the frequency of sterile-site bacterial infections, including gram-positive infections.[11] However, emergence of drug resistance remains a concern.[12, 13]

We examined the impact of antibiotic prophylaxis on the frequency of bacteremia and other clinically or microbiologically documented bacterial infections, on antibiotic sensitivity, and on nasal and rectal culture findings in the full cohort of 103 AML02 patients treated at St. Jude.

PATIENTS AND METHODS

Patients

This retrospective study included all patients enrolled in AML02 at St. Jude between October 2002 and October 2008[14] except those with mixed-phenotype acute leukemia and those who had not completed at least one course of chemotherapy. The study was approved by the St. Jude Institutional Review Board. Written informed consent was obtained from patients or their legal guardians and assent was given by the patients, as appropriate. This study was performed during 2 induction and 3 consolidation chemotherapy courses (previously described).[14] Induction 1 therapy comprised either high-dose (3 g/m^2/dose × 6 doses) or low-dose (100 mg/m^2/dose × 20 doses) cytarabine combined with daunorubicin and etoposide (ADE).[15] Initially, patients with minimal residual disease (MRD) >25% after

induction 1 received gemtuzumab ozogamicin (GO) with induction 2 therapy (ADE) and those with MRD ≥0.1% after induction 2 were given single-agent GO. The protocol was amended to administer ADE and GO as induction 2 to all patients with MRD ≥1% after induction 1, while others received ADE alone. Consolidation therapy was based on final risk assignment.[14]

Antibiotic Prophylaxis

For this study, prophylaxis comprised outpatient administration of antibacterial drugs after myelosuppressive therapy and at the onset of absolute neutrophil count [ANC] ≤ 0.5×10^9/L in the absence of fever or other indicators of infection. Prophylaxis was discontinued when the ANC exceeded 0.1×10^9/L. Complete blood counts were performed at least twice weekly. The prophylactic regimens used in AML02 were amended when short-term findings indicated the superiority of certain drug combinations.[7] Initial prophylaxis comprised oral cephalosporins, which did not prevent bacteremia. IV cefepime (1500 mg/m^2 every 12 h) was next introduced, followed by IV vancomycin (400 mg/m^2 every 12 h) given with oral cephalosporin (cefpodoxime 5 mg/kg every 12 h or cefuroxime 10 mg/kg every 12 h), oral ciprofloxacin (250 mg/m^2 every 12 h), or IV cefepime. All patients received antifungal prophylaxis with voriconazole or an echinocandin (caspofungin or micafungin) and *Pneumocystis jirovecii* prophylaxis with trimethoprim-sulfamethoxazole. Granulocyte colony-stimulating factor was not routinely given. Patients were hospitalized only during chemotherapy, and parents were trained to administer outpatient parenteral prophylactic antibiotics. During outpatient antibiotic therapy, patients either stayed at their local residences (if within 35 miles of St. Jude) or were housed in local domiciliary apartments. Neutropenic patients presenting with fever or apparent infection were admitted and treated empirically with vancomycin and cefepime (vancomycin and meropenem if they had received cefepime prophylaxis or clinically indicated). They were discharged if their blood cultures were negative for 48 hours and they became afebrile for 24 hours, and prophylactic antibiotics were resumed until count recovery.

Infection and Febrile Episodes

Infection events, including febrile neutropenia, were defined by the Common Terminology Criteria for Adverse Events (CTCAE) v3.0, and episodes ≥ grade 3 were recorded.[16] Fever was defined as an oral temperature of 38.0 °C persisting for at least 1 hour or a single oral temperature of 38.3 °C. Clinically or microbiologically documented infection events were grouped together. Blood cultures were routinely obtained from patients presenting with fever or other signs of infection. Samples obtained from all lumens of the central venous catheter were inoculated into a pair (per lumen) of vials (Bactec Plus Aerobic/F and Bactec Myco/F Lytic). Peripheral blood was cultured in parallel when feasible. A weight-based scale was used to determine the volume of blood for cultures.[17] Bloodstream infection was defined by Centers for Disease Control and Prevention (CDC) criteria,[18] with the following exception for common commensals. Because of the high risk posed by bacteremia, in patients with grade 3 or 4 neutropenia we considered even one positive blood culture to indicate a bloodstream infection with viridans streptococci or *Bacillus cereus*. All positive blood cultures obtained for febrile neutropenia or other reasons at any time during treatment were reported.

