MAJOR ARTICLE

Association between Antifungal Prophylaxis and Rate of Documented Bacteremia in Febrile Neutropenic Cancer Patients

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(See the editorial commentary by Wenzel et al. on pages 1538–9)

Published data have suggested a correlation between antifungal prophylaxis and bacteremia in febrile neutropenia. This correlation was investigated among 3002 febrile neutropenic patients enrolled in 4 trials during 1986–1994. Globally, 1322 patients (44%) did not receive antifungal prophylaxis; 835 (28%) received poorly absorbable antifungal agents and 845 (28%) received absorbable antifungal agents. The rates of bacteremia for these groups were 20%, 26%, and 27%, respectively ($P = .0001$). In a multivariate model without including antifungal prophylaxis, factors associated with bacteremia were: age, duration of hospitalization, duration of neutropenia before enrollment, underlying disease, presence of an intravenous catheter, shock, antibacterial prophylaxis, temperature, and granulocyte count at onset of fever. When antifungal prophylaxis was included, the adjustment quality of the model improved slightly ($P = .05$), with an odds ratio of 1.19 (95% confidence interval [CI], 0.92–1.55) for patients receiving nonabsorbable and 1.42 (95% CI, 1.07–1.88) for those who were receiving absorbable antifungal agents. Antifungal prophylaxis with absorbable agents might have an impact on the rate of documented bacteremia in febrile neutropenia. This effect should be confirmed prospectively.

In a previous study that sought to identify, at the onset of fever during neutropenia, those patients who will eventually have documented bacteremia, we found administration of antifungal prophylaxis to be an independent prognostic factor for bacteremia. We found an OR estimate of 2.48, with 95% CI ranging from 1.49 to 4.13 on a derivation set of 558 episodes [1]. Although lacking a satisfactory clinical explanation, our group [2] and others [3–5] had already shown antifungal prophylaxis to be associated with a higher rate of bacteremia among febrile and neutropenic patients, although it may possibly be only a marker for other prognostic factors. With the aim of exploring more deeply and in a larger patient population the existence of a possible effect of antifungal prophylaxis on the rate of documented bacteremia among febrile neutropenic patients, we reviewed the whole experience of the International Antimicrobial Therapy Cooperative Group (IATCG) of the European Organization for Research and Treatment of Cancer (EORTC).

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PATIENTS AND METHODS

Patients. We analyzed data for patients who were entered in 4 trials of empirical antibiotic therapy for patients with febrile neutropenia that were undertaken by our cooperative group from 1986 through 1994 [6–9]. Multiple patient entries were not allowed in IATCG trials beginning in 1991 (trial IX) [8]. Therefore, to avoid a potential dependency between outcome data, we analyzed only first patient entries in all trials, including those in which multiple entries were allowed.

Statistical methods. The binary outcome we assessed was the presence of documented bacteremia ("yes" or "no"). The baseline characteristics of patients were analyzed by descriptive statistics, by use of frequency tabulations for categorical or categorized variables, and addition of summary parameters (median and range) for continuous variables. Independent variables were measured when the patient was randomized to a treatment group, at the onset of fever, and were those retrievable in the same way for all trials. Antifungal prophylaxis status was classified into one of the following categories: no prophylaxis, prophylaxis with only poorly absorbable agents, or prophylaxis with at least 1 absorbable agent. Poorly absorbable agents included amphotericin B, nystatin, cotrimoxazole, and miconazole. Absorbable agents included ketoconazole, fluconazole, and itraconazole. Univariate analyses were done with χ^2 tests for categorical variables and analyses of variance for continuous variables.

To assess the impact of antifungal prophylaxis on the rate of documented bacteremia, we first fitted the data with the best logistic regression model without taking into account antifungal prophylaxis. The modeled probability was the probability of final documentation of bacteremia. The variables included in the model were selected by means of a backward-forward stepwise procedure on a restricted set of covariates selected according to the results of univariate analysis. The coefficients of the logistic equation were estimated with the maximum likelihood method, and the hypothesis of the equality to 0 of these coefficients was tested by use of a likelihood ratio. All of the reported probabilities were 2-tailed, and 95% CIs were computed. In a second step, we reestimated the coefficients of the model with the addition of antifungal prophylaxis, and we compared the models by use of a likelihood ratio.

RESULTS

The characteristics of the 3080 patients with febrile neutropenia who were grouped together are shown in table 1. These patients were enrolled in the trials by 70 institutions during 1986–1994. The table also includes the number of missing observations according to each variable. The median age of patients was 38 years; 1309 patients (42%) were female, and 1619 (52%) had acute leukemia. The median granulocyte count at trial entry was 0.04×10^9 cells/L.

