Fluconazole to Prevent Yeast Infections in Bone Marrow Transplantation Patients: A Randomized Trial of High versus Reduced Dose, and Determination of the Value of Maintenance Therapy

Margaret L. MacMillan, MD, Jesse L. Goodman, MD, Todd E. DeFor, MS, Daniel J. Weisdorf, MD

PURPOSE: To determine the optimal dose and duration of fluconazole antifungal prophylaxis therapy in bone marrow transplantation patients.

SUBJECTS AND METHODS: Two hundred and fifty-three pediatric and adult bone marrow transplantation patients were randomly assigned to receive fluconazole 400 mg daily (high dose) or 200 mg daily (low dose) while they were neutropenic. After neutrophil recovery, patients were randomly assigned to receive maintenance therapy with either fluconazole (100 mg daily) or clotrimazole troches (10 mg 4 times daily) until 100 days after transplantation. Patients were monitored until 2 weeks after completion of early prophylaxis and to 100 days after transplantation.

RESULTS: During the early prophylaxis phase, rates of yeast colonization and infections were similar in both treatment groups. By day 50, the incidence of *Candida* infections in the high-dose group was 4% (95% confidence interval [CI]: 1% to 7%; n = 5), compared with 1% in the low-dose fluconazole group (95% CI: 0% to 3%; n = 1; $P = 0.08$). During the same period, the incidence of *Aspergillus* infections was 4% (95% CI: 1% to 7%; n = 5) in the high-dose group and 2% (95% CI: 0% to 4%; n = 2; $P = 0.33$) in the low-dose group. During the maintenance prophylaxis phase, rates of yeast colonization and superficial infections were similar in the fluconazole and clotrimazole groups. Four patients developed systemic fungal infection in the maintenance phase (1 who received clotrimazole and 3 who received fluconazole).

CONCLUSION: High-dose (400 mg daily) and low-dose (200 mg daily) fluconazole have similar efficacy in reducing the incidence of yeast colonization, superficial infection, and systemic infection in neutropenic pediatric and adult patients undergoing bone marrow transplantation. Rates of yeast colonization after neutrophil recovery were similar in patients treated with fluconazole or clotrimazole. **Am J Med. 2002;112:369–379.**

Invasive fungal infections are a major cause of morbidity and mortality in neutropenic patients (1–6). Fluconazole, an orally absorbable triazole antifungal agent, is active against a variety of yeast infections both for treatment and prophylaxis (7). Two large multicenter trials have demonstrated the effectiveness of fluconazole (400 mg/d) in preventing fungal infections in bone marrow transplant recipients (8,9). Extended fluconazole use to 75 days after transplantation was reported to be associated with a survival advantage (9), however, the reported mortality benefit was not related to a reduction in fungal infections. In a follow-up study of one of these trials (9), long-term survival was significantly better in fluconazole recipients (10). In an analysis of 355 bone marrow transplant recipients who underwent autopsies, patients who had not received antifungal prophylaxis had 5 times the risk of *Candida* infection compared with those who had received fluconazole from conditioning until day 75 after transplantation (11). However, clinical infection with yeast species that are able to evade fluconazole prophylaxis, either by innate or acquired resistance, is a potential concern (12–16).

There are several unresolved questions about fluconazole prophylaxis. A lower dose (200 mg/d) may be sufficient as a prophylactic dose against yeast. Additionally, yeast infections remain a problem among transplant recipients who have recovered their neutrophil count (2,4–6), and the optimal dose and duration of fluconazole prophylaxis beyond engraftment remains to be determined. We therefore conducted a randomized controlled trial to compare the optimal dose and duration of fluconazole prophylaxis therapy in pediatric and adult patients. We determined the species of yeast organisms that were recovered from patients to see if strains known to be fluconazole resistant emerged with the use of fluconazole.

From the Departments of Pediatrics (MLM), Infectious Diseases (JLG), Biostatistics (TED), and Medicine (DJW); and the Blood and Marrow Transplant Program (MLM, TED, DJW), University of Minnesota, Minneapolis, Minnesota.

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Request for reprints should be addressed to Margaret L. MacMillan, MD, University of Minnesota, MMC 484, 420 Delaware Street Southeast, Minneapolis, Minnesota 55455.

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MATERIALS AND METHODS

The protocol was reviewed and approved by the Institutional Review Board at the University of Minnesota. All patients or parents signed informed consent prior to treatment.

Patients

Two hundred fifty-three bone marrow transplantation patients with a median age of 34 years (range, 2 to 67 years) were enrolled at the University of Minnesota. All patients met standard transplantation criteria, including adequate organ function at time of transplantation. All patients who received blood stem cells or underwent bone marrow transplantation at the University of Minnesota were eligible. Other eligibility requirements were age $\geq$2 years, and a negative pregnancy test and effective contraception use in female patients who had childbearing potential. Patients were excluded if they had a history of allergy or intolerance to azoles. Further exclusion criteria included moderate or severe liver disease (9), moderate or severe renal insufficiency, life expectancy $<$3 weeks, or prior treatment with systemic antifungal agents within 2 weeks of entering the study.