All patients underwent surveillance cultures of the nares and rectum at each admission. Nasal surveillance was conducted to detect methicillin-resistant *Staphylococcus aureus* (MRSA) and fungal pathogens. Rectal surveillance was performed to detect vancomycin-resistant *Enterococcus* (VRE) species, MRSA, *Pseudomonas* species, and fungi. *Bacillus cereus* was also noted if detected in these cultures.

Statistical Analysis

For analysis, patients were separated into three groups reflecting their prophylactic regimen during each course of treatment. Group A received no prophylaxis or only oral cephalosporin (found ineffective in reducing bacteremia[7]; no longer used prophylactically at St. Jude). Group B received IV cefepime alone or IV vancomycin plus oral cephalosporin, oral ciprofloxacin, or IV cefepime. Group C was already receiving antibiotics for fever at AML presentation or before onset of neutropenia, and therefore was unevaluable for that chemotherapy cycle.

Fisher's exact test was used to compare events of interest with prophylactic antibiotic use. A generalized linear model was used to model antibiotics, treatment phase, and treatment arm as class predictors of adverse events, with an autoregressive 1-correlation structure to account for correlation of observations within subjects. All tests were 2-sided, and $P < .05$ was considered to indicate a statistically significant difference; there was no adjustment for multiple testing. All analyses used SAS software version 9.2 (Cary, NC).

RESULTS

Patients and Infectious Adverse Events

The characteristics of the 103 children are shown in Table 1. Median age at diagnosis was 8.7 years. Neutropenia with fever of unknown origin was the most common type of infectious event, followed by infection of the bloodstream, skin/mucosa, gastrointestinal tract, and upper respiratory tract (Table 2). One patient on oral cephalosporin prophylaxis died of *Bacillus cereus* sepsis after consolidation course 2, and one died of complications of respiratory syncytial virus pneumonia after consolidation course 3.

Effect of Prophylaxis on Infectious Episodes

Table 3 lists infectious events according to antibiotic prophylaxis. Group A underwent 113 chemotherapy courses (101 without antibiotic prophylaxis, 12 with oral cephalosporin alone); group B underwent 274 courses (64 with IV cefepime alone; 210 with IV vancomycin plus oral cephalosporin [33], oral ciprofloxacin [146], or IV cefepime [31]). Group B had significantly fewer episodes of infection (any episodes) than did group A during induction 1 ($P = .002$), induction 2 ($P = .0002$), and consolidation 2 ($P = .0001$). The frequency of episodes of febrile neutropenia of unknown origin were not found to differ significantly between Groups A and B. Group B had significantly fewer clinically or microbiologically documented infections (10.9%–29.4%) than group A (40.0%–89.5%) ($P < .05$ for all chemotherapy courses except single-agent GO course). Most infectious episodes in Groups A and B occurred during consolidation 2, which had the longest median duration (44 days). When the effects of prophylaxis were evaluated in all courses combined

by taking treatment arms and courses into account in a generalized linear model, the frequency of febrile neutropenia of unknown source was similar in Groups A (33.6%) and B (30.7%; $P = .73$; hazard ratio [HR] 1.09, 95% confidence interval [CI], 0.68–1.74) but the frequency of clinically or microbiologically documented infections was significantly lower in Group B (55.8% vs. 19.7%; $P < .0001$; HR, 0.20; 95% CI, 0.13–0.31). No significant difference was seen between the incidence of clinically or microbiologically documented infections in patients who received prophylaxis with vancomycin combinations and that in those who received cefepime alone ($P = .43$; HR, 0.71; 95% CI, 0.30–1.67).