Antifungal prophylaxis in EORTC-IATCG trials. Information about the administration of antifungal prophylaxis was available for 3002 of 3080 patients. Of those, 1322 (44%) did not receive any antifungal prophylaxis, 835 (28%) received poorly absorbable agents, and 845 (28%) received absorbable drugs. As shown in table 2, the use of absorbable agents increased significantly over time (from 35 patients [5%] in the first trial to 514 [50%] in the last trial; χ^2 test for trend, 281.0; $P < .0001$). Characteristics significantly associated with a higher rate of administration of antifungal prophylaxis were adult age ($P < .001$), smaller size of institution (expressed by the number of patients entered in the trials), longer duration of hospitalization before the development of fever, longer duration of granulocytopenia ($<0.5 \times 10^9$ cells/L) before enrollment, a diagnosis of hematologic malignancy or bone marrow transplantation (BMT), having an iv catheter in situ, and receiving antibacterial prophylaxis ($P <$ .0001 for each of the aforementioned characteristics).

Factors associated with a diagnosis of bacteremia. A diagnosis of bacteremia was obtained in 708 (24%) of 3080 episodes of febrile neutropenia, and had a statistically significant univariate relationship with the administration of antifungal prophylaxis (χ^2 test for trend, 14.7; $P = .0001$). Indeed, the rate of bacteremia was 20% among patients not receiving any antifungal prophylaxis, 26% among those receiving poorly absorbable agents, and 27% for those taking absorbable agents. Other characteristics associated with a higher (univariate) risk of bacteremia were the following: diagnosis of hematologic malignancy ($P < .001$), underlying disease in maintenance therapy or in relapse ($P < .0001$), longer duration of granulocytopenia before fever ($P < .0001$), granulocyte count $<0.1 \times 10^9$ cells/L ($P < .0001$), presence of an iv catheter ($P < .0001$), temperature at presentation >39°C ($P < .0001$), and status of septic shock ($P < .0001$).

The covariates with values of $P < .20$ in univariate analysis were then tested in a multivariate logistic regression model, without including the antifungal prophylaxis status. The multivariate analysis included the following covariates: age, underlying disease and its status (onset or relapse), length of hospital stay before enrollment, duration of granulocytopenia before enrollment, presence of an iv catheter, presence of shock, temperature, granulocyte count, and administration of antibacterial prophylaxis. The specifications of the model are presented in table 3 with OR estimates for the listed categories (an OR>1 was associated with a higher rate of bacteremia). In this model, the characteristics identified as independently associated with a higher rate of documented bacteremia were age >30 years, diagnosis of acute lymphoblastic leukemia, disease status different from acute leukemia in first induction treatment, longer

Table 1. Characteristics of 3080 patients enrolled in study of 4 trials of antifungal prophylaxis and bacteremia.

Characteristic (no. of patients with data missing)	No. of patients	% of total sample
Trial [reference]		
V [6]	688	22
VIII [7]	672	22
IX [8]	686	22
XI [9]	1034	34
Institution, no. of patients enrolled		
<30	531	17
30–150	1596	52
>150	953	31
Sex		
Male	1771	58
Female	1309	42
Age, y		
<15	630	20
15–30	602	20
>30	1848	60
Underlying disease (16)		
Acute nonlymphocytic leukemia	1115	36
Acute lymphoblastic leukemia	504	16
Lymphoma	345	11
Solid tumor	377	12
BMT	548	18
Other condition	175	6
Disease status		
First induction	876	28
Relapse	520	17
Maintenance	347	11
Not applicable	1337	43
Presence of an iv catheter at enrollment (20)		
None	741	24
Peripheral	349	11
Central	721	24
Hickman	934	31
TIC	278	9
Other	37	1
Antibacterial prophylaxis		
No	1323	43
Yes	1757	57
Duration of hospitalization before enrollment, d [a] (55)		
0	711	24
1–10	850	28
>10	1464	48
Duration of granulocytopenia before enrollment, d [b] (449)		
0	203	8
1–5	1340	51
6–15	878	33
>15	210	8
Granulocyte count at enrollment $\times 10^9$ cells/L [c] (40)		
<0.1	2068	68
0.1–0.499	665	22
⩾0.5	307	10
Temperature at enrollment , °C [d] (25)		
38.0–38.9	2041	67
39.0–39.9	901	29
⩾40.0	113	4
Shock at enrollment (23)		
No	3002	98
Yes	55	2
Site of infection at enrollment		
No site detectable	1882	61
Upper respiratory tract	470	15
Lung	311	10
Gut	102	3
IV catheter	78	3
Other site	237	8
Antifungal prophylaxis (78)		
None	1322	44
Poorly absorbable agent	835	28
Absorbable agent	845	28

(*continued*)

NOTE. ALL, acute lymphoblastic leukemia; ANLL, acute nonlymphoblastic leukemia; BMT, bone marrow transplantation; TIC, totally implantable catheter.