Study Design

Two randomizations took place separately to address the issues of fluconazole dose and maintenance therapy duration. After eligibility was determined and written consent was obtained, patients were randomly assigned to a study regimen (in a 1:1 ratio by a third party, according to a computer-generated schedule) for both study phases. In the initial randomization, all patients were assigned to receive fluconazole 400 mg daily (high dose) or 200 mg daily (low dose), which was to continue until neutrophil engraftment (absolute neutrophil count $\geq 1.0 \times 10^9$/L for 3 consecutive days). Patients who weighed $<$40 kg were treated with either fluconazole 6 mg/kg/d (high dose) or 3 mg/kg/d (low dose). In the second randomization, engrafted non-neutropenic transplant recipients with no active fungal infections were randomly assigned to receive either fluconazole 100 mg daily (1.5 mg/kg if $<$40 kg) or clotrimazole troches 10 mg four times daily from the time of this second randomization until 100 days after transplantation.

Fluconazole was administered orally, as 100-mg and 200-mg tablets, or as a suspension of 5 mg/mL. Doses were rounded to the nearest 50 mg for patients weighing $<$20 kg. Dose adjustments were made for renal dysfunction (9). Compliance with fluconazole and dose regimen was recorded. Noncompliance was not a reason for withdrawal unless it occurred on more than 3 consecutive study days or the patient refused further treatment.

Early prophylaxis began within 72 hours of initiation of pretransplantation conditioning and was continued until neutrophil engraftment. Prophylaxis was discontinued for development of a systemic fungal infection, use of a different systemic antifungal agent, drug toxicity, or inability or refusal to continue in the study. Patients who developed superficial fungal infection were treated with topical medications (clotrimazole or nystatin) and continued on study medication if there was no evidence of systemic infection. Maximum duration of topical therapy was 14 days. If amphotericin B was administered empirically during the period of neutropenia but no systemic infection was documented, patients remained eligible for the maintenance randomization.

Patient Evaluation

All study participants were evaluated at baseline, weekly from the initiation of study drug until discontinuation, and 2 weeks after completion. Along with routine evaluations, fungal surveillance cultures (throat and stool) and a fungal blood culture were obtained within 72 hours of initiating study drug and then weekly. Signs and symptoms of possible breakthrough fungal infection and adverse effects were recorded at each evaluation. Patients who participated in the maintenance phase of the study were seen either in person or contacted by telephone monthly during the period of maintenance therapy. Laboratory information and surveillance cultures were obtained on a monthly basis until 100 days after transplantation.

Classification of Response

Fungal colonization was considered to be present if surveillance cultures demonstrated a fungus isolated from skin, mucous membrane, or both in the absence of clinical findings of fungal infection. A superficial fungal infection was defined as a clinically apparent infection of the oropharynx, skin, or genitalia, along with positive cultures. A definite systemic fungal infection was defined if there was clinical evidence of blood or tissue infection and a culture or biopsy specimen from the involved site demonstrating a pathogenic fungal organism.

Management of Adverse Effects

Date of onset, duration, severity, and possible relation to therapy were recorded for potential adverse effects. Temporary suspension of study drug was permitted for 3 days. Decisions to discontinue or to reinstate the study drug were made on a case-by-case basis after discussion between the patient's primary clinician and the investigator, with the patient's approval.

Statistical Analysis

To compare characteristics between randomized groups, Pearson's chi-squared test was used for categorical variables and the general Wilcoxon test was used for continuous variables (17). Estimates of the incidence of study endpoints were calculated by the Kaplan-Meier method (18). For systemic and superficial infections, patients were censored at date of death or last contact. Rates of

Table 1. Patient Characteristics during Early Prophylaxis Phase of the Study, by Randomization Group (High-Dose vs. Low-Dose Fluconazole)

Characteristic	Daily Fluconazole Dose		*P* Value
	400 mg (n = 124)	200 mg (n = 129)	
	Number (%)		
Male sex	61 (49)	83 (64)	0.02
Age (years)			0.80
0–19	36 (29)	38 (29)	
20–49	66 (54)	78 (61)	
≥50	22 (18)	13 (10)	
Median (range)	33 (2–62)	35 (2–67)	0.80
Disease category			0.50
Nonmalignant	12 (10)	10 (8)	
Acute leukemia	45 (36)	46 (36)	
Chronic myelogenous leukemia	32 (26)	31 (24)	
Lymphoma	16 (13)	27 (21)	
Other malignancy	19 (15)	15 (11)	
Colonized with yeast at entry	22 (18)	33 (26)	0.13
Donor type among transplant recipients			0.47
Related	41 (33)	34 (26)	
Unrelated	30 (24)	37 (29)	
Autologous	53 (43)	58 (45)	
Transplant number among transplant recipients			>0.80
1st	121 (98)	127 (98)	
2nd	3 (2)	1 (1)	
3rd	0	1 (1)	

yeast colonization after the primary randomization were calculated by dividing the number of patients with yeast colonization in a specified week by the number of surviving patients during that period. (Patients who were discharged from the hospital or enrolled in the maintenance phase of the study were excluded from this calculation.) Rates of yeast colonization after randomization in the maintenance phase were calculated by dividing the number of patients colonized during the specified period by the mean number of surviving patients. The risks of yeast colonization were compared using the chi-squared test. Kaplan-Meier curves were compared using the log-rank test.

