

# Randomized Trial of Fluconazole Versus Low-Dose Amphotericin B in Prophylaxis Against Fungal Infections in Patients Undergoing Hematopoietic Stem Cell Transplantation

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Over the past decade, invasive fungal infections have become an increasingly important problem in patients undergoing hematopoietic stem cell transplantation (HSCT). The optimal approach for prophylactic antifungal therapy has yet to be determined. To resolve this issue, we performed a prospective randomized study to compare the efficacy of fluconazole (FL) versus low-dose amphotericin B (AmB) in preventing fungal infections during the first 100 days after HSCT. Patients undergoing allogeneic or autologous HSCT were randomized to receive fluconazole 200 mg/day PO or amphotericin B 0.2 mg/kg/day IV beginning 1 day prior to commencement of conditioning regimen and continuing until engraftment, drug-associated toxicity was suspected, or systemic fungal infection was suspected or proven. High-dose amphotericin B (0.5–1.0 mg/kg/day) was started for patients with suspected or proven fungal infections. From January 1993 to December 1998, a total of 186 patients were enrolled into the trial, with 100 receiving FL and 86 receiving AmB. Eighty (43%) patients were removed from prophylaxis for persistent fever despite broad-spectrum antibacterial therapy or suspected fungal infections (FL 46 vs. AmB 34,  $P > 0.05$ ). The incidence of proven fungal infections (FL 12% vs. AmB 12.8%), suspected fungal infections (FL 4% vs. AmB 2.3%), superficial fungal infections (FL 1% vs. AmB 4.6%) did not show any significant difference. The survival at 100 days post transplant was similar between the 2 groups (FL 78% vs. AmB 70%,  $P = 0.254$ ). Death attributable to fungal infections was similar in both groups (6% vs. 7%,  $P > 0.05$ ). We conclude that fluconazole is as effective as low-dose amphotericin B in prophylaxis against fungal infections in patients undergoing hematopoietic cell transplantation. *Am. J. Hematol.* 71:260–267, 2002. © 2002 Wiley-Liss, Inc.

**Key words:** fungal prophylaxis; stem cell transplant; fluconazole; amphotericin

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## INTRODUCTION

In hematopoietic stem cell transplant recipients who have prolonged neutropenia or who receive immunosuppressants, fungal infections remain important causes of morbidity and mortality. Studies reviewing the yearly incidence of candidiasis [1] and aspergillosis [2] from single institutions have shown increases in recent years. Effective prevention of invasive fungal infection has been unsatisfactory because of either inadequate antifungal spectrum or drug-associated toxicity. Fluconazole has been shown in randomized trials to reduce the incidence of fungemia [3,4], death attributable to fungal in-

fection, and, in one study, overall mortality [4]. However, fluconazole has notable shortcoming in its lack of activity against *Aspergillus*, and, moreover, its use has resulted in an increased incidence of *Candida krusei* and

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*Candida glabrata* [5–7]. Amphotericin B is an antifungal agent with a greater spectrum of activity including *Aspergillus* species, and yeasts form, such as *C. krusei*, that are resistant to fluconazole [5]. One study has shown that low-dose amphotericin B (0.2 mg/kg/day IV) was as effective as fluconazole prophylaxis in the prevention of fungal infections in patients undergoing bone marrow transplantation but had higher incidence of renal toxicity [8]. Three other studies using a slightly lower dose of amphotericin B (0.1 mg/kg/day) showed a reduction in oropharyngeal yeast colonization, a reduction in the overall incidence of fungal infections, and a delay in switching to high-dose amphotericin B [9–11]. We performed a study to compare the efficacy of fluconazole with low-dose amphotericin B in preventing fungal infections during the first 100 days after hematopoietic stem cell transplantation.