[a] Median, 10 d; range, 0–175 d.
[b] Range, 0–690 d.
[c] Median, 0.04; range, 0–0.998.
[d] Median, 38.6°C; range, 38.0–41.5 °C.

duration of in-hospital stay, granulocyte count $<0.1 \times 10^9$ cells/L, presence of a central venous access other than a totally implantable catheter, presence of fever >39°C, and presence of septic shock.

Impact of antifungal prophylaxis on the risk of bacteremia. Table 4 shows the coefficient estimates, with ORs and CIs, of the model of factors including antifungal prophylaxis that predict bacteremia. The addition of antifungal prophylaxis slightly improved the quality of the model ($P = .05$), whereas the ORs of the other variables remained similar to those identified in the logistic model, not including antifungal prophylaxis. This suggests that antifungal prophylaxis had a possible prognostic value for documented bacteremia, which was independent from the variables previously considered. However, only the CI for the category of absorbable agents did not overlap 1 (point estimate, 1.42; CI, 1.07–1.88), suggesting that the effect on the rate of documented bacteremia was restricted to this type of prophylaxis.

DISCUSSION

The possible role of antifungal prophylaxis with azole compounds in increasing the rate of bacteremia among febrile neutropenic patients was first raised by Palmblad et al. [4] in 1992. In a small, randomized, double-blind trial of ketoconazole versus placebo, they found that the incidence of febrile episodes

Table 2. Use of antifungal prophylaxis in trials of the International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer.

Antifungal prophylaxis	Trial, year			
	V, 1991	VIII, 1993	IX, 1995	XI, 1996
No	329 (49)	355 (58)	298 (43)	340 (33)
Yes				
PAA	304 (46)	195 (32)	156 (23)	180 (17)
AA	35 (5)	64 (10)	232 (34)	514 (50)

NOTE. Data are no. (%) of patients. χ^2 test for trend, $P <$ .0001. PAA, poorly absorbable agent; AA, absorbable agent.

was the same in both groups but that the administration of ketoconazole was apparently affecting the type of fever documentation. Indeed, the rate of bacteremia was higher among patients who received ketoconazole than among those who received placebo (74% vs. 37%). Because of the small size of the study (107 patients), there was the possibility that this difference was due to chance. However, similar results were also reported by Schaffner and Schaffner [5] in a slightly larger study of fluconazole versus placebo. They reported a 36% incidence rate of bacteremia in fluconazole recipients versus 21% in placebo recipients. Both studies found some evidence suggesting that this effect might have been related to a longer duration of neutropenia in patients receiving antifungal prophylaxis.

In a randomized, prospective study of fluconazole prophylaxis, Kern et al. [10] also found that microbiologically documented infections were more frequent among patients who received fluconazole (50% vs. 31%) and that this was mainly due to a higher incidence rate of bacteremia (42% vs. 22%). More recently, in a large prospective, randomized clinical trial of itraconazole oral solution versus placebo, Menichetti et al. [11] again found a higher rate of bacteremia among patients who were receiving prophylaxis. Although the duration of neutropenia was the same in both groups, the rate of bacteremia was 23% among itraconazole recipients versus 15% among placebo recipients ($P = .037$). As reviewed by Palmblad [12], other authors apparently did not find the same effect, although the incidence of bacteremia was rarely reported in these studies.

The present study shows that antifungal prophylaxis, especially with absorbable antibiotics, has been administered with increasing frequency over 10 years, at least among patients entered in the 4 trials performed by the IATCG of the EORTC. This was likely related to the impact of 2 large clinical trials that showed that fluconazole, at dosages of 400 mg/day, was able to reduce the incidence of fungal infections in patients undergoing allogeneic BMT [13, 14]. However, our data show

Table 3. Factors associated with documentation of bacteremia in 2507 case patients by logistic regression model without including antifungal prophylaxis.

