Bone Marrow Transplantation (2006) 38, 127–134

www.nature.com/bmt

ORIGINAL ARTICLE

A prospective randomized trial of itraconazole vs fluconazole for the prevention of fungal infections in patients with acute leukemia and hematopoietic stem cell transplant recipients

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Fluconazole antifungal prophylaxis is standard care in allogeneic hematopoietic stem cell transplant (HSCT) recipients, but this drug lacks anti-*Aspergillus* activity, the primary cause of invasive fungal infection (IFI) in many transplantation centers. We performed a randomized trial to compare itraconazole vs fluconazole, for prevention of IFIs in patients with acute leukemia (AL) and HSCT recipients. One hundred and ninety-five patients were randomly assigned to either fluconazole or itraconazole antifungal prophylaxis, after stratification into high-risk and low-risk groups. Antifungal prophylaxis was started at the beginning of chemotherapy and continued until resolution of neutropenia, or until amphotericin B treatment was started. IFI occurred in 11 (11%) of itraconazole, and in 12 (12%) fluconazole recipients. Invasive candidiasis (IC) developed in two (2%) itraconazole and one (1%) fluconazole recipients, while invasive aspergillosis (IA) developed in nine (9%) itraconazole and 11(11%) fluconazole recipients. There was no difference in the incidence of total IFI, IC and IA between the two study arms. However, there was a nonsignificant trend towards reduced mortality among patients who developed IA while receiving itraconazole prophylaxis (3/9 = 33% vs 8/11 = 73%, $P = 0.095$).
Bone Marrow Transplantation (2006) **38,** 127–134. doi:10.1038/sj.bmt.1705418; published online 5 June 2006
Keywords: itraconazole; fluconazole; fungal infections; acute leukemia; hematopoietic stem cell transplantation

Introduction

Invasive fungal infections (IFI) are a major determinant of morbidity and mortality in patients undergoing treatment for hematological malignancies. IFIs are difficult to diagnose, expensive to treat, and have a high treatment failure rate.[1,2] Many agents have been used for prophylaxis, mostly different formulations of amphotericin B and fluconazole, but studies of efficacy show conflicting results.[3–9] Fluconazole prophylaxis in hematopoietic stem cell transplant (HSCT) recipients reduces morbidity and mortality[10] and has become the standard of care in this setting.[11] However, routine use is associated with the emergence of fluconazole-resistant *Candida* infections.[12–14] Furthermore, fluconazole is ineffective against *Aspergillus*, an organism which has now become the primary cause of IFIs in many transplantation centers,[15,16] including ours.[17] Recently, two new itraconazole formulations, an oral hydroxypropyl-β-cyclodextrin solution, and an intravenous formulation, have become available and provide favorable pharmacological profiles and good anti-*Candida* as well as anti-*Aspergillus* activity.[18] Studies to support the superiority of itraconazole over placebo in preventing IFIs are already available[19–21] and three recent studies comparing itraconazole with fluconazole as prophylaxis have shown equivalence, or a slight superiority for itraconazole.[22–24]

We performed a randomized trial comparing oral and intravenous itraconazole with oral and intravenous fluconazole, administered to HSCT recipients and patients with acute leukemia (AL), to determine whether itraconazole is superior to fluconazole in the prevention of IFIs, particularly invasive aspergillosis (IA).

Materials and methods

Study center

The study was performed in a single hematology and bone marrow transplant (BMT) center, comprising a 15-bed

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Received 28 November 2005; revised 7 March 2006; accepted 8 March 2006; published online 5 June 2006

BMT unit and an 11-bed hematology unit. Annually, 150 BMT procedures are performed (90 autologous and 60 allogeneic) and 70 new AL patients are treated in the center. The study was conducted on hospitalized patients in these two units, in a protected environment employing a high efficiency particulate air filtration (HEPA) system.

Patients

Patients aged $\geqslant 16$ years, undergoing HSCT or intensive chemotherapy treatment for AL, and expected to experience a long neutropenic period (>7 days), were eligible for the study.