Effect of Prophylaxis on Episodes of Bacteremia

Fifty patients had 82 episodes of bacteremia (Tables 2 and 3). Bacteremia occurred most frequently during consolidation 2 (24/73 patients, 32.9%). Ninety-four microorganisms were isolated; one microorganism in 75 episodes and 2 or more in 7 episodes. All 7 polymicrobial episodes occurred during consolidation courses. Viridans group streptococci were isolated most commonly (37 isolates) followed by *E. coli* (11), *Enterococcus* species (8), and *Pseudomonas aeruginosa* (7) (Table 4).

Antibiotic prophylaxis significantly reduced the incidence of bacteremia, except during the single-agent GO treatment phase ($P < .001$) (Table 3); the frequency of bacteremia was 28.0%–78.9% in Group A and 0%–16.7% in Group B, depending on treatment phase. When all courses were analyzed together, bacteremia was significantly less frequent in Group B than Group A ($P < .0001$; HR, 0.38; 95% CI, 0.02–0.10). Both gram-positive ($P = .0003$; HR, 0.26; 95% CI, 0.13–0.53) and gram-negative ($P = .001$; HR, 0.17; 95% CI, 0.06–0.48) isolates were significantly less frequent in Group B (Table 4). This decrease in Group B was seen in patients who had only one episode of bacteremia as well as in those who experienced multiple episodes. In all, bacteremia occurred during 48.6% of Group A courses (55 of 113 courses; 1 patient experienced 2 episodes in a course) (Table 4); 13 of these courses were in patients who experienced only one bacteremia episode, and 42 were in those who had recurrent episodes. However, bacteremia occurred during only 8% of Group B courses (22 of 274 courses); 9 of these courses were in patients who had a single bacteremia episode, and 13 were in those with multiple events. There was no significant difference between the incidence of bacteremia in patients receiving prophylaxis with vancomycin combinations and that in patients receiving cefepime alone ($P = .08$; HR, 0.37; 95% CI, 0.12–1.14).

The incidence of viridans streptococcal bacteremia was strikingly reduced, from 33 in 113 courses (29.2%) in Group A to only 3 in 274 courses (1.0%) in Group B ($P = .001$; Table 4). All 3 viridans streptococci in Group B were isolated during polymicrobial bacteremia in consolidation course 2 or 3. All viridans streptococci tested were sensitive to vancomycin (n=36; 32 Group A, 3 Group B, and 1 Group C) or clindamycin (n=22; 20 Group A, 1 Group B, and 1 Group C). Reduced penicillin sensitivity was observed in 17 of 23 isolates tested (15/20 in Group A, 1/2 in Group B, 1/1 in Group C); 2/14 isolates tested showed reduced cefepime susceptibility (Group A, 1/12; Group B, 1/2).

We observed 7 episodes (22.6%) of enterococcal bacteremia in Group B during single-agent GO (n=1) or consolidation (n=6) therapy but only 1 (1.7%, single-agent GO phase) in Group A. The isolate in Group A was vancomycin-sensitive, while 5 of the 7 isolates in Group B

showed reduced vancomycin susceptibility; 3 had received vancomycin prophylaxis and 2 had received cefepime prophylaxis. Two of 5 were ampicillin-sensitive and no linezolid or quinupristin/dalfopristin resistance was noted.

Eight of 32 gram-negative isolates had reduced sensitivity to our first-line antibiotics; all eight were isolated during consolidation therapy; 5 were isolated from Group B. Seven isolates showed cefepime resistance (1 *E. coli*, 3 *Pseudomonas aeruginosa*, 1 *Enterobacter cloacae*, 2 *Klebsiella pneumoniae*), 1 (*E. coli*) showed ciprofloxacin resistance, 2 (*E. coli*, *Klebsiella pneumoniae*) showed tobramycin resistance, and 2 (both *Pseudomonas aeruginosa*) had meropenem resistance.