The Cox proportional hazards regression model was used to adjust analyses for potential confounding variables, as well as to identify interactions between randomized treatment and other factors (19). Sex, age, baseline colonization, donor type, and time-dependent onset of acute graft-versus-host disease were included in these models; only factors that affected risk or confounded the risk of the randomized groups were retained in the final models.

The original design for this study included a sample size estimate of 258 patients, which was powered as an equivalency study, with a two-sided alpha of 0.05. Assuming a 5% infection rate in the high-dose arm, this sample size could detect a 10% difference in the rate of proven infections with 80% power. In the maintenance phase of the study, a sample size of at least 160 patients was needed to detect a 20% difference in yeast colonization rates with 80% power and an assumption of 25% yeast colonization in the high-dose arm.

RESULTS

Early Prophylaxis

At study entry, the characteristics of patients in the high-dose fluconazole group (n = 124) and the low-dose group (n = 129) were similar, except that a greater percentage of male subjects received the low-dose therapy (Table 1). Slightly fewer patients treated with high-dose fluconazole had positive baseline fungal surveillance cultures than did those in the low-dose group (18% vs. 26%).

Yeast Colonization and Superficial Infections

At the end of early prophylaxis, 20 (16%) of the high-dose recipients and 23 (18%) of the low-dose recipients had a positive surveillance culture for yeast ($P = 0.35$). Among all patients, the estimated incidence of acquired yeast colonization by 30 days (in those free of colonization at study entry) was 31% (95% confidence interval [CI]: 25% to 37%). Colonization rates at all sites, and by type of

Table 2. Colonizing Yeast Species during the Early Prophylaxis Phase of the Study

	Study Week									
	1		2		3		4		5	
	Fluconazole Dose (mg)									
	400	200	400	200	400	200	400	200	400	200
	Number of Patients									
Colonizing organisms										
Candida albicans	7	12	0	1	4	3	7	6	2	5
Candida glabrata or *Candida krusei*	5	3	12	6	9	6	14	11	10	9
Other yeast*	14	21	11	8	9	8	6	18	8	9
Patients with colonization (%)†	18	26	15	9	16	10	19	20	18	13
P value‡	0.13		0.14		0.15		0.79		0.35	

* *Candida guilliermondii, lusitaniae, parapsilosis,* or *zeylanoides*, or not otherwise specified.
† Patients with one or more positive yeast cultures during the interval.
‡ For comparison of proportions of patients with colonization by fluconazole dose.

organism (Table 2), were similar in the two groups. There was no difference between groups in the incidence of superficial fungal infections during neutropenia. Twenty patients (16%) receiving high-dose fluconazole (95% CI: 10% to 22%) and 23 patients (18%) receiving low-dose fluconazole (95% CI: 11% to 25%) developed superficial fungal infections ($P = 0.66$).

Systemic Fungal Infections

The incidence of systemic candidiasis was similar in the two groups (Table 3). By day 50, there were 12 systemic fungal infections (5 with *Candida* species; 6 with *Aspergillus* species; 1 with both). Fungal infections occurred in 9 (8%) high-dose recipients (95% CI: 3% to 13%) and 3 (2%) low-dose recipients (95% CI: 0% to 4%; $P = 0.06$). The incidence of systemic candidiasis was 4% in the high-dose group (95% CI: 1% to 7%; n = 5) and 1% in the low-dose group (95% CI: 0% to 3%; n = 1; $P = 0.08$; Figure 1). During the same period, the incidence of aspergillosis was 4% (95% CI: 1% to 7%; n = 5) in the high-dose group and 2% (95% CI: 0% to 4%; n = 2) in the low dose group ($P = 0.33$; Figure 2).

Baseline fungal colonization (relative risk [RR] = 23; 95% CI: 2.7 to 198; $P < 0.01$) and perhaps use of high-dose fluconazole (RR = 7.7; 95% CI: 0.9 to 67; $P = 0.06$) were associated with proven systemic candidiasis. Age, sex, donor type, underlying diagnosis, preparative therapy, regimen-related toxicity, and time to engraftment were not associated with systemic candidiasis. The incidence of candidiasis was highest (18%; 95% CI: 2% to 34%) in patients colonized at study entry who were assigned to high-dose fluconazole (Figure 3). In multiple regression analysis, no factors were associated significantly with aspergillosis infections.

