

CORRESPONDENCE

Systemic antifungal prophylaxis reduces invasive fungal infections in acute myelogenous leukemia: a retrospective review of 833 episodes of neutropenia in 322 adults

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TO THE EDITOR

Although antifungal prophylaxis is thought to reduce invasive fungal infections in at least some neutropenic patients,¹ limited data exists on its utility in adults receiving chemotherapy for acute myelogenous leukemia (AML). Despite the lack of focused data on its utility in AML, prophylaxis is now commonly used. As the available large studies report patients with a mixture of underlying types of leukemia, we have retrospectively examined the impact of antifungal prophylaxis in a large consecutive series of adults with AML. To evaluate simultaneously a control population that did not receive prophylaxis, we reviewed the medical records, mycological reports and autopsy reports of patients 14 years of age or older treated at the University of Texas MD Anderson Cancer Center for AML from January 1988 to December 1992. As noted below, this period spans the introduction of fluconazole and a local change in practice towards extensive use of antifungal prophylaxis. Only patients who received remission-induction chemotherapy were eligible. Patients were excluded if they had received systemic antifungal therapy or had documented fungal or mould infection within the month prior to study entry or if they had *Aspergillus* colonization of the nasal cavity.

Three hundred and thirty-one patients with 974 episodes of neutropenia met enrolment criteria. Of these, complete records were available on 851 episodes of neutropenia in 322 patients. After excluding 18 episodes of neutropenia because of an invasive fungal infection during a prior episode of neutropenia, 833 episodes of neutropenia in 322 patients remained. These episodes of neutropenia spanned two significant time frames. Between January 1988 and December 1990 there were 453 qualifying episodes of neutropenia in 186 patients. Fluconazole was largely unavailable during this time, a systemic antifungal agent was given in only 174 (38%) of episodes, and that agent was amphotericin B (49%), fluconazole (34%) and other agents (17%). However, systemic antifungal prophylaxis was given during 305 (80%) of the 380 episodes of neutropenia in 151 patients that occurred after January 1991 (15 patients had episodes both before and after December 1990) and was fluconazole in 304 (99.7%) of episodes. Other than 90 patients who were randomized to receive either fluconazole or amphotericin B prophylaxis between May 1989 and December 1990,² the decision to give prophylaxis during either time frame was at the discretion of the attending physician.

Patients were considered to have received potentially effective antifungal prophylaxis if an antifungal agent was initiated within 4 days of the onset of an episode of neutropenia and if the drug was given by a route that reliably produced meaningful serum and tissue levels of the drug. Oral polyene therapy was not counted as potentially effective prophylaxis. Systemic fungal infection was diagnosed by the presence of fungi in blood or tissue samples. Hematogenously disseminated candidiasis was defined as involvement of one or more internal organs via bloodstream inoculation.³ Candidemia was defined as fungemia without clinically apparent involvement of any organ, retinal or skin site. Infections due to moulds (eg *Aspergillus*) required a positive culture or pathology for a mould in association

with a compatible clinical syndrome (eg pulmonary infiltrate). These definitions are similar to the proven infection categories of recently proposed research criteria for diagnosis of invasive fungal infections.⁴ Relapse in AML was defined as the appearance of 5% blasts or cytopenia of the bone marrow secondary to persistent leukemia (eg <5% blasts, but a current or continuing cytogenetic aneuploidy).

Analyses considering only the first episode of neutropenia for each patient and all episodes of neutropenia (considered as separate occurrences) were performed. Assessed risk factors for fungal infection included the status of underlying disease, Zubrod performance score, early risk of mortality (ERM) score,⁵ duration of neutropenia (absolute neutrophil count of <1 × 10⁹/l), and use of antibacterial therapy (prophylactic and therapeutic), and the nature of the antibacterial therapy.

The patients given and not given prophylaxis were not significantly different at the first episode of neutropenia ($P > 0.05$ by Fisher's exact test for 2 × 2 comparisons, the χ^2 test for more complex comparisons, or t test for continuous variables) with an age of 53 ± 1 (mean ± s.e.), 53% male, 17 ± 1 days of neutropenia, administration of granulocyte or granulocyte-macrophage colony-stimulating factor in 39% of cases, and 30 ± 1 days in the hospital. The majority (93%) of the patients had AML, including acute monocytic leukemia (1%), acute myelomonocytic leukemia (6%) and acute promyelocytic leukemia (5%), with the remainder having acute undifferentiated leukemia (4%) or refractory anemia with excess of blasts (3%). Many slightly different chemotherapy regimens were used during the study period, but most were based on cytosine arabinoside and there were no meaningful shifts in therapy regimens. The patients receiving prophylaxis did have a slightly lower (better) early risk of mortality score⁵ at the first episode of neutropenia (0.29 ± 0.02 vs 0.22 ± 0.02, $P = 0.012$).