Fungal and *Clostridium Difficile* Infection Episodes

We identified 15 invasive fungal infections (12 culture- or histology-proven, 3 clinically diagnosed), most frequently during consolidation 2 (8 episodes), despite routine antifungal prophylaxis (Table 5). Eleven episodes occurred in Group B, although we detected no statistically significant difference between the two groups ($P = .30$; HR, 2.24; 95% CI, 0.48–10.32). Six episodes involved the lungs and 5 each, the sinuses and skin. All 12 proven cases were mold infections and were treated with posaconazole and/or liposomal amphotericin B. No deaths were related to fungal infection. *Clostridium difficile* toxin was identified in 14 episodes (8 in Group A, 5 in Group B, 1 in Group C).

Effect of Prophylaxis on Surveillance Results

Fifty six of 709 rectal surveillance cultures (7.2%) were positive, comprising 36 independent microbes (Table 6). Three (0.4%) preceded bacteremia, and 3 of the 16 bacteremia episodes of interest (18.8%) followed positive rectal surveillance. Of the 8 VRE isolates, 1 was from Group A and 7 from Group B. Three of the 7 Group B patients also had VRE bacteremia, preceding VRE bacteremia in two. All 5 *Pseudomonas aeruginosa* isolates were sensitive to cefepime, ciprofloxacin, meropenem, and tobramycin; 1 positive surveillance culture preceded bacteremia. *Candida* species were isolated in 18 surveillance cultures (17 in Groups B and C), but not associated with infectious episodes.

Nasal surveillance among 1,094 tests revealed an organism of interest in only 4 (0.2%); 2 *Aspergillus* species, 1 *Candida lusitaniae*, and 1 MRSA. None of these were associated with fungal infection or bacteremia.

DISCUSSION

Infection is a major complication of treatment for pediatric AML.[3, 19] We demonstrated that prophylaxis with vancomycin-containing regimens or cefepime alone markedly reduced the frequency of gram-positive and gram-negative bacteremia, especially viridans streptococcal bacteremia, although VRE infection was observed. Infection-related mortality rates of those treated with or without antibiotic prophylaxis were not different.

Although the incidence of nonspecific febrile neutropenia was not reduced by our prophylaxis, the incidence of clinically or microbiologically documented infection, including bacteremia, was reduced during all courses of induction and consolidation. There

was no significant difference between the incidence of clinically or microbiologically documented infections or bacteremia in those receiving vancomycin combinations and that in those receiving cefepime alone. Cefepime-only prophylaxis is useful for younger children, who cannot take oral antibiotics, and we currently use vancomycin and ciprofloxacin combination otherwise. Supportive management, including routine antibiotic and antifungal prophylaxis, routine use of granulocyte colony-stimulating factor, and criteria for discharge during neutropenia, varies considerably both within and outside of the U.S.[20, 21] At some centers, penicillin is thought to provide effective prophylaxis of viridans streptococcal infection. In our study viridans streptococci were the main cause of bacteremia, and more than half of tested isolates were penicillin-resistant; however, sensitivity patterns may differ substantially between countries or facilities. Our prophylactic antibiotic approach (cefepime alone or vancomycin-containing combinations) markedly reduced the incidence of viridans streptococcal bacteremia, as previously reported.[7] The three episodes in Group B involved polymicrobial infection and occurred during consolidation therapy. Although the primary etiology of polymicrobial infections is unclear, the greater frequency of documented infection and bacteremia during consolidation therapy is likely to reflect cumulative chemotherapy doses and prolonged myelosuppression.