Clinical Consequences of Early Prophylaxis

Fluconazole was discontinued before neutrophil recovery because of persistent neutropenic fever and initiation of alternate antifungal therapy in 74 (60%) of the patients treated with high-dose fluconazole and in 76 (59%) of the patients treated with low-dose fluconazole ($P > 0.80$) at a median duration of 10 days (range, 3 to 24 days) in the high-dose group and 11 days (range, 3 to 50 days) in the low-dose group after initiation of the study drug ($P > 0.80$). Most commonly, fluconazole was discontinued due to persistent fever leading to the use of amphotericin B for suspected fungal infection (87% [64] of the high-dose recipients and 88% [67] of the low-dose recipients). Discontinuation of fluconazole because of drug toxicity, or abnormal laboratory values was uncommon and did not differ between fluconazole groups (10 in the high-dose group and 9 in the low-dose group).

Clinical outcomes were similar in the two groups (Table 4). Twenty-nine (24%) of the high-dose recipients (95% CI: 16% to 32%) and 35 (28%) of the low-dose recipients (95% CI: 20% to 36%) developed bacteremia during the early prophylaxis phase ($P = 0.57$). There were no significant differences between the two groups in the number of patients with any clinical adverse effects due to treatment (6 in the high-dose group and 5 in the low-dose group).

Maintenance Fungal Prophylaxis: Fluconazole versus Clotrimazole

Similar proportion of patients in the second randomization for maintenance prophylaxis after neutrophil engraftment had received high- or low-dose early prophylaxis (Table 5). However, fewer allogeneic and more autologous transplant recipients were assigned to clotrimazole than to fluconazole (56% vs. 34%, $P = 0.01$; Table 5). There were no differences between the fluconazole and clotrimazole groups in recipient sex, age, or disease category. During the week before the maintenance randomization, the incidence of fungal coloniza-

Table 3. Systemic Infections Occurring within 50 Days after Bone Marrow Transplantation

Fluconazole Dose	UPN	Type of Transplant	Days to Engraftment*	Colonization at Study Entry	Day of Onset of Infection after Transplantation	Organism(s)	Site(s)	Outcome of Infection
400 mg	1804	Unrelated	32	None	19	*Aspergillus fumigatus*	Blood, skin	Fatal
					33	*Aspergillus* NOS	Kidney	
	1831	Autologous	23	Yeast, NOS	16	*Candida tropicalis*	Blood	Fatal
	1840	Unrelated	Graft failure	None	19	*Candida tropicalis*	Blood, respiratory tract, peritoneal fluid	Fatal
	1850	Unrelated	28	None	40	*Aspergillus fumigatus*	Brain	Fatal
	1907	Unrelated	17	None	50	*Aspergillus fumigatus*	Sinuses	Fatal
	2005	Related	32	*Candida albicans*	26	*Candida albicans*	Blood	Resolved
	2035	Autologous	11	*Candida glabrata*	11	*Candida glabrata*	Blood	Resolved
	2053	Related	20	*Candida albicans*	17	*Candida glabrata*	Blood	Fatal
					26	*Aspergillus fumigatus*†	Respiratory tract	
	2095	Related	Graft failure	None	24	*Aspergillus glaucus*	Respiratory tract	Fatal
200 mg	1904	Unrelated	32	*Candida krusei*	46	*Candida glabrata*	Blood, respiratory tract	Fatal
	2057	Related	26	None	28	*Aspergillus* NOS	Blood, respiratory tract	Fatal
	2122	Unrelated	Graft failure	None	32	*Aspergillus flaxus*	Central nervous system, mouth, tongue, lip	Fatal

* Absolute neutrophil count $\geq 5 \times 10^8$/L $\times$ 3 consecutive days.
† Second infection in same patient within 50 days after transplantation.
NOS = not otherwise specified; UPN = unique patient number.