## PATIENTS AND METHODS

### Patients

Patients undergoing autologous or allogenic marrow or peripheral blood stem cell (PBSC) transplant were eligible for the study. Patients were excluded if there is (i) history of allergy to study drugs, (ii) evidence of pre-existing systemic fungal infection or systemic antifungal agents having been received within 2 weeks of study, (iii) evidence of significant hepatic or renal dysfunction (defined as a level of bilirubin, alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase that was more than three times the upper limit of normal and a serum creatinine level of more than two times the upper limit of normal). All patients were given oral antibiotics for Gram-negative bacterial prophylaxis, which was begun 1 day before the conditioning regimen. The first 33 patients were given oral pefloxacin 400 mg twice daily, and the subsequent 153 patients were given oral ciprofloxacin 500 mg twice daily from the beginning of conditioning regimen until neutrophil engraftment. All the patients were treated in conventional private, nonlaminar airflow rooms. Informed consent was obtained from each patient.

### Study Design and Drug Administration

The study was a prospective, randomized, and non-blinded trial comparing antifungal prophylaxis with amphotericin B with fluconazole. Fluconazole was administered at a dose of 200 mg/day orally. Amphotericin B was administered intravenously at a daily dose of 0.2 mg/kg with a maximum dose of 10 mg. Both drugs were started 1 day prior to commencement of the conditioning regimen and continued until engraftment (defined as absolute neutrophil count achieving more than 500/ $\mu$ L for 3 consecutive days), drug-associated toxicity was suspected, or a systemic fungal infection was suspected or

proven. High-dose amphotericin B (0.5–1.0 mg/kg/day) was initiated for patients with suspected or proven fungal infections.

The fluconazole dose of 200 mg/day was chosen for our study because of the following reasons: (i) fluconazole has excellent in-vitro activity against *Candida albicans*, and therefore a lower dose of the drug would be adequate for prophylaxis against *Candida*; (ii) several studies showed that, even at doses of 400 mg, fluconazole does not provide protection against *C. krusei* [3] or *Aspergillus* sp. [3,12]; (iii) the lower dose of fluconazole is also cost saving.

### Study End-Points

The primary end-point of the study was the incidence of proven invasive fungal infection. The secondary end-points were the incidence of suspected infection and superficial fungal infections, toxicity of the antifungal prophylaxis, the probability of empirical amphotericin B being initiated, and overall survival at 100 days post transplant.

### Definition of Fungal Infection

A proven invasive fungal infection was defined as one in which there was both clinical evidence of blood or tissue infection and a culture or biopsy specimen from the involved site demonstrating a pathogenic fungal organism.

Suspected invasive fungal infections was defined broadly as any episode, based on clinical, radiological, or microbiological grounds, for which the physician felt compelled to treat empirically with amphotericin B but for which a fungal infection could not be established.

Superficial fungal infections were diagnosed by the isolation of a fungus from the skin, oropharynx, or gastrointestinal tract in association with signs of inflammation, ulcerations, plaques, or exudates not explainable by other pathogens.

### Assessment

Patients were clinically evaluated at baseline, twice weekly for the duration of treatment, again 2 weeks after the treatment was stopped. Full blood counts with differential and platelet counts and serum biochemical analyses were performed at least twice per week as inpatients and weekly as outpatients until 2 weeks after the end of the study. Chest X-ray was performed weekly both as inpatients and outpatients until 2 weeks after the end of the study.

When patients developed fever of  $\geq 38^{\circ}\text{C}$  or infection was suspected, cultures from blood, urine, and other suspected sites of fungal infection were obtained, prophylactic oral antibacterial therapy was stopped, and broad-spectrum intravenous antimicrobial therapy (usually a  $\beta$ -lactamase plus aminoglycoside and glycopeptide com-

bination) was started; if the fever persisted despite 3–5 days of systemic antibiotics or fungal infection was suspected but not proven, empirical intravenous amphotericin B of 0.5–1 mg per kg of body weight was initiated at the discretion of the individual physician.