Fluconazole was the most frequently used agent and was given at a median dose of 400 mg/day (Table 1). Amphotericin B was given intravenously at a median dose of 40 mg/day. Antifungal prophylaxis was associated with fewer invasive fungal infections and less frequent use of empiric amphotericin B therapy (Table 1). Antifungal prophylaxis appeared to act primarily by reducing the rate of yeast infections rather than mould infections (Table 2). Slightly more than 50% of the infections were bloodstream infections.

To assess further the effect of antifungal prophylaxis on risk of invasive fungal infection and in an effort to compensate for differences between the treatment groups, stepwise multivariate logistic regression was used to examine the effect of a variety of factors on risk for fungal infection (Table 3). Factors considered included age, gender, severity of illness (as ERM score and as Zubrod performance score), days of neutropenia, type of underlying leukemia, status of leukemia (initial therapy vs relapse), use of prophylactic broad-spectrum antibiotics (analyzed both as any use and specifically as use of a quinolone- or a sulfa-based regimen), treatment with corticosteroids, year of treatment, type of chemotherapy, and type of antifungal prophylaxis. Only use of prophylaxis, duration of neutropenia, increasing age, and male gender emerged as significant factors. The type of prophylaxis did not seem relevant: both fluconazole and amphotericin B were associated with protection, although the protective effect of fluconazole tended towards greater efficacy than non-fluconazole-based regimens. The effect of gender was surprising, has not been seen in previous studies, but was seen only at the first episode of neutropenia. In a stratified analysis, antifungal prophylaxis was associated with protection in both men and women. For the first episode of neutropenia, antifungal prophylaxis reduced the rate of invasive fungal infection from 30% to 6% for men and from 12% to 2% for women. Likewise, prophylaxis reduced the rate of invasive fungal infection at all episodes of neutropenia from 18% to 6% for men and from 8% to 4% for women. Thus, gender emerged in the

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Table 1 Prophylaxis and outcome

	First episode of neutropenia		P	All episodes of neutropenia		P
	Given antifungal prophylaxis?			Given antifungal prophylaxis?		
	No	Yes		No	Yes	
n	115	207		354	479	
Prophylaxis with						
Fluconazole (PO/IV)		148 (71%)			363 (76%)	
Ketoconazole (PO)		12 (6%)			27 (6%)	
Amphotericin B (IV)		47 (23%)			86 (18%)	
Other ^a					3 (1%)	
None	115 (100%)			354 (100%)		
Superficial fungal infection	14/115 (12%)	9/207 (4%)	0.012	21/354 (6%)	18/479 (4%)	0.184
Invasive fungal infection	24/115 (21%)	9/207 (4%)	<0.001	45/354 (13%)	23/479 (5%)	<0.001
Empiric amphotericin B	55/115 (48%)	66/207 (32%)	0.006	121/354 (34%)	126/477 (26%)	0.017
FUO	80/115 (70%)	147/207 (71%)	0.800	208/354 (59%)	263/479 (55%)	0.289
Days of FUO	15 ± 1 (79)	14 ± 1 (135)	0.811	13 ± 1 (210)	13 ± 1 (242)	0.800
Death within 30 days	40/115 (35%)	47/207 (23%)	0.026			

Results are given as number of patient (% of total) or mean ± s.d. (number of patients with valid data). P values by chi-square. FUO, fever without an apparent source that persists despite 4 days of broad-spectrum antibiotics.

^aTwo patients received flucytosine monotherapy and one received an experimental azole antifungal agent.