A major concern we identified is the emergence of resistance, particularly VRE and resistance of gram-negative bacteria to our first-line antibiotics. Patients colonized and/or infected with such bacteria must typically undergo contact isolation, and strict infectious disease control protocols are recommended.[22–25] Antibiotic options for VRE are limited to linezolid, daptomycin, and quinupristin/dalfopristin. Patients with hematological malignancies are more susceptible to VRE than patients with other malignancies because of the routine use of broad-spectrum antibiotics.[23, 24] In our study, all five patients with VRE bacteremia were receiving antibiotic prophylaxis. Further, 8 of the 32 gram-negative bacteremia isolates obtained during consolidation phases showed reduced sensitivity to first-line antibiotics, although no substantial morbidity or mortality was associated with these bacteria. Importantly, we cannot completely differentiate the relative contributions of antibiotic prophylaxis versus routine antibiotic therapy to the emergence of resistance, because antibiotic resistance was seen primarily during later treatment phases and VRE bacteremia was observed not only in patients who received vancomycin combinations but also in those who received cefepime only. Antimicrobial stewardship can improve appropriate selection, dosing, route, and duration of overall antimicrobial use in cancer patients and limit the emergence and transmission of antimicrobial-resistant bacteria.[26]

At our hospital, rectal and nasal surveillance at admission has been routine since the 1990s. The low frequency of positive nasal findings and their lack of association with microbiologically documented infections in this study suggest that nasal surveillance offers little value. Bacteremia was not often preceded by positive rectal surveillance in this study. However, 8 of our patients had VRE rectal colonization, which preceded VRE bacteremia in 2 patients. These patients' antibiotics were changed to a VRE-appropriate regimen before the bloodstream pathogen was identified. As many as 30% of VRE-colonized patients have experienced VRE bacteremia.[23, 24] We observed *Candida* species colonization in 18 cultures (17 in patients receiving antibiotic prophylaxis or treatment) but no invasive fungal

infection. In the AML97 study, which did not use prophylactic antifungals, *Candida* and *Aspergillus* species were predominantly isolated.[27] Our routine use of antifungals likely prevented invasive candidiasis. Mold infections were noted and treated with posaconazole and liposomal amphotericin B.[28] The cost-effectiveness of rectal surveillance should be examined, especially for detection of VRE and impact on antibiotic prescription and isolation practices in patient populations heavily exposed to antimicrobials, such as ours.

Effective prophylaxis is possible but not always feasible, being prone to logistical and financial limitations. First, each center would have to train caregivers to administer outpatient IV antibiotics. Second, the cost of medication and equipment must be covered, although it would be offset by the reduced costs associated with infection.[7] Finally, this is a retrospective and sequential study with potential inherent confounding factors due to the several-year time span.

In conclusion, we have demonstrated that IV antibacterial prophylaxis is feasible in children with AML; reduces the incidence of clinically and/or microbiologically documented infection, including bacteremia; and enables outpatient management rather than the mandated hospitalization until count recovery. Although VRE infection was noted with antibiotic prophylaxis, there was no related mortality. We conclude that the benefits favor use of outpatient prophylactic antibiotics. Creative approaches are necessary to reduce the intensity and duration of prophylaxis so as to minimize the development of resistant bacterial strains.

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Table 1

Patient Characteristics at the Time of Diagnosis

Category	Clinical Feature	Number (Total, 103)
Sex		
	Female	49
	Male	54
Age (years)		
	< 1	14
	1 ~ 9	43
	10 ~ 21	46
WBC ($\times 10^9$/L)		
	< 50	71
	≥ 50	32
Race		
	White	73
	Black	23
	Other	7
FAB		
	M0	0
	M1	9
	M2	10
	M4	30
	M5	28
	M6	1
	M7	15
	MDS	0
	Unknown	10
Cytogenetics		
	t(8;21)	10
	inv(16)	16
	t(9;11)	8
	Other 11q23	14
	Normal	25
	Miscellaneous	29
	Unknown	1

WBC, white blood cell count; FAB, French-American-British; MDS, myelodysplastic syndrome