### Definition of Drug-Related Toxicity

Drug-related nephrotoxicity was defined as an increase in serum creatinine level to more than 1.5 times baseline and beyond the normal range. Drug-related hepatotoxicity was defined as an increase in serum bilirubin, aminotransferase, or alkaline phosphatase levels to more than 1.5 times baseline and beyond the normal range. Toxicity was considered to be drug related if the elevated value persisted until the discontinuation of the study drug.

### Statistical Analysis

The proportions of patients with a given characteristic were compared by the  $\chi$ -square test or by Fisher's exact test. Differences in the means of continuous measurements were tested by either Student's *t*-test or the Mann-Whitney *U*-test. All tests were two-tailed. Curves for the overall survival were plotted according to the method of Kaplan and Meier [13] and were compared by the log-rank test. All randomized patients were studied in their assigned treatment groups on an intention-to-treat basis.

## RESULTS

### Patients

Between January 1993 and December 1998, a total of 186 patients were enrolled into the trial, with 100 patients receiving fluconazole and 86 patients receiving amphotericin B. There were no significant difference among the two treatment arms for any of the clinical features with regard to age, gender, underlying disease, type of transplantation, duration of neutropenia, duration of prophylaxis, duration of fever, severity of graft-versus-disease (GVHD), systemic glucocorticosteroid therapy, use of Gram-negative bacterial prophylaxis, duration of therapeutic amphotericin B, and total dose of therapeutic amphotericin B (Table I).

### Discontinuation of Prophylactic Anti-fungal Therapy

A total of 96 (51.6%) patients were removed from prophylaxis for various reasons. The reasons for discontinuing antifungal prophylaxis early were compared between the two arms, and they did not differ significantly ( $P = 0.72$ ). As shown in Table II, 46 patients (46%) in the fluconazole arm and 34 patients (39.5%) in the amphotericin B arm had prophylactic antifungal therapy withdrawn because of persistent fever while on broad-spectrum anti-bacterial therapy or suspected fungal in-

**TABLE I. Demographics of the Transplant Patients Receiving Either Fluconazole or Amphotericin B**

	Fluconazole ( <i>n</i> = 100)	Amphotericin B ( <i>n</i> = 86)	<i>P</i>
Median age, years (range)	29.57 (4–62)	29.83 (4–63)	0.90
Sex			
Male	63	51	
Female	37	35	0.65
Transplant type			
Allogeneic	74	66	
Autologous	26	20	0.86
Underlying conditions			
Acute myeloid leukemia	31	20	
Acute lymphocytic leukemia	15	13	
Chronic myeloid leukemia	21	24	
Non-Hodgkin's lymphoma	6	7	
Hodgkin's disease	2	3	
Multiple myeloma	8	7	
Aplastic anemia	11	7	
Others	6	5	0.89
Duration of neutropenia (days)	13 (0–62)	12 (0–48)	0.65
Mean (range)			
Graft versus host disease (for allograft recipients)			
No GVHD	16	10	
Grade 1	13	7	
Grade 2	19	15	
Grade 3	17	22	
Grade 4	9	12	0.44
Steroids ( $\geq 0.5$ mg/kg)	50	50	0.30
Gram-negative bacterial prophylaxis			
Pefloxacin	17	16	0.226
Ciprofloxacin	83	70	
Duration of prophylaxis (days)	20 (4–37)	20 (5–44)	0.86
Mean (range)			
Total duration of fever			
$>38^\circ\text{C}$ (days)	5 (0–27)	5 (0–33)	0.70
Mean (range)			
Total therapeutic dose			
of amphotericin	580 (40–400)	531 (49–1720)	0.36
B (mg)			
Mean (range)			

fections. Four fluconazole recipients (4%) and 6 amphotericin B recipients (7%) discontinued prophylactic antifungal therapy because of proven fungal infections ( $P = 0.52$ ). There were 3 patients in each arm who were removed from the study because of renal or liver toxicity.

The probability of empirical amphotericin B being initiated was equal between the treatments (fluconazole 55% vs. amphotericin B 49%,  $P = 0.45$ , Fig. 1). The median number of days after transplantation until amphotericin B was begun for persistent febrile neutropenia was 9 for both fluconazole and amphotericin B recipients ( $P = 0.74$ ).