Exclusion criteria:

1. Documented IFI at the time of enrollment, or during previous chemotherapy.
2. Allergy to azole drugs.
3. Liver function abnormalities: bilirubin or alkaline phosphatase >3 times the upper limit of normal, or liver enzymes >5 times the upper limit of normal.
4. Concurrent acute hepatitis or chronic liver disease.
5. Use of azole drugs within 10 days before enrollment.
6. Pregnancy or breast-feeding.
7. Concomitant therapy with drugs (terfenadine, astemazole, triazolam, midazolam, cisopride, CoA reductase inhibitors) having potential interactions with azole antifungal agents.

All patients gave written informed consent, and the study was approved by the Institutional Review Board.

Study drugs

Fluconazole was administered at a dose of 400 mg once daily orally or intravenously when a patient was unable to tolerate oral intake. Dose adjustment was made for renal function impairment.

Oral itraconazole was given at a dose of 200 mg twice daily or intravenously 200 mg once daily when oral administration was impossible. Intravenous itraconazole was not used for patients with a creatinine clearance <30 ml/min due to accumulation of carrier, cyclodextrin.

Study design

Patients were stratified to either high- or low-risk strata. High risk included patients undergoing allogeneic (matched related or genotypically haploidentical) HSCT, or patients with relapsed or resistant AL. Low risk included patients undergoing autologous HSCT, or treated for new onset AL. Patients were randomized to fluconazole or itraconazole prophylaxis in each stratum, using a random number generator, in blocks of four.

Oral anti-fungal prophylaxis was started at the beginning of chemotherapy. Intravenous preparations were used if and when patients were unable to tolerate oral medications, and switched back to oral preparations when possible. Anti-fungal prophylaxis was continued until resolution of neutropenia, for a maximum of 8 weeks. Premature discontinuation of anti-fungal prophylaxis occurred when: (1) Empirical amphotericin B treatment was administered for prolonged fever unresponsive to broad-spectrum antibiotics. (2) Possible, probable or definite IFI was diagnosed. (3) A serious adverse event related to study drug occurred. (4) The patient died.

Chemotherapy and transplantation regimen

Chemotherapy regimens included standard induction and consolidation regimens for AL and chemotherapy-based conditioning regimens for autologous BMT (group 1); total body irradiation-based conditioning regimens for autologous or allogeneic BMT (group 2); reduced intensity or T-cell depleted conditioning regimens which include anti thymocyte globulin (ATG) and/or fludarabine for allogeneic or haploidentical BMT (group 3).

Graft-versus-host disease (GVHD) prophylaxis included cyclosporine A and methotrexate.

Anti-bacterial prophylaxis was not administered.

Anti-viral prophylaxis included high-dose acyclovir.

Laboratory procedures and definitions

Toxicity was graded from 0 to 4, according to the National Cancer Institute Common Toxicity Criteria.

Superficial fungal cultures were obtained weekly from oral and perianal sites to detect fungal colonization.

Fungal cultures from blood and other suspected sites of fungal infection were obtained when clinically indicated.

Computerized tomography, bronchoscopy with bronchoalveolar lavage (BAL), and biopsies were performed when clinically indicated.

Serum galactomannan antigen detection was performed when IA was suspected using ELISA (Platelia *Aspergillus:* Saofi Diagnostics Pasteur, Marnes-La-Cosuette, France). Assays were classified as positive when optical density index was >1.0.

Aspergillus sp. DNA detection was performed on BAL fluid, when IA was suspected, using a local protocol (manuscript in preparation). Briefly, a two-step (nested) polymerase chain reaction (PCR), which specifically amplifies a region of the 18S rRNA gene that is highly conserved in *Aspergillus* sp., was performed on DNA samples extracted using Qiamp DNA mini kit (QIAgen, Hilden, Germany).

Candida sp. were identified to the species level using API ID32C system (Biomerieux, Marcy l'Etoile, France).

Fungal susceptibility testing was performed for yeasts using the E-test stable agar gradient MIC technology (AB Biodisk, Solna, Sweden). MIC breakpoints were determined according to the National Committee for Clinical Laboratory Standards (NCCLS) M27A2 reference. Itraconazole resistance was determined when MIC was $\geqslant 1\,\mu$g/ml, while fluconazole resistance was determined when MIC was $\geqslant 8\,\mu$g/ml.