Table 2

Episodes of Febrile Neutropenia or Site-specific Clinically or Microbiologically Documented Infection, According to Treatment Phase

Anatomic Site	Induction 1 *n* (%) (101 patients)	Induction 2 *n* (%) (100 patients)	GO alone *n* (%) (12 patients)	Consolidation 1 *n* (%) (87 patients)	Consolidation 2 *n* (%) (73 patients)	Consolidation 3 *n* (%) (53 patients)	Total
(Febrile neutropenia)	64 (67.4)	33 (57.9)	7 (58.3)	25 (39.7)	33 (44.0)	9 (28.1)	171 (51.2)
Blood	9 (9.5)	14 (24.6)	3 (25.0)	19 (30.2)	24 (32.0)	13 (40.6)	82 (24.6)
Skin/mucosa	6 (6.3)	4 (7.0)	1 (8.3)	5 (7.9)	8 (10.7)	4 (12.5)	28 (8.4)
Gastrointestinal tract	4 (4.2)	2 (3.5)	0	7 (11.1)	1 (1.3)	1 (3.1)	15 (4.5)
Upper respiratory tract	5 (5.3)	0	0	4 (6.3)	2 (2.7)	1 (3.1)	12 (3.6)
Pulmonary	2 (2.1)	0	0	2 (3.2)	3 (4.0)	0	7 (2.1)
Sinus	1 (1.1)	0	0	0	3 (4.0)	1 (3.1)	5 (1.5)
Urinary tract	1 (1.1)	0	0	0	0	1 (3.1)	2 (0.6)
Other	3 (3.2)	4 (7.0)	1 (8.3)	1 (1.6)	1 (1.3)	2 (6.3)	12 (3.6)
Total	95	57	12	63	75	32	334

Febrile neutropenia was defined by Common Terminology Criteria for Adverse Events (CTCAE) v3.0. Values are the number (%) of all episodes in each treatment course. Some patients had more than one site.

GO: Gemtuzumab ozogamicin.

Table 3

Patients with Infectious Adverse Events according to Prophylactic Antibiotic Regimen