### Effect on Fungal Infection

During the first 100 days post transplant, a total of 17 patients (17%) in the fluconazole arm and 17 patients (19.8%) in the amphotericin arm developed documented

TABLE II. Outcome of Prophylactic Anti-fungal Therapy

	Fluconazole (n = 100)	Amphotericin (n = 86)	P value
Reasons for discontinuation of prophylactic anti-fungal therapy			0.72
Persistent fever or suspected fungus	46	34	
Proven fungus	4	6	
Organ toxicity	3	3	
Total	53	43	
Incidence of fungal infection within 100 days post transplantation			0.50
Proven invasive fungal infection	12	11	
Suspected fungal infection	4	2	
Superficial fungal infection	1	4	
Total	17	17	

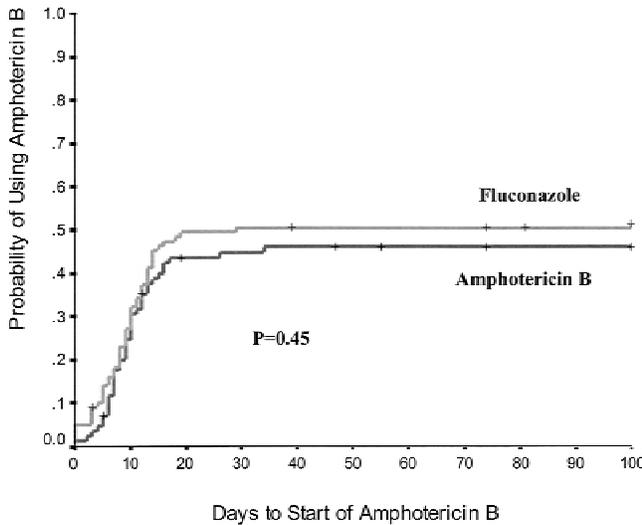


Fig. 1. Kaplan-Meier estimates of empirical initiation of amphotericin B during the first 100 days of transplantation.

or suspected fungal infections (Table II). These included infections noted during and after discontinuation of prophylaxis. The difference in incidence between the two arms was not statistically significant ( $P = 0.50$ ). The subgroups of fungal infections were compared between the two groups (Table II), and the difference was not statistically significant ( $P = 0.50$ ). The probability of developing fungal infection during the first 100 days post transplantation was not significantly different between the two treatment arms ( $P = 0.52$ ; Fig. 2). Eight patients (8%) in the fluconazole arm developed fungal infections up to the day of engraftment, compared to 8 patients (9%) in the amphotericin arm ( $P = 0.752$ ). The risk of fungal infection was also not significantly different between the two treatment arms when the patients are stratified according to the type of Gram-negative bacterial prophylaxis ( $P = 0.23$  for pefloxacin recipients;  $P = 0.24$  for ciprofloxacin recipients), the type of transplan-

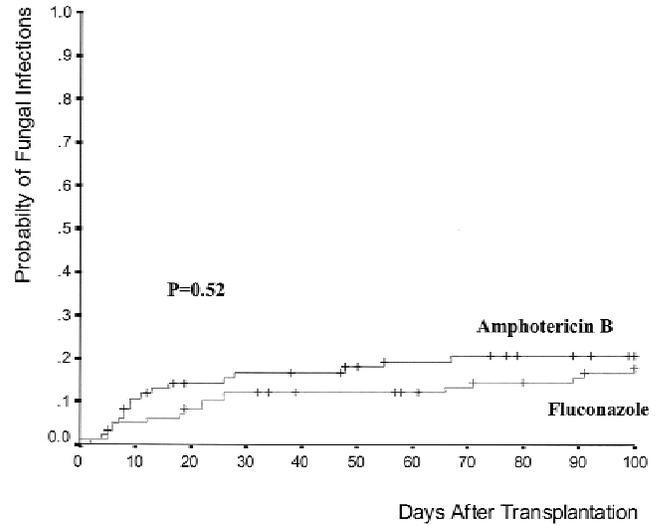


Fig. 2. Kaplan-Meier estimates of developing systemic fungal infections during the first 100 days of transplantation.