Table 2 Microbiology

	First episode of neutropenia Received antifungal prophylaxis?		All episodes of neutropenia Received antifungal prophylaxis?	
	No	Yes	No	Yes
Number of episodes	115	207	354	479
Invasive fungus				
<i>C. albicans</i>	2	1	4	2
<i>C. tropicalis</i>	1	1	3	2
<i>C. parapsilosis</i>	1	1	1	2
<i>C. glabrata</i>	2		4	
<i>C. krusei</i>				1
<i>C. lusitaniae</i>	2		2	
<i>Candida</i> spp.	1		2	
<i>Candida</i> + <i>Aspergillus</i>	1		1	
<i>Candida</i> + <i>Penicillium</i>			1	
Unidentified yeast	7	2	13	3
Total yeast	17 (15%)	5 (2%)	31 (8%)	10 (2%)
<i>A. fumigatus</i>				1
<i>A. flavus</i>				1
<i>A. terreus</i>	1	2	1	2
<i>Aspergillus</i> spp.	3	1	5	4
<i>Fusarium</i> spp.		1	3	4
<i>Mucor</i> spp.	1		1	
<i>Penicillium</i> spp.			1	
<i>Curvularia</i> , <i>Acremonium</i>			1	1
Unidentified moulds	2		2	
Total moulds	7 (6%)	4 (2%)	14 (4%)	13 (3%)
Total, all fungi	24 (21%)	9 (4%)	45 (13%)	23 (5%)
Location of infection				
Blood	13 (54%)	5 (56%)	27 (60%)	13 (54%)
Respiratory tract	4 (17%)	4 (44%)	6 (13%)	6 (29%)
Liver-spleen	1 (4%)		1 (2%)	
Skin and soft tissue	3 (13%)		6 (13%)	3 (13%)
Mixed (respiratory and other)	1 (4%)		2 (4%)	1 (4%)
Other	2 (8%)		3 (7%)	

Shown is the number of episodes of invasive fungal infection (% of total episodes for the breakdown by fungi, % of episodes of infection for list of locations).

Table 3 Factors predicting increased risk of invasive fungal infection by logistic regression

	First episode of neutropenia		All episodes of neutropenia	
	OR	P	OR	P
Use of any prophylaxis	0.17 (0.1–0.28)	0.003	0.32 (0.23–0.44)	0.004
Days of neutropenia (per day)	1.05 (1.03–1.07)	0.0341	1.04 (1.03–1.06)	0.0018
Male gender	3.52 (2.11–5.88)	0.0141		
Age (per year)			1.03 (1.02–1.04)	0.0027
Sub-analysis contrasting type of prophylaxis				
Non-fluconazole	0.21 (0.11–0.42)	0.0237	0.48 (0.3–0.76)	0.1124
Fluconazole	0.15 (0.08–0.26)	0.001	0.27 (0.19–0.39)	0.004

OR, odds ratio. An OR > 1 indicates an increased risk, whereas an OR < 1 indicates reduced risk.

logistic regression because of this difference in baseline rates of fungal infection. With the exception of a trend towards a slightly lower (better) early risk of mortality score in the women (0.22 ± 0.02 vs 0.27 ± 0.02 , $P = 0.09$), the men and women were otherwise similar. The cause of the increased baseline rate of invasive fungal infections in men at the first episode of neutropenia is unexplained.

Death within 30 days of the first episode of neutropenia is shown in Table 1 and was also analyzed by step-wise logistic regression using underlying disease, disease status, severity of illness (as measured by ERM score), use of prophylaxis, and gender. Only ERM score was significant, with the likelihood of death increasing with increasing ERM score (odds ratio = 1.02 per 0.01 point, $P = 0.0001$).

Our results indicate that antifungal prophylaxis is associated with a reduction in the rate of invasive fungal infections in adults undergoing standard chemotherapy for acute myelogenous leukemia. Although our data are from patients cared for almost a decade ago, these results are relevant as they are drawn from a large group of relatively homogeneous patients and because the reasonably common use of antifungal prophylaxis in many settings makes it difficult to acquire new data on patients not given prophylaxis.

As fluconazole was the most commonly used antifungal agent, it is not surprising that the major effect we observed was a reduction in the rate of yeast infections. Fluconazole has no clinically meaningful activity vs *Aspergillus* and an effect on the rates of this infection would thus not be expected. While increased rates of mould infections in association with reduction in yeast infections have been reported by some,^{6,7} we did not observe this.

Our findings with regard to the increased risk for invasive fungal infections in male patients are interesting but of unclear significance. Both men and women appeared to benefit from antifungal prophylaxis. Our study also confirms previous findings of the association between invasive fungal infections and the proportion of time with severe neutropenia.⁸ Similar to other studies in cancer patients, severity of illness was predictive of mortality in this patient population.⁵

Our study suffers from all the limitations of retrospective analyses, including the lack of uniformity in the diagnosis and management of the underlying disease and its complications. Nonetheless, this is the largest study published to date of prophylaxis in a uniform population of adults with AML and its results indicate that at least some patients with AML would benefit from antifungal prophylaxis.

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