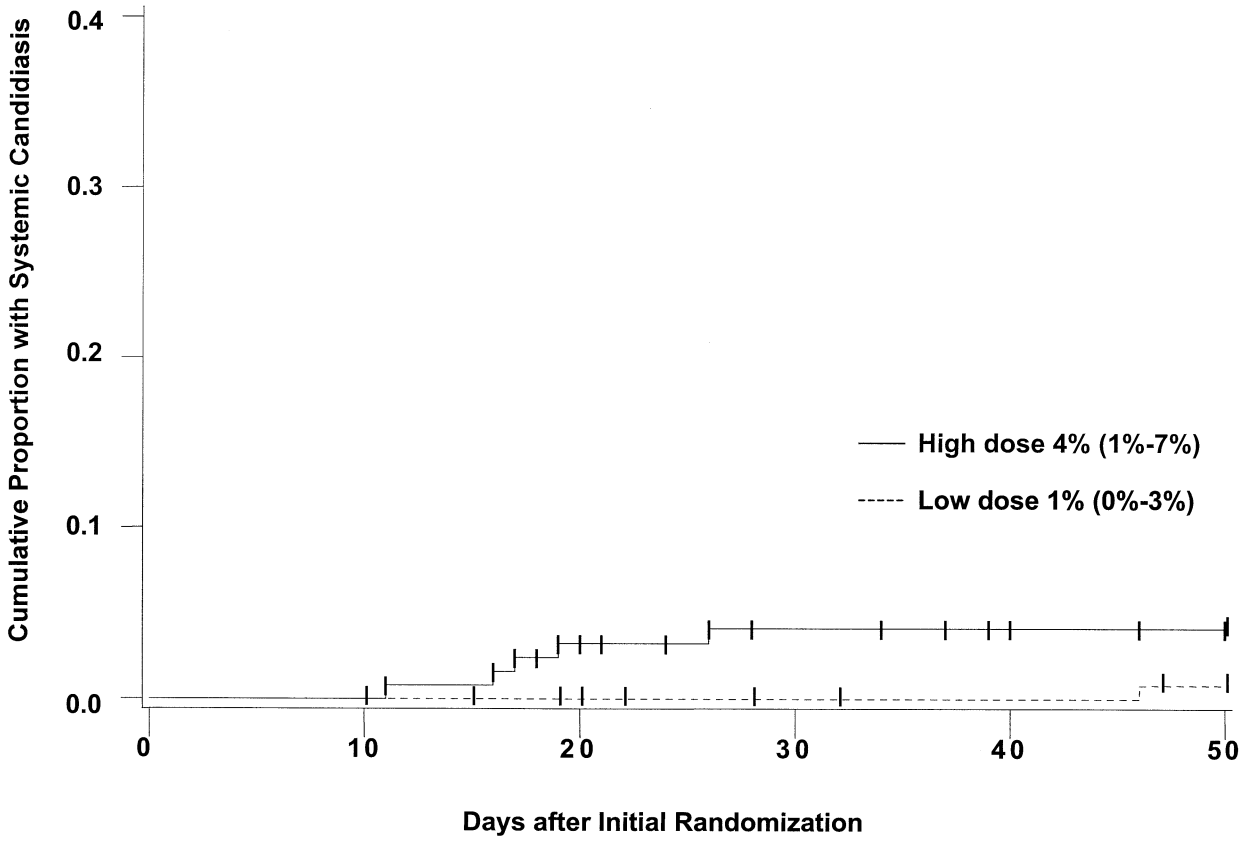

Figure 1. Time to first proven systemic candidiasis during early prophylaxis with high-dose (400 mg; n = 124) or low-dose (200 mg; n = 129) fluconazole ($P = 0.08$). Cumulative risks (with 95% confidence intervals) are presented.

tion was somewhat lower in the fluconazole group (Table 5).

Yeast Colonization and Superficial Infections

Rates of yeast colonization in the fluconazole and clotrimazole groups were 21% and 26% at 1 month ($P = 0.45$), 11% and 9% at 2 months ($P = 0.58$), and 13% and 18% at 3 months ($P = 0.67$) after initiation of maintenance therapy. During the 3 months of assigned maintenance therapy, colonization with resistant yeast species (*Candida krusei* and *C. glabrata*) persisted in 5 of 88 patients treated with fluconazole, but fell to 1 of 84 patients treated with clotrimazole (Table 6). Superficial candidiasis during maintenance therapy occurred in 4 of the fluconazole recipients and 6 of the clotrimazole recipients. The estimated risk of superficial infections by day 100 after transplantation was 5% (95% CI: 0% to 10%) in the fluconazole recipients and 9% (95% CI: 3% to 15%) in the clotrimazole recipients ($P = 0.43$).

Systemic Fungal Infections

Four patients developed proven systemic fungal infections during maintenance therapy. One patient, an autologous transplant recipient, had received low-dose fluconazole during early prophylaxis and clotrimazole as maintenance therapy. The other 3 patients, all allogeneic transplant recipients, had received high-dose fluconazole during early prophylaxis and fluconazole as maintenance therapy. None of these 4 patients had been colonized with fungus before the initiation of maintenance therapy. One patient developed *C. krusei* infection after neutrophil engraftment; the infection was treated successfully with amphotericin B, but the patient died 9 months after transplantation from severe graft-versus-host disease. The 3 other patients developed invasive pulmonary *Aspergillus fumigatus* infections (1 had concurrent *A. nidulans*), from which they died 2 to 4 months after transplantation, despite intensive therapy with amphotericin B. Two of these patients had experienced primary graft failure after transplantation.

Survival after Maintenance Prophylaxis

There was no significant difference in mortality after transplantation between the two randomized maintenance groups. Among the 88 fluconazole recipients, 72 (82%) were alive 6 months after randomization, compared with 70 (83%) of the 84 clotrimazole recipients ($P > 0.80$). A survival analysis stratified by the types of early and maintenance prophylaxis showed no differences ($P = 0.57$) between the cohorts.