tation ( $P = 0.16$  for autologous recipients;  $P = 0.80$  for allogeneic recipients) and whether or not the patients developed grade 2-4 GVHD ( $P = 0.1$  for those without grade 2-4 GVHD;  $P = 0.63$  for those with grade 2-4 GVHD). Among the allogeneic transplant recipients, proven fungal infections occurred in 21 patients (12 fluconazole recipients and 9 amphotericin B recipients) with grade 2-4 GVHD. This is not significantly higher than the group without grade 2-4 GVHD, in which only 4 patients developed fungal infections (22% vs. 9%,  $P = 0.06$ ) (Table III). In the subgroup of 21 patients with grade 2-4 GVHD, 10 patients (47.6%, 7 fluconazole vs. 3 amphotericin;  $P = 0.03$ ) developed documented or suspected fungal infections at the median time of 34 days (range, 14-78) after engraftment.

**Proven Invasive Fungal Infections**

Proven invasive fungal infection occurred in 12 (12%) fluconazole recipients and 11 (12.8%) amphotericin recipients within the first 100 days of transplantation. The types of fungi causing the systemic fungal infections are shown in Table IV. There was no significant difference in the occurrence of the subtypes of fungi in the two treatment arms ( $P = 0.09$ ). Of interest, there seemed to be more *Candida parasilopsis* infections in the fluconazole arm ( $P = 0.09$ ). The incidence of infections due to *Aspergillus* and other fungi, such as *Penicillium* and *Pae-cilomyces*, was low and similar between the two treatment arms. The predominant site of infection was blood stream for both treatment groups, and this occurred in similar proportions. There was one patient from each treatment arm who had disseminated fungal infections due to *Aspergillo-sis*. Pulmonary infection due to *C. al-*

**TABLE III. Incidence of Fungal Infections as Stratified by the Type of Gram-Negative Bacterial Prophylaxis, Type of Transplantation, and Whether Grade 2–4 GVHD was Present (Among the Allogeneic Transplant Recipients)**

	Gram-negative bacterial prophylaxis											
	Pefloxacin (33)		Ciprofloxacin (153)		Autologous transplant (n = 46)		Allogeneic transplant (n = 140)		No grade 2–4 GVHD (n = 46)		With grade 2–4 GVHD (n = 94)	
	Fluconazole	Ampho B	Fluconazole	Ampho B	Fluconazole	Ampho B	Fluconazole	Ampho B	Fluconazole	Ampho B	Fluconazole	Ampho B
No fungal infection	15	15	68	54	23	14	60	55	27	15	33	40
Proven invasive fungal infection	2	1	10	11	3	4	9	7	0	0	9	7
Suspected fungal infection	0	0	4	1	0	0	4	2	2	0	2	2
Superficial fungal infection	0	0	1	4	0	2	1	2	0	2	1	0
Total	17	16	83	70	26	20	74	66	29	17	45	49

*bicans* occurred in one patient who received prophylactic amphotericin B.

### Superficial Fungal Infections

Oropharyngeal candidiasis occurred in 1 (1%) patient receiving fluconazole and 4 (4.6%) of those receiving low-dose amphotericin B. The incidence of superficial infections was not found to be significantly different between the two treatment groups ( $P = 0.58$ ). *Candida* of undetermined species accounted for almost all cases of documented oropharyngeal fungal infections in both groups.

### Suspected Invasive Fungal Infections

Four patients receiving fluconazole and 2 patients receiving amphotericin B developed clinical and radiological features consistent with suspected invasive fungal infections. All of these patients had persistent fever associated with single or multiple nodular lesions demonstrated on chest radiography or computerized tomography. Invasive procedures to establish histological or microbiological diagnosis were precluded by cytopenia and by the critical conditions in these patients. All 6 of these patients succumbed to the illness eventually, and no post-mortem study was carried out.