Fungal colonization was defined when a fungus was isolated from cultures of the oropharynx or the perianal area.

IFI was diagnosed using criteria published by the NIH Mycoses Study Group and the EORTC.[25]

Statistical analysis

The primary end point for this study was the incidence of definite, probable or possible IFI. It was estimated that 20% of patients in the fluconazole arm would develop IFI.

Using these assumptions, 200 patients would be required to detect a reduction in IFI rate from 20% in the fluconazole arm to 10% in the itraconazole arm (70% power and one-tailed α of 0.05). Data analysis was performed using the SPSS 11.0 statistical package. Comparison of continuous variables between the two groups was done by the *t*-test or Mann–Whitney test. χ^2 test or Fisher's exact test were performed for the comparison of proportions between the two groups.

Results

Patient characteristics (Table 1)
Between 1.12.2001 and 1.8.2003, 200 consecutive eligible patients were randomized to receive anti-fungal prophylaxis with either fluconazole or itraconazole. Five patients were subsequently withdrawn from the study when a past history of IFI had been noted, and they were excluded from all analyses. Ninety-nine patients received fluconazole and 96 patients were given itraconazole. The two groups were similar with respect to demographics, risk groups, underlying malignancies, disease state, chemotherapy regimen, type of HSCT and duration of neutropenia.

Study drug administration (Table 2)
The duration of administration was similar in both groups (17 days). However, significantly more patients required itraconazole intravenously compared to fluconazole (71% vs 45%, $P<0.001$) and for a longer duration (9 vs 7 days, $P<0.01$).

The reason for study drug discontinuation was resolution of neutropenia in about 2/3 of patients, and amphotericin B administration in 1/3 of patients in both groups.

Adverse clinical events or laboratory abnormalities that led to study drug discontinuation occurred in two fluconazole recipients and one itraconazole recipient.

There was no significant difference between the two groups in overall renal or hepatic toxicity; however, hyperbilirubinemia developed more often in itraconazole recipients (53% vs 35%, $P<0.02$).

Table 1 Baseline characteristics

Characteristic	*Fluconazole (99)*	*Itraconazole (96)*	P
Median age (range), years	49 (18–73)	50 (17–75)	NS
Sex, n (%)			NS
Male	56 (57)	63 (66)	
Female	43 (43)	33 (34)	
Underlying disease, n (%)			
Hematological malignancy			NS
AML	33 (33)	28 (29)	
ALL	4 (4)	5 (5)	
CML	7 (7)	7 (7)	
CLL	0	1 (1)	
MDS	1 (1)	2 (2)	
MM	18 (18)	27 (28)	
Hodgkin's disease	5 (5)	3 (3)	
NHL	29 (29)	16 (17)	
Nonhematological malignancy	1 (1)	5 (5)	NS
Nonmalignant	1 (1)	2 (2)	NS
Type of transplant, n (%)			NS
No transplant	21 (21)	22 (23)	
Autologous	56 (57)	52 (54)	
Allogeneic	19 (19)	18 (19)	
With TCD	5/19	5/18	
Haploidentical	3 (3)	4 (4)	
Type of chemotheray, n (%)			NS
Group 1	77 (78)	76 (79)	
Group 2	10 (10)	8 (8)	
Group 3	12 (12)	12 (13)	
Less myeloablative	3	2	
Risk group, n (%)			NS
Low risk	74 (75)	72 (75)	
High risk	25 (25)	24 (25)	
Mean duration of neutropenia, d $\pm$ s.d.	11.4 $\pm$ 6.4	11.9 $\pm$ 7.9	NS
High risk	13.4 $\pm$ 6.1	15.4 $\pm$ 9.7	NS
Low risk	10.7 $\pm$ 6.4	10.8 $\pm$ 7.0	NS

Abbreviaions: AML = acute myeloid leukemia; ALL = acute lymphoblastic leukemia; CML = chronic myeloid leukemia; CLL = chronic lymphocytic leukemia; MDS = myelodysplastic syndrome; MM = multiple myeloma; NHL = non-Hodgkin's lymphoma; TCD = T-cell depletion; NS = not significant.