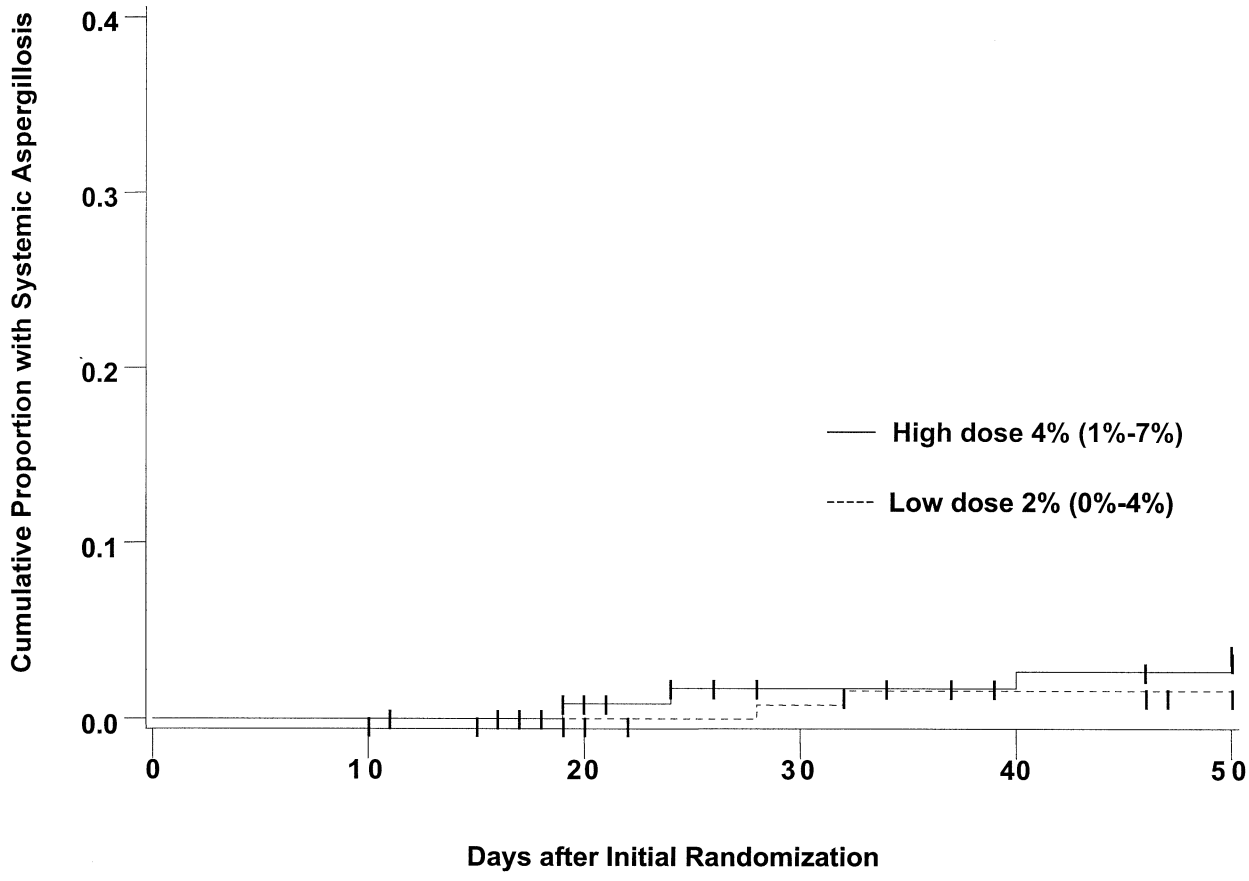

Figure 2. Time to first proven systemic aspergillosis during early prophylaxis with high-dose (400 mg; n = 124) or low-dose (200 mg; n = 129) fluconazole ($P = 0.33$). Cumulative risks (with 95% confidence intervals) are presented.

DISCUSSION

This randomized study demonstrates that high-dose (400 mg daily) and low-dose (200 mg daily) fluconazole have equivalent efficacy in reducing the incidence of *Candida* colonization, superficial infections, and systemic infections in neutropenic pediatric and adult patients undergoing bone marrow transplantation.

Within the early prophylaxis period, 4% of the patients treated with high-dose (400 mg/d) fluconazole and 1% of the low-dose (200 mg/d) patients developed systemic candidiasis, similar to the rates observed in earlier prospective studies that used fluconazole 400 mg daily during neutropenia (8,9). In our study, systemic candidiasis were more common in patients with fungal colonization at study entry and perhaps in those assigned the higher fluconazole dose. In a retrospective analysis of 665 bone marrow transplant recipients, *Candida* colonization detected just before transplantation or during the early post-transplantation period was associated with subsequent *Candida* infection (2). Similarly, in a series of 115 pediatric patients with acute leukemia, having 2 or more surveillance culture sites that were positive for fungal organisms was a risk factor for developing invasive fungal disease (20).

During the maintenance antifungal prophylaxis in the present study, there were few systemic fungal infections, and only one with yeast, and there was no association of fungal colonization with subsequent systemic mycosis. The potential value of extended suppression of mucosal colonization using ongoing antifungal prophylaxis is still uncertain, although the low incidence of late systemic infections is encouraging.