### Toxicity

There was no significant difference between the 2 treatment arm groups in the number of patients who were withdrawn from the study as a result of organ toxicity. Thirteen patients (13%) from the fluconazole arm and 18 patients (21%) from the amphotericin B arm developed renal toxicity during the first 100 days post transplantation. Only 3 amphotericin B recipients developed renal dysfunction, leading to discontinuation of antifungal prophylaxis. Patients who developed renal toxicity had normal creatinine values (median 78  $\mu\text{mol/L}$ , range 45–131  $\mu\text{mol/L}$ ) prior to initiation of prophylactic amphotericin B therapy. There are multiple etiologies for the renal dysfunction, and these included sepsis, nephrotoxic antimicrobial agents, and immunosuppressants such as cyclosporin and tacrolimus. The mean maximum creatinine levels within the first 100 days of transplantation was 187  $\mu\text{mol/L}$  (range, 10–786  $\mu\text{mol/L}$ ) for fluconazole recipients and 92  $\mu\text{mol/L}$  for amphotericin B recipients (range, 9–1,085  $\mu\text{mol/L}$ ) ( $P = 0.85$ ). The maximum change in creatinine level (baseline to peak) during the period the prophylactic antifungal therapy was given until 1 week after discontinuation, was not significantly different between the two treatment groups (mean value: 7  $\mu\text{mol/L}$  in fluconazole vs. 20  $\mu\text{mol/L}$  in amphotericin;  $P = 0.096$ ).

Liver dysfunction leading to discontinuation of fluconazole occurred in only 3 patients. All 3 of these patients had abnormal liver functions attributed to either

TABLE IV. Types of Fungi Isolated in the Subgroup of Fungal Infections During the First 100 Days of Transplantation

Fungus	Proven invasive fungal infections		Superficial fungal infections	
	Fluconazole (number)	Amphotericin B (number)	Fluconazole (number)	Amphotericin B (number)
<i>Candida</i> , type unknown	0	2	1	3
<i>Candida albicans</i>	0	2	0	1
<i>Candida parasilopsis</i>	6	2	0	0
<i>Candida tropicalis</i>	2	0	0	0
<i>Candida krusei</i>	1	0	0	0
<i>Candida glabrata</i>	1	0	0	0
<i>Aspergillus</i> species	1	2	0	0
Others	1	3	0	0
Total	12	11	1	4

veno-occlusive or graft-versus-host disease of the liver. Two patients had elevated bilirubin associated with other signs of veno-occlusive disease such as hepatomegaly and fluid retention between the first and second weeks of transplantation. The third patient had elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) coinciding with the engraftment of neutrophils and was treated as for acute graft-versus-host disease of the liver with corticosteroids. Fluconazole was withdrawn in all these 3 patients so as to not aggravate the liver dysfunction further. The liver function in all 3 of these patients returned to normal baseline level subsequently.

The maximum changes in values (baseline to peak) for bilirubin, ALT, and AST were also compared between the two treatment arms during the period when prophylactic antifungal therapy was administered until 1 week after discontinuation. The mean rise in bilirubin level was 7 µmol/L for fluconazole recipients and 20 µmol/L for amphotericin B recipients ( $P = 0.096$ ); the mean rise in ALT was 33 U/L for fluconazole recipients and 30.5 U/L for amphotericin B recipients ( $P = 0.688$ ); the mean rise in AST was 11 U/L for fluconazole recipients and 9 U/L for amphotericin B recipients ( $P = 0.407$ ).

**Death**

There were 47 (25%) deaths within the first 100 days of transplantation: 22 in the fluconazole arm and 25 in the amphotericin B arm. Causes of death included relapse of underlying hematological malignancies, infection, hemorrhage, and graft-versus-host disease. Death was attributed to fungal infections in 6 (6%) fluconazole recipients and 6 (7%) amphotericin B recipients. Kaplan–Meier analysis of the survival at 100 days of transplantation was similar between the 2 treatment arms (fluconazole 78% vs. amphotericin 70%,  $P = 0.254$ , Fig. 3).