Invasive fungal infections (Tables 3, 4)
During the study period, and within 3 months from study entry, 23 (12%) patients developed IFIs. Twelve episodes of IFI occurred among fluconazole recipients and 11 in the itraconazole group. There was no difference in the incidence, type or the level of certainty of diagnosis of IFI between the two study groups. IFI developed in 28% of high-risk fluconazole recipients and in 29% of high-risk itraconazole recipients (all were allogeneic HSCT recipients), while in the low-risk patients the incidence was 7 and 6%, respectively. Time to diagnosis of the infection was similar in both groups (22 vs 21 days).

Invasive candidiasis (IC), diagnosed by isolation of *Candida* sp. from blood, developed in one (1%) fluconazole recipient and in two (2%) itraconazole recipients (P = NS). The fluconazole recipient developed *Candida krusei* fungemia and the isolate was resistant to both fluconazole (MIC $>32\,\mu$g/ml) and itraconazole (MIC $=1.5\,\mu$g/ml). One itraconazole recipient developed *C. tropicalis* fungemia, which was itraconazole-resistant (MIC $=1\,\mu$g/ml) but fluconazole-sensitive (MIC $=0.75\,\mu$g/ml), and the second patient had *C. glabrata* fungemia, resistant to both drugs (MIC for fluconazole $=12\,\mu$g/ml, itraconazole $=1\,\mu$g/ml). These three infections developed in high-risk patients, and no single IC episode occurred in low-risk patients in any study group.

IA was the only type of invasive mold infection diagnosed in 20 patients in both study groups, and all IA cases were invasive pulmonary aspergillosis (IPA). Definite IA was found in three patients. Two patients were diagnosed during post-mortem examination, and one by open lung biopsy. Eleven patients had probable IA. Probable IA was diagnosed in patients at risk with characteristic clinical signs and symptoms (fever, pleuritic chest pain, hemoptysis, hypoxemia), as well as radiological signs (pulmonary nodules and opacities with halo sign),

Table 2 Study drug administration

	Fluconazole (99)	*Itraconazole (96)*	P
Duration, median (range), days	17 (2–41)	17 (4–56)	NS
PO	14 (2–41)	9 (1–42)	$P<0.01$
IV	7 (1–18)	9 (1–42)	$P<0.01$
n (%) of patients receiving IV	45 (45)	68 (71)	$P<0.001$
Reason for study drug discontinuation, *n* (%)			NS
Recovery of neutropenia	64 (65)	64 (67)	
Amphotericin B administration	33 (33)	30 (31)	
Toxicity	2 (2)	1 (1)	
Death	0	1 (1)	
Toxicity, *n* (%)			
Hepatotoxicity			
Overall $\geqslant$ Grade 1	68 (69)	73 (76)	NS
Bilirubin $\geqslant$ Grade 1	35 (35)	51 (53)	$P<0.02$
Renel toxicity			
Creatinine $\geqslant$ grade 1	12 (12)	10 (10)	NS

Abbreviaions: PO = oral; IV = intravenous; NS = not significant.

Table 3 Invasive fungal infections; incidence and mortality

	Incidence rate (%)		P	*Mortality rate (%)*		P
	Fluconazole (99)	*Itraconazole (96)*		*Fluconazole (99)*	*Itraconazole (96)*	
IFI, *n* (%)	12/99 (12)	11/96 (11)	NS	9/12 (75)	5/11 (45)	0.154
High risk[a]	7/25 (28)	7/24 (29)	NS	6/7 (86)	4/7 (57)	0.28
Low risk	5/74 (7)	4/72 (6)	NS	3/5 (60)	1/4 (25)	0.36
IC, *n* (%)	1/99 (1)	2/96 (2)	NS	1/1 (100)	2/2 (100)	
IA, *n* (%)	11/99 (11)	9/96 (9)	NS	8/11 (73)	3/9 (33)	0.095
High risk	6/25 (24)	5/24 (21)	NS	5/6 (83)	2/5 (40)	0.20
Low risk	5/74 (7)	4/72 (6)	NS	3/5 (60)	1/4 (25)	0.36
Died of IA				3/11 (27)	0/9 (0)	0.14
Unrelated death				5/11 (45)	3/9 (33)	0.54
Definite IA, *n* (%)	2/11 (18)	1/9 (11)	NS	2/2 (100)	1/1 (100)	
Probable IA, *n* (%)	6/11 (55)	5/9 (56)	NS	4/6 (66)	2/5 (40)	0.31
Possible IA, *n* (%)	3/11 (27)	3/9 (33)	NS	2/3 (67)	0/3 (0)	0.20