Covariate	Coefficient	SE	OR (95% CI)	*P*
Age >30 y (reference, ≤30 y)	0.32	0.11	1.38 (1.11–1.71)	.003
Underlying disease (reference, acute nonlymphocytic leukemia)				<.0001
Acute lymphoblastic leukemia	0.40	0.14	1.49 (1.13–.96)	.005
Other	−0.45	0.12	0.64 (0.50–0.81)	<.001
Disease status other than first induction (reference, first induction)	0.60	0.12	1.82 (1.44–2.31)	<.0001
Hospitalization, d (reference, 0)				<.0001
1–10	0.36	0.17	1.43 (1.03–2.00)	.04
>10	0.80	0.16	2.23 (1.63–3.05)	<.0001
Granulocytopenia, d (reference, 0)				.001
1–15	0.50	0.24	1.64 (1.03–2.64)	.04
>15	0.98	0.28	2.65 (1.54–4.61)	<.001
IV catheter (reference, none)				.009
Central/Hickman	0.39	0.15	1.48 (1.10–1.98)	.008
Peripheral	0.24	0.20	1.27 (0.86–1.88)	.23
TIC	0.03	0.21	1.03 (0.68–1.56)	.90
Shock (reference, none)	1.66	0.32	5.24 (2.81–9.85)	<.0001
Antibacterial prophylaxis (reference, none)	−0.25	0.11	0.78 (0.63–0.97)	.02
Temperature, °C (reference, 38.0–38.9°C)				<.0001
39.0–39.9	0.60	0.10	1.82 (1.50–2.22)	<.0001
≥40.0	1.50	0.23	4.51 (2.86–7.03)	<.0001
Granulocyte count ≥0.1×10^9 cells/L (reference, <0.1)	−0.37	0.12	0.69 (0.55–0.87)	.002

NOTE. OR>1 was associated with a higher rate of bacteremia. TIC, totally implantable catheter.

Table 4. Factors associated with documentation of bacteremia in 2507 case patients by logistic regression model including antifungal prophylaxis.

Covariate	Coefficient	SE	OR (95% CI)	*P*
Age >30 y (reference, ⩽30 y)	0.31	0.11	1.37 (1.10–1.69)	.004
Underlying disease (reference, acute nonlymphocytic leukemia)				<.0001
Acute lymphoblastic leukemia	0.41	0.15	1.51 (1.12–2.02)	.005
Other	−0.45	0.12	0.64 (0.50–0.81)	<.001
Disease status other than first induction (reference, first induction)	0.59	0.13	1.81 (1.40–2.33)	<.0001
Hospitalization, d (reference, 0)				<.0001
1–10	0.31	0.18	1.36 (0.96–1.94)	.08
>10	0.73	0.17	2.07 (1.49–2.90)	<.0001
Granulocytopenia, d (reference, 0)				.002
1–15	0.49	0.24	1.64 (1.02–2.61)	.04
>15	0.97	0.28	2.63 (1.52–4.57)	<.001
IV catheter (reference, none)				.05
Central/Hickman	0.33	0.15	1.39 (1.04–1.87)	.03
Peripheral	0.29	0.20	1.34 (0.90–1.98)	.14
TIC	−0.05	0.22	0.96 (0.62–1.46)	.83
Shock (reference, none)	1.70	0.33	5.47 (2.86–10.5)	<.0001
Antibacterial prophylaxis (reference, none)	−0.36	0.12	0.70 (0.55–0.88)	.003
Temperature, °C (reference, 38.0–38.9°C)				<.0001
39.0–39.9	0.64	0.11	1.90 (1.54–2.35)	<.0001
⩾40.0	1.60	0.23	4.95 (3.14–7.81)	<.0001
Granulocyte count ⩾0.1×10^9 cells/L (reference, <0.1)	−0.38	0.12	0.69 (0.54–0.87)	.002
Antifungal prophylaxis (reference, none)				.05
Poorly absorbable agent	0.18	0.13	1.19 (0.92–1.55)	.19
Absorbable agent	0.35	0.14	1.41 (1.07–1.88)	.01

NOTE. TIC, totally implantable catheter.

that antifungal prophylaxis might have an impact on the rate of documented bacteremia. Indeed, in univariate analysis we found a statistically significant increasing rate of bacteremia correlated with the administration of antifungal prophylaxis.

When analyzing this phenomenon in a multivariate setting, we found that administration of antifungal prophylaxis improved the quality of the model predicting bacteremia, showing a possible true impact of this procedure on the rate of bacteremia. As suggested by the OR and CI, this effect seems to be relevant mainly for patients receiving absorbable drugs. Moreover, our data indicate that there is no confounding relationship between antifungal prophylaxis and other variables significantly associated with the rate of documented bacteremia, thus confirming the possible independent role of antifungal prophylaxis, especially with absorbable drugs. We recognize that this variable might be a marker for other variables not recorded in our database. In addition we also recognize that changes might have occurred during the time of study, potentially able to affect the results of the analysis (e.g., type and frequency of antifungal prophylaxis, intensity of chemotherapy, and use of growth factors). For this reason, we believe that only studies prospectively designed with the purpose of evaluating this possible effect as a prespecified hypothesis might be able to give a definitive answer to this question.

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APPENDIX

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