Chemotherapy phase (No. patients)	**Induction 1 (*n* = 101)**	**Induction 2 (*n* = 100)**	**GO alone (*n* =12)**	**Consolidation 1 (*n* = 87)**	**Consolidation 2 (*n* = 73)**	**Consolidation 3 (*n* = 53)**	**Total**
Course duration (days): median (range)	30 (20–54)	33 (16–53)	24 (15–44)	31 (20–88)	44 (21–121)	41 (26–120)	
Any episodes							
Patients with episodes/All patients (%)	**69/101 (68.3)**	**49/100 (49.0)**	**8/12 (66.7)**	**45/87 (51.7)**	**49/73 (67.1)**	**24/53 (45.3)**	**244/426 (57.3)**
A	22/25 (88.0)	24/32 (75.0)	4/5 (75.0)	16/23 (69.6)	19/19 (100.0)	7/9 (77.8)	92/113 (81.4)
B	24/47 (51.1)	22/64 (34.4)	4/6 (66.7)	27/62 (53.6)	28/51 (54.9)	17/44 (38.6)	122/274 (44.5)
C	23/29 (79.3)	3/4 (75.0)	0/1 (0.0)	2/2 (100.0)	2/3 (66.7)	0/0	30/39 (76.9)
***P*-value (A vs. B)**	**0.002**	**0.0002**	**1.0**	**0.05**	**0.0001**	**0.06**	**<0.0001**
Febrile neutropenia of unknown origin							
Patients with episodes/All patients (%)	**51/101 (50.5)**	**31/100 (31.0)**	**6/12 (50.0)**	**21/87 (24.1)**	**26/73 (35.6)**	**9/53 (17.0)**	**144/426 (33.8)**
A	14/25 (56.0)	11/32 (34.4)	3/5 (60.0)	4/23 (17.4)	6/19 (31.6)	0/9 (0.0)	38/113 (33.6)
B	20/47 (42.6)	18/64 (28.1)	3/6 (50.0)	15/62 (24.2)	19/51 (37.3)	9/44 (20.5)	84/274 (30.7)
C	17/29 (58.6)	2/4 (50.0)	0/1 (0.0)	2/2 (100.0)	1/3 (33.3)	0/0	22/39 (56.4)
***P*-value (A vs. B)**	**0.33**	**0.64**	**1.0**	**0.57**	**0.78**	**0.33**	**0.73**
Clinically or microbiologically documented infection							
Patients with episodes/All patients (%)	**25/101 (24.8)**	**22/100 (20.0)**	**4/12 (33.3)**	**27/87 (31.0)**	**34/73 (46.6)**	**17/53 (32.1)**	**129/426 (30.3)**
A	10/25 (40.0)	13/32 (40.6)	3/5 (60.0)	13/23 (56.5)	17/19 (89.5)	7/9 (77.8)	63/113 (55.8)
B	8/47 (17.0)	7/64 (10.9)	1/6 (16.7)	13/62 (21.0)	15/51 (29.4)	10/44 (22.7)	54/274 (19.7)
C	7/29 (24.1)	2/4 (50.0)	0/1 (0.0)	1/2 (50.0)	2/3 (66.7)	0/0	12/39 (30.8)
***P*-value (A vs. B)**	**0.046**	**0.0013**	**0.24**	**0.003**	**<0.0001**	**0.003**	**<0.0001**
Bacteremia							
Patients with episodes/All patients (%)	**9/101 (8.9)**	**13*/100 (13.0)**	**3/12 (25.0)**	**19/87 (21.8)**	**24/73 (32.9)**	**13/53 (24.5)**	**81*/426 (19.0)**
A	7/25 (28.0)	12*/32 (37.5)	2/5 (40.0)	12/23 (52.2)	15/19 (78.9)	7/9 (77.8)	55*/113 (48.7)
B	0/47 (0.0)	1/64 (1.6)	1/6 (16.7)	6/62 (9.7)	8/51 (15.7)	6/44 (13.6)	22/274 (8.0)
C	2/29 (6.9)	0/4 (0.0)	0/1 (0.0)	1/2 (50.0)	1/3 (33.3)	0/0	4/39 (10.3)
***P*-value (A vs. B)**	**0.0003**	**<0.0001**	**0.55**	**<0.0001**	**<0.0001**	**0.0003**	**<0.0001**

Values are the number (%) of patients with episodes in each treatment course.

* One patient had 2 episodes during induction 2.

GO: Gemtuzumab ozogamicin

A: Either patients received no prophylactic antibiotics or they received only prophylactic oral cephalosporins.
B: Prophylaxis with IV cefepime only or IV vancomycin plus an oral cephalosporin, oral ciprofloxacin, or IV cefepime.
C: Not evaluable.

Table 4

Isolation of Organisms from Blood Cultures, according to Prophylactic Antibiotic Regimen

Antibiotic Regimen	All	A	B	C	*P* value, A vs. B
No. evaluable courses	426	113	274	39	
No. of courses with bacteremia	81	55*	22	4	<0.0001
No. of identified bacteria	94	59	31	4	<0.0001
Gram-positive bacteria (*n*)					
Viridans group streptococci	37	33 (7)	3 (2)	1 (1)	0.001
Enterococcus species	8	1	7	0	
Bacillus cereus	4	2 (1)	2	0	
Coagulase-negative *Staphylococcus*	4	0	1	3	
Stomatococcus mucilaginosus	4	3	1	0	
Streptococcus pneumoniae	1	1	0	0	
Abiotrophia defectiva	1	0	1	0	
Lactobacillus rhamnosus/casei	1	0	1	0	
Rothia dentocariosa	1	0	1	0	
Granulicatella adiacens	1	0	1	0	
Total gram-positive (*n*)	62	40	18	4	0.0003
Gram-negative bacteria (*n*)					
Escherichia coli	11	7	4	0	
Pseudomonas aeruginosa	7	3	4	0	
Enterobacter cloacae	6	4	2	0	
Klebsiella pneumoniae	3	2	1	0	
Neisseria subflava/sicca	1	0	1	0	
Moraxella nonliquefaciens	1	1	0	0	
Burkholderia cepacia	1	1	0	0	
Capnocytophaga sputigena	1	0	1	0	
Sphingomonas species	1	1	0	0	
Total gram-negative (*n*)	32	19	13	0	0.001