Abbreviaions: IFI = invasive fungal infection; IC = invasive candidiasis; IA = invasive aspergillosis; NS = not significant.
[a]All high-risk patients who developed IFI were allogeneic HSCT recipients.

together with supportive microbiological evidence. The microbiological evidence included different combinations of culture of respiratory secretions, DNA detection in BAL fluid and serum galactomannan antigen detection (Table 4). Possible IA was diagnosed in six patients at risk, with characteristic clinical and radiological signs and symptoms, with no supportive microbiological evidence, but with no alternative diagnosis after bronchoscopy and BAL examination. There was no statistically significant difference between the incidence of IA in the fluconazole and the itraconazole recipients in the whole groups (11/99(11%) vs 9/96 (9%)), in either risk group and at all levels of certainty of diagnosis.

Lower mortality rates were consistently observed among patients who developed IA while on itraconazole prophylaxis. Although this was 73% among fluconazole recipients compared to 33% among itraconazole recipients, this difference was not significant ($P=0.095$). This trend toward reduced mortality was observed in both risk groups and at all levels of certainty of diagnosis. Aspergillosis-related mortality occurred in 27% of fluconazole recipients, and not in a single patient treated with itraconazole ($P=0.14$).

Fungal colonization, fever, amphotericin B administration, and overall mortality (Table 5)

Fungal colonization (mostly *candida* sp.) was documented in 22% of fluconazole recipients and in 19% of itraconazole recipients ($P=$NS). *C. glabrata* was isolated significantly more frequently in itraconazole-treated patients compared to fluconazole (11/18(61%) vs 5/22(23%), $P=0.02$), while *C. krusei* was isolated more frequently from fluconazole recipients (5/22(23%) vs 0/18(0%), $P=0.054$). There was

Table 4 Laboratory evidence for the diagnosis of Invasive aspergillosis

Category of diagnosis	*Case number*	*Culture (source)*	*GM in serum*	*PCR in BAL*
Definite	1	+ (lung)	–	ND
	2	+ (lung – PM)	–	–
	3	+ (lung – PM)	+	ND
Probable	1	+ (sputum)	ND	ND
	2	+ (BAL)	ND	+
	3	+ (BAL)	–	+
	4	+ (nose)	–	+
	5	–	+	ND
	6	+ (BAL, sputum)	+	+
	7	–	+	+
	8	–	–	+
	9	+ (nose)	–	+
	10	–	–	+
	11	–	–	+
Possible	1	–	–	–
	2	–	–	–
	3	–	–	–
	4	–	–	–
	5	–	–	ND
	6	–	ND	–

Abbreviaions: BAL = bronchoalveolar lavage; PM = post mortem; GM = galactomannan; ND = not determined; PCR = polymerase chain reaction.

Table 5 Fungal colonization, Amphotericin B administration and overall mortality

	Fluconazole (99)	*Itraconazole (96)*	P
Fungal colonization			
Cultures obtained, *n*	101	95	NS
Positive cultures, *n* (%)	22 (22)	18 (19)	NS
Fungal spieces			
Aspergillus sp., *n* (%)	0 (0)	1 (6)	NS
Candida albicans, *n* (%)	5 (23)	2 (11)	NS
Candida tropicalis, *n* (%)	6 (27)	3 (16)	NS
Candida glabrata, *n* (%)	5 (23)	11 (61)	0.02
Candida krusei, *n* (%)	5 (23)	0 (0)	0.054
Candida sp., *n* (%)	1 (4)	1 (6)	NS
AB administration			
Patients treated, *n* (%)	34 (34)	30 (31)	NS
Start day, mean no. of days after enrollment ± s.d.	15.9 ± 6.5	20.4 ± 12.7	NS
Duration, mean no. of days ± s.d.	14.6 ± 13.8	13.2 ± 11.4	NS
Indication for AB			NS
Persistent fever, *n* (%)	26 (26)	17 (18)	
Susp. IFI, *n* (%)	8 (8)	13 (13)	
Fever			
Patients, *n* (%)	84 (85)	81 (84)	NS
Duration until AB, mean no. of days ± s.d.	4.35 ± 3.33	4.35 ± 4.45	NS
Overall mortality			
During hospitalization, *n* (%)	11 (11)	9 (9)	NS
In 3 months, *n* (%)	17 (17)	16 (17)	NS
In 12 months, *n* (%)	30 (30)	28 (29)	NS