**DISCUSSION AND CONCLUSION**

In the present study, invasive fungal infection developed in 23 (12.3%) of the 186 patients during the first

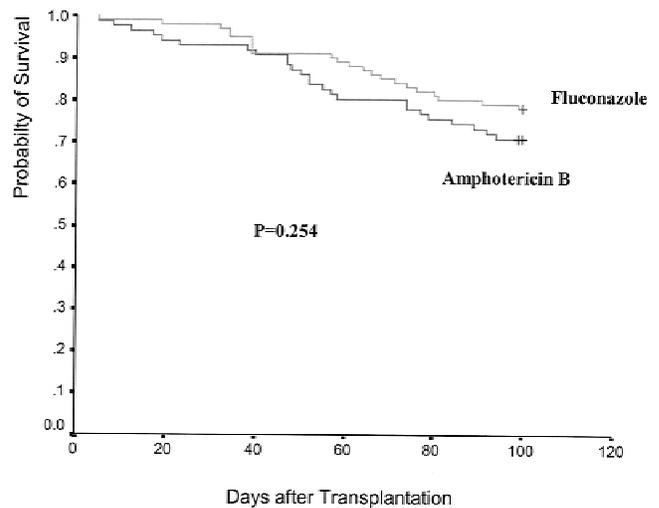


Fig. 3. Kaplan–Meier estimates of survival for patients receiving fluconazole or amphotericin B during the first 100 days after transplantation.

100 days of hematopoietic stem cell transplantation. This is higher than the rate of 2.8–7.0% seen in other randomized trials involving patients receiving either fluconazole or low-dose amphotericin B [3–5,8,14]. The aseptic measures used at our center are similar to other bone marrow transplant centers throughout the world. We postulate that our tropical climate may have influenced the transmission of fungal infection in our immunocompromised patients, which has been observed elsewhere as well [15].

Our study also showed similar prophylactic efficacy between fluconazole and amphotericin B. This result is consistent with the study by Wolff et al. [8], although their study showed a higher incidence of renal toxicity in amphotericin B recipients. In our study, the incidence of renal toxicity between the 2 treatment arms did not differ significantly. Antifungal therapy was discontinued in only 3 patients (3%) from the amphotericin B arm as a result of renal toxicity.

The optimal prophylactic dose of fluconazole has not been standardized. Although the usual dose of fluconazole for the treatment of candidal infections was 100–400

mg/day, a dose of 400 mg/day was chosen for prophylaxis in 3 randomized studies [3,4,12] because it was anticipated that such a high dose might offer some protection against *Aspergillus* species [16]. It is now clear that fluconazole is clinically ineffective against *Aspergillus*, even at a dose of 2 g/day [17]. More recent data has shown that daily doses of 200 or 400 mg were equally effective in the prophylaxis against candidiasis after bone marrow transplantation [18]. A much lower prophylactic dose of 50–150 mg/day has been shown to result in low incidences of proven deep fungal infection in several European randomized clinical trials [19–21]. The lower dose of 200 mg fluconazole is also cost saving.

Hepatotoxicity has always been a concern in patients receiving fluconazole therapy. However, evaluation of liver function tests in patients undergoing stem cell transplantation is often difficult due to competing effects of myeloablative chemo- and radiotherapy, veno-occlusive disease, other drugs, blood transfusions, sepsis, and the underlying hematological malignancy itself on hepatic function. In our study, we did not observe any patient who developed liver dysfunction solely attributable to fluconazole therapy. There was no difference between the two treatment arms of the study in the number of patients reaching the criteria for the withdrawal from the study. Using the rise in liver enzymes as objective assessment of liver toxicity, we did not detect any significant difference between the two treatment arms.