*One patient had 2 episodes of bacteremia in a course.

Bloodstream infection was defined by Centers for Disease Control and Prevention (CDC) criteria, with the following exception for common commensals: even one positive blood culture was considered to indicate a bloodstream infection with viridans streptococci or *Bacillus cereus* in patients with grade 3 or 4 neutropenia. These episodes are shown in the parentheses.

A: Either patients received no prophylactic antibiotics or they received only prophylactic oral cephalosporins.
B: Prophylaxis with IV cefepime only or IV vancomycin plus an oral cephalosporin, oral ciprofloxacin, or IV cefepime.
C: Not evaluable.

Table 5

Fifteen Fungal Infections according to Chemotherapy Phase

Chemotherapy phase	Organism	Anatomic site	Antibiotic prophylaxis group
Induction 1	(Rare septate hyphae)	Lung	B
Induction 1	*Rhizopus* species	Skin	B
Induction 2	(Clinical diagnosis)	Spleen	B
Induction 2	*Fusarium oxysporum*	Sinus and skin	C
Consolidation 1	(Clinical diagnosis)	Lung	A
Consolidation 2	(Clinical diagnosis)	Lung	A
Consolidation 2	*Fusarium* species	Lung and sinus	A
Consolidation 2	*Mucor* species	Lung	B
Consolidation 2	*Exserohilum rostratum/Alternaria* species	Sinus	B
Consolidation 2	*Alternaria* species	Sinus	B
Consolidation 2	*Fusarium* species	Skin	B
Consolidation 2	*Alternaria* species/*Curvularia* species	Skin	B
Consolidation 2	*Aspergillus* species	Lung	B
Consolidation 3	*Bipolaris* species	Skin	B
Consolidation 3	*Curvularia* species	Sinus	B

A: Either patients received no prophylactic antibiotics or they received only prophylactic oral cephalosporins.
B: Prophylaxis with IV cefepime only or IV vancomycin plus an oral cephalosporin, oral ciprofloxacin, or IV cefepime.
C: Not evaluable.

Table 6

Microorganisms Isolated in Rectal Surveillance Cultures

	All	A	B	C
Microorganisms identified (*n*)	36	5	27	4
Gram positive (*n*)				
Vancomycin-resistant *Enterococcus*	8	1	7 (2)	0
Bacillus cereus	2	1	1	0
Methicillin-resistant *Staphylococcus aureus*	1	0	1	0
Total (*n*)	11	2	9	0
Gram negative (*n*)				
Pseudomonas aeruginosa	5	2 (1)	3	0
Fungus (*n*)				
Candida albicans	11	1	7	3
Candida glabrata	5	0	4	1
Saccharomyces cerevisiae	2	0	2	0
Candida parapsilosis	1	0	1	0
Candida guilliermondii	1	0	1	0
Total (*n*)	20	1	15	4

Numbers in parentheses indicate number of positive blood cultures after identification in rectal culture.

A: Either patients received no prophylactic antibiotics or they received only prophylactic oral cephalosporins.
B: Prophylaxis with IV cefepime only or IV vancomycin plus an oral cephalosporin, oral ciprofloxacin, or IV cefepime.
C: Not evaluable.