Abbreviaions: IFI = invasive fungal infection; IC = invasive candidiasis; IA = invasive aspergillosis; AB = amphotericin B; NS = not significant; s.d. = standard deviation.

no difference in the rate of isolation of other *Candida* species between the groups.

There was no significant difference in the incidence and duration of fever, incidence and indications for amphotericin B administration and overall mortality between both study groups.

Discussion

In this study, itraconazole was not more effective than fluconazole in preventing IFIs in neutropenic patients after chemotherapy for AL or after HSCT.

Fluconazole has been shown to prevent candidal infections, resulting in fewer candidiasis-related deaths in high-risk patients.[3,10,26] When itraconazole was introduced, it was shown to prevent candidal infections as well.[19,27] In this study both drugs successfully prevented IC. In the high-risk group, IC developed in one of the fluconazole-treated patients and in two of those who received itraconazole, while among the low-risk patients, no IC was documented in either regimen.

As for invasive mold infections, itraconazole was expected to be effective in the prevention of aspergillosis. The first studies, using itraconazole capsules, failed to show efficacy in anti-*Aspergillus* prophylaxis.[20,21,28,29] When oral solution itraconazole was introduced, some studies reported reduction in the incidence of IA with itraconazole prophylaxis compared to historical controls, placebo or polyenes.[19,27,29] There are three randomized prospective studies comparing itraconazole with fluconazole as antifungal prophylaxis. The first study by Morgenstern *et al*.,[22] compared itraconazole oral solution 5 mg/kg/day with fluconazole 100 mg/day, and found that itraconazole provided greater protection against proven aspergillosis (0/293 vs 6/288, $P = 0.038$) in patients with hematological malignancies. However, at that time, strict definitions of IFIs and guidelines for IA diagnosis had yet not been published,[25] and results are difficult to compare with subsequent studies. Moreover, the dose of fluconazole was lower than the subsequent recommended dose. The second study,[23] compared oral solution and intravenous itraconazole with oral and intravenous fluconazole in allogeneic HSCT recipients for long-term prophylaxis. This study demonstrated a slight but not statistically significant reduction in the incidence of IA in itraconazole treated patients (3/71 vs 8/67, $P = 0.12$). The third study[24] also compared oral solution and intravenous itraconazole with oral and intravenous fluconazole for long-term prophylaxis. The study did not demonstrate a difference in the incidence of invasive mold infection in the intention to treat analysis, but fewer invasive mold infections occurred in the itraconazole arm while on treatment (5% vs 12% $P = 0.03$).

In the current study, IA was the only invasive mold infection diagnosed in both study groups. The incidence of IA was higher in our study compared to many previously published series. This is most probably due to the ongoing construction work that has been taking place in our hospital over the last several years. In the high-risk

patients, incidence of IA was 6/25 (24%) in fluconazole-treated patients, and 5/24 (21%) in itraconazole-treated patients. In comparison, the IA incidence in high-risk fluconazole-treated patients, in the study performed by Winston *et al*.,[23] was 12%, and 4% in the itraconazole arm. In the study reported by Marr *et al*.[24] it was 12% and 5% in fluconazole and itraconazole arms respectively, even though these rates were calculated over a period of 180 days post transplantation, and in our study only infections developed in the early period at risk were included. Despite the high incidence of IA in our study, we could not demonstrate an incidence reduction in the itraconazole arm compared to fluconazole arm, either in the whole groups or after stratification to high- and low-risk groups. There was also no difference in the incidence of definite, probable and possible IA between the two study arms.