In our study, there was a potential bias toward more infections in the fluconazole maintenance arm because more patients were allogeneic transplant recipients. However, during this phase of the study, only 4 of 172 patients developed systemic fungal infections, one of whom was an autologous transplant recipient. This rate of infection is markedly less than was previously reported. In the study by Goodman et al. (8), 10% of transplant recipients developed fungal infections from day 32 to 100, a time during which no antifungal prophylaxis had been administered. In that study, rates of fungal infection did not differ between patients who had been

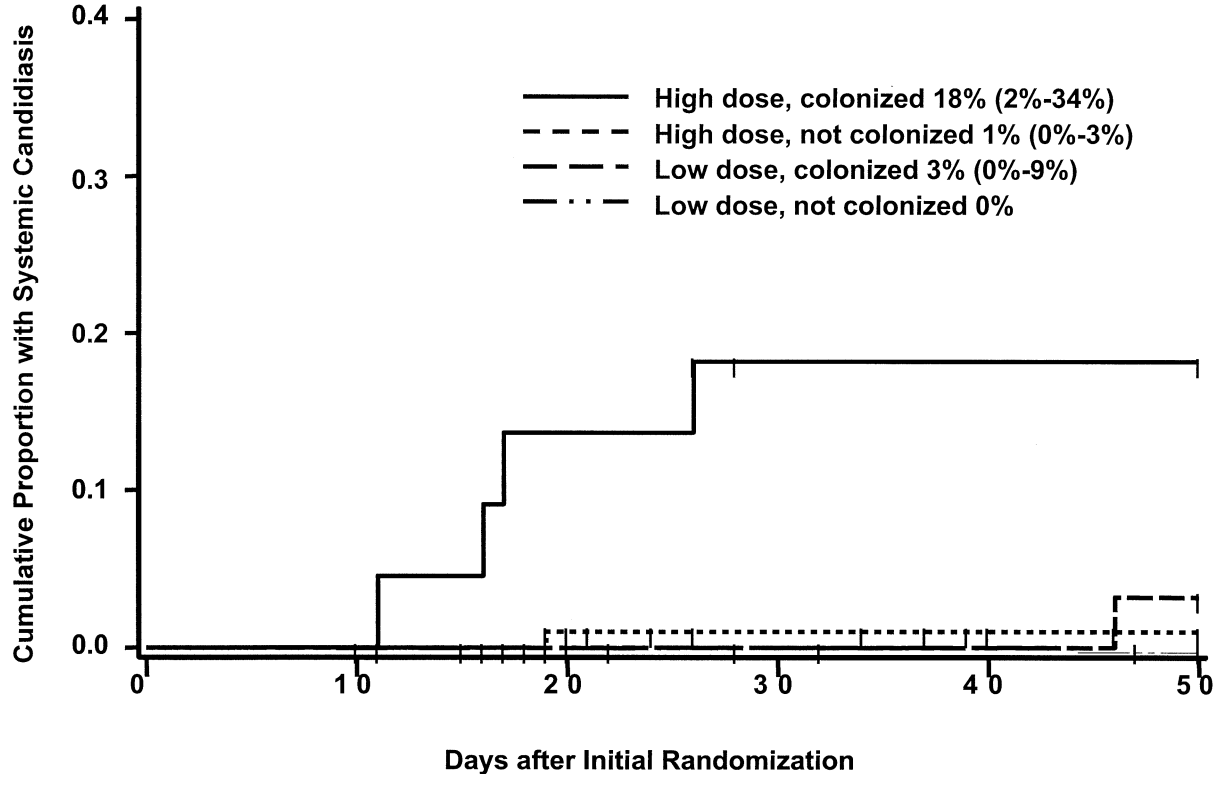

Figure 3. Time to first proven systemic candidiasis during early prophylaxis stratified by fluconazole dose and baseline colonization status ($P < 0.01$). *P* value reflects the difference between the 4 groups: high-dose fluconazole, colonized (n = 22); high-dose fluconazole, not colonized (n = 102): low-dose fluconazole, colonized (n = 33); and low-dose fluconazole, not colonized (n = 96). Cumulative risks (with 95% confidence intervals) are presented.

treated previously with fluconazole or placebo during the neutropenia period, and the majority of infections were due to potentially fluconazole-susceptible infections such as *Candida*, although fluconazole resistance was not tested. In an analysis of 249 allogeneic bone marrow transplant recipients at the University of Minnesota, late

Table 4. Clinical Outcomes of Patients in the Early Prophylaxis Phase of the Study, by Randomization Group (High-Dose vs. Low-Dose Fluconazole)

	Daily Fluconazole Dose		
	400 mg (n = 124)	200 mg (n = 129)	*P* Value >0.80
	Number (%) or Median (Range)		
Engraftment status			0.16
Dead before day 45	10 (8)	5 (4)	
Engrafted*	114 (92)	124 (96)	
Time to engraftment (days)	21 (8–87)	21 (8–87)	>0.80
Discharge status			0.42
Dead	24 (19)	20 (16)	
Discharged	100 (81)	109 (84)	
Time to discharge (days)	34 (12–85)	32 (13–109)	>0.80
Acute graft-versus-host disease 100 days after bone marrow transplantation	52 (42)	55 (43)	0.71
Survival rate 3 months after transplantation	98 (79)	110 (85)	0.17

* Achieved absolute neutrophil count >5 x 10^8/L for at least 3 consecutive days by day 45 after bone marrow transplantation.