The proportion of patients withdrawn from prophylactic therapy as a result of abnormal liver function in previously reported series varies widely between 0% and 21% [3,4,8]. Our results compare favorably with these studies. It is possible that the lower dose of fluconazole may have played a part in reducing incidence of fluconazole-associated liver dysfunction. However, as another series using the higher 400-mg fluconazole dose has reported a lower rate of abnormal liver function than our study [8], clearly there are other factors that may have influenced the incidence of hepatic dysfunction.

Most of the fungal infections were due to the *Candida* species and the incidence between the fluconazole and amphotericin B recipients did not differ significantly. One of the concerns about using fluconazole for prophylactic and empirical antifungal therapy is its lack of activity for *Aspergillus* and certain *Candida* species, such as *C. glabrata* and *C. krusei*. In our series, only one of the patients developed *C. glabrata* fungemia. As such, our experience concurs with other studies in that no significant increase in the incidence of opportunistic infection by these non-susceptible organisms was seen [3,4,12].

There is an apparent low incidence of *Aspergillosis* in this study perhaps due to the difficulty in diagnosing this condition. Absolute certainty about the diagnosis is seldom attained before death due to the nature of the refer-

ence standard [22]. Many patients with suspicious radiological features were precluded from invasive diagnostic procedures because of cytopenia or critical conditions. The limitations of current diagnostic technique has further been highlighted in previous studies showing a lower incidence of proven and suspected *Aspergillus* and *Candida* infections in the control arms (between 15% and 30%) [4, 23,24] than that determined by autopsy [25].

Six (6%) patients developed *C. parasilopsis* fungemia isolated from the central venous catheter while receiving fluconazole prophylaxis. This was unexpected because *C. parasilopsis* is ordinarily susceptible to fluconazole. Unfortunately, the susceptibility of these *C. parasilopsis* isolates was not tested in our laboratory. In any case, the in vitro sensitivity testing of fungal isolates is not well standardized, and results do not always correlate with in vivo activity [26]. Similar breakthrough candidemia has also been reported previously [27]. In that study, central catheter infection with fluconazole susceptible *C. parasilopsis* occurred in 10 out of 20 candidemic patients despite fluconazole prophylaxis. None of these patients demonstrated evidence of invasive infection, and all had blood culture sterility upon catheter removal. Similar to that study, none of the patients in our series developed deep-seated fungal infection. All the patients were successfully treated with catheter removal, and there was no fatality directly related to *C. parasilopsis* infection.

In allogeneic bone marrow transplantation, the risk of invasive fungal infection extends well beyond the period of neutropenia when GVHD, and its treatment, results in pronounced immunosuppression [17]. In our study, the patients were given antifungal prophylaxis during the period of neutropenia, and the mean total duration of antifungal prophylaxis was only 20 days in both treatment arms. We recognize that this prophylactic regimen may not have conferred adequate protection against invasive fungal infections, which may arise as a result of graft-versus-host disease and its treatment. This is because in the event of late-onset GVHD, the patients will no longer be on prophylactic antifungal therapy. A previous study [28] has demonstrated that the use of fluconazole 400 mg/day for 75 days after allogeneic donor BMT not only resulted in a decrease in mortality early after BMT, but it is also associated with an independent, long-term mortality benefit. Our study, in the absence of an untreated controlled group and with the use of antifungal prophylaxis only until engraftment, is not able to address this issue. However, among our 21 allogeneic transplant patients with grade 2–4 GVHD who developed documented or suspected fungal infections, 10 (47.5%) of them patients had a delay onset at the median time of 34 days (range, 14–78 days) after engraftment. This finding provides further evidence of the potential benefit of

continuing prophylaxis beyond the period of neutropenia among these high-risk patients.

In summary, our study showed that, when compared to amphotericin B, fluconazole is equally safe and effective as an antifungal prophylaxis agent in patients undergoing hematopoietic stem cell transplantation. The ease of administration, high oral bioavailability [29], and excellent tolerance of oral fluconazole make it an attractive alternative to intravenous amphotericin.

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