The mortality with IA was lower in itraconazole recipients compared to fluconazole recipients, in both risk groups, and at all levels of certainty of diagnosis, but these differences did not reach statistical significance. Moreover, there was not a single infection-related death among patients who developed aspergillosis while on itraconazole prophylaxis. Although one can speculate that IA developing during itraconazole treatment, a drug with considerable anti-*Aspergillus* activity, could run a more benign course, it is not possible to be categorical about such a hypothesis based on the data from this study.

Itraconazole superiority was not demonstrated in the incidence of fever, in amphotericin B administration rate or in overall mortality.

Intravenous itraconazole was administered to more patients than intravenous fluconazole, and for a longer duration, although the total duration of study drug administration was similar. These data suggest that itraconazole oral solution is less well tolerated than oral fluconazole. Indeed, oral itraconazole solution has been associated often with gastrointestinal side effects,[18,19,22] attributed to the osmotic effect of the hydroxypropyl-β-cyclodextrin. However, none of the itraconazole treated patients was withdrawn from the study because of gastrointestinal complaints, unlike in the study reported by Marr *et al*.,[24] where almost one quarter of the itraconazole recipients were withdrawn from the study. There was no difference in the frequency of hepatotoxicity and renal toxicity between the two study groups, except for hyperbilirubinemia, usually mild, that developed more frequently in the itraconazole arm.

There are several limitations to this study. The study was not blinded and thus, despite well defined pre-study criteria for assessment of efficacy and adverse events, evaluation of response and causes for adverse events could have been somewhat biased. This study may be limited also by lack of itraconazole blood level measurment. However, in contrast to itraconazole capsule formulation with its known erratic bioavailability, oral itraconazole solution used in this study contains hydroxypropyl-β-cyclodextrin, which greatly increases bioavailability of itraconazole and eliminates the need for food or gastric acidity for optimal absorption.[18] In the study performed by Winston *et al*.,[23] plasma levels were measured, and mean trough plasma concentrations of itraconazole were greater than 500 ng/ml throughout the study. These levels have recently been correlated with effective prophylaxis in neutropenic patients.[30] We used the same dosing regimen as Winston *et al*.,[23] which was relatively well tolerated, and although blood levels were not measured, it can be safely assumed that itraconazole concentrations were above the 500 ng/ml threshold. The third limitation of our study is the use of anti-fungal prophylaxis only for the early period at risk, that is, during the neutropenic period. For the low-risk group of our patients, this indeed is the only period at risk. However, for the high-risk patients, the allogeneic HSCT recipients, there is a late period at risk as well.[2,5,31] Based on this changing epidemiology, anti-fungal prophylaxis in allogeneic HSCT recipients, should probably be continued for an extended period, after engraftment.

In summary, the results of this randomized controlled trial, performed in a single center, suggest that itraconazole is as effective as fluconazole in preventing IC in HSCT recipients and AL patients, both in high- and low-risk patients; Itraconazole prophylaxis did not reduce the incidence of IA compared to fluconazole prophylaxis; a nonsignificant trend toward reduced mortality in patients who developed IA while on itraconazole prophylaxis was demonstrated; Itraconazole oral solution was less well tolerated, but no significant adverse events were observed. Despite similar three previous studies, this trial may provide important additional information, especially in light of the prevailing conditions with a higher than expected incidence of aspergillosis. The absence of infection related mortality in the itraconazole arm may lend further support to the importance of prophylaxis, especially with itraconazole.

Several new second-generation azoles have recently become available, with greater activity against fluconazole-resistant *Candida* species as well as *Aspergillus* species and several other molds. Agents of this class include voriconazole, posaconazole and ravuconazole.[32] A new class of anti-fungal drugs, the echinocandines, with broad anti-fungal spectrum of activity, have also recently become available. Agents of this class include caspofungin, micafungin, and anidulafungin.[33] More effective anti-*Aspergillus* prophylaxis is definitely needed, especially in centers with high rate of this infection such as our center. The question whether these drugs can provide improved prophylactic efficacy over itraconazole, requires investigation in randomized controlled trials.

Acknowledgements

We thank Mrs Dorit Dotan for her technical assistance.

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