Table 5. Characteristics of Patients Enrolled in Second Randomization for Maintenance Prophylaxis, by Randomization Group (Fluconazole 100 mg Daily vs. Clotrimazole 10 mg 4 Times Daily)

Characteristic	Fluconazole (n = 88)	Clotrimazole (n = 84)	*P* Value >0.80
	Number (%)		
Fluconazole dose during early prophylaxis period			0.08
400 mg	40 (32)	44 (46)	
200 mg	48 (37)	40 (33)	
Time to second randomization (days)	28 (13–50)	26 (11–50)	>0.80
Donor type			0.01
Related	33 (38)	19 (23)	
Unrelated	25 (28)	18 (21)	
Autologous	30 (34)	47 (56)	
Male sex	57 (65)	43 (51)	0.07
Age at transplantation (years)			0.17
0–19	30 (34)	25 (30)	
20–49	50 (57)	44 (52)	
≥50	8 (9)	15 (18)	
Median (range)	30 (2–67)	35 (2–60)	
Disease category			0.15
Acute leukemia	39 (44)	22 (26)	
Chronic myelogenous leukemia	20 (23)	21 (25)	
Lymphoma	12 (14)	17 (20)	
Other malignancy	10 (11)	15 (18)	
Nonmalignant	7 (8)	9 (11)	
Colonized with fungi during week before randomization	16 (18)	22 (26)	0.06

infections (after day 50) were the most important risk factor for nonrelapse-related mortality (5). Fungi were involved in 24% of these late life-threatening infectious events, 80% of which were fatal (5). In a long-term follow-up study of one of the large randomized trials (9), administration of fluconazole (400 mg daily) for 75 days after transplantation was associated with persistent protection against candidiasis-related deaths and an overall survival benefit (10).

Two of 3 patients in our study who died from systemic fungal infections after transplantation had experienced primary graft failure. Prolonged neutropenia is an important risk factor for fungal infection in cancer and bone marrow transplantation patients (1,2,16,20–22).

Table 6. Colonizing Yeast Species during Maintenance Phase of the Study

	Months after Transplantation					
	1		2		3	
	Maintenance Drug					
	Fluconazole	Clotrimazole	Fluconazole	Clotrimazole	Fluconazole	Clotrimazole
	Number of Patients					
Colonizing organisms						
Candida albicans	4	7	0	1	1	4
Candida glabrata or *Candida krusei*	7	11	7	3	5	1
Other yeast*	12	11	2	4	3	4
Patients with colonization (%)†	21	26	11	9	13	18
P value‡	0.45		0.58		>0.80	

* *Candida guilliermondii, lusitaniae, parapsilosis, zeylanoides*, or not otherwise specified.
† Patients with one or more positive yeast cultures during the interval.
‡ For comparison of proportions of patients with colonization by use of fluconazole versus clotrimazole.

The roles of granulocyte colony-stimulating factor (G-CSF) (23,24), granulocyte-macrophage colony-stimulating factor (GM-CSF) (25), and G-CSF– or GM-CSF–stimulated granulocyte transfusions (26–28) for the adjunctive treatment of neutropenic patients with invasive fungal infections requires additional study. However, effective prophylaxis of mycotic infections remains essential for satisfactory management of patients who have prolonged neutropenia.

In evaluating options of extended prophylaxis in large numbers of patients, the associated expenses must also be considered. In the early prophylaxis phase of our study, the two doses of fluconazole had similar efficacy in preventing yeast infections, with similarly low rates of adverse effects. Thus, we recommend the use of fluconazole, administered 200 mg daily, as initial fungal prophylaxis in neutropenic bone marrow transplantation patients. During the maintenance phase of the study, we observed low rates of yeast colonization using fluconazole 100 mg orally or four 10-mg clotrimazole troches. Using either regimen, the occurrence of systemic yeast infections was lower than previously reported in patients who were not receiving effective antifungal prophylaxis (1,2,5). The costs of fluconazole 100 mg daily and clotrimazole 10 mg four times daily are similar (daily wholesale pharmacy costs are $6.00 for fluconazole and $4.68 for clotrimazole). Because of similar efficacy in reducing yeast colonization and the advantage of once-daily dosing, we routinely administer fluconazole 100 mg orally from the day of engraftment until 100 days after transplantation.

Limitations of this study include the lack of fluconazole resistance data to explain the higher rate of *Candida* isolates recovered from the high-dose dose fluconazole group compared with the low-dose fluconazole group. In addition, although there was a balance of allogeneic and autologous transplantation patients at the time of initial randomization, there was a potential bias toward more infections in the fluconazole maintenance arm because more patients were allogeneic transplant recipients.

Our findings show that fluconazole administered at 400 mg and 200 mg daily have similar efficacy in reducing the incidence of *Candida* colonization, superficial infections, and systemic infections in neutropenic pediatric and adult patients undergoing bone marrow transplantation. Nevertheless, fluconazole-resistant organisms, especially molds, remain a major cause of morbidity and mortality in these patients. The effects of new broad-spectrum antifungal agents, particularly for the extended risk associated with graft-versus-host disease and prolonged corticosteroid therapy, require study.

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