Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants

Kieren A. Marr, Fulvio Crippa, Wendy Leisenring, Maggie Hoyle, Michael Boeckh, S. Arunmozhi Balajee, W. Garrett Nichols, Benjamin Musher, and Lawrence Corey

Prophylactic fluconazole prevents candidiasis; however, this drug has no activity against molds. We performed a randomized trial to determine whether prophylactic itraconazole prevents invasive mold infections (IMIs). A total of 304 patients receiving allogeneic stem cell transplants (SCT) were randomized to receive fluconazole (400 mg/d) or itraconazole (oral solution 2.5 mg/kg 3 times daily, or intravenous 200 mg daily) for 180 days after SC transplantation, or until 4 weeks after discontinuation of graft-versus-host disease (GVHD) therapy. Proven or probable invasive fungal infections (IFI) were evaluated by intent-to-treat and “on-treatment” analyses. More patients in the itraconazole arm developed hepatotoxicities, and more patients were discontinued from itraconazole because of toxicities or gastrointestinal (GI) intolerance (36% versus 16%, \( P < .001 \)). Intent-to-treat analysis demonstrated no difference in the incidence of IFI during the intended study period (fluconazole 16% versus itraconazole 13%, \( P = .46 \)); however, fewer patients in the itraconazole arm developed IFI on treatment (fluconazole 15% versus itraconazole 7%, \( P = .03 \)). Itraconazole provided better protection against IMI (fluconazole 12% versus itraconazole 5%, \( P = .03 \)), but similar protection against candidiasis (3% versus 2%, \( P = .69 \)). There was no difference in overall or fungal-free survival. Itraconazole appears to prevent IMI in the subset of patients who tolerate the drug; however, toxicities and poor tolerability limit its success as prophylactic therapy. (Blood. 2004;103:1527-1533)

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Introduction

Invasive fungal infections are a frequent cause of transplantation-related mortality. Randomized studies performed during the early 1990s established the efficacy of fluconazole for preventing invasive infection caused by Candida albicans.\(^1\)\(^,\)\(^2\) In high-risk recipients of allogeneic stem cell transplants (SCTs), prevention of candidiasis improved overall survival.\(^3\) However, invasive mold infections (IMIs), especially those caused by Aspergillus species, have become increasingly important. Studies report that the incidence of invasive aspergillosis may be as high as 10% to 20% in patients receiving allogeneic SCTs.\(^4\)\(^-\)\(^7\) Mold infections now typically occur both early after SC transplantsations, during the neutropenic period, and later, during graft-versus-host disease (GVHD) and its treatment.\(^6\)\(^,\)\(^8\)

Itraconazole is an azole antifungal that has activity against both Candida species and molds. Availability of a well-absorbed oral solution and an intravenous formulation has made prophylactic administration feasible in patients with gastrointestinal (GI) tract mucositis. In patients with hematologic malignancies and neutropenia, prophylactic itraconazole successfully prevents candidiasis; however, efficacy in preventing Aspergillus infections is unclear.\(^9\)\(^-\)\(^12\) We performed the current randomized trial in patients who received allogeneic SCTs to determine whether itraconazole, administered long term during GVHD, prevents invasive fungal infections, particularly aspergillosis, better than fluconazole.

Patients, materials, and methods

Patients

Patients who underwent allogeneic SCT after receipt of myeloablative conditioning at the Fred Hutchinson Cancer Research Center (FHCRC) between March 1999 and July 2001 were approached for participation in this study. People aged 13 years or older who weighed 40 kg or more were considered for inclusion. Exclusion criteria included pre-existing moderate-to-severe hepatic abnormalities (transaminase, total bilirubin, or alkaline phosphatase levels > 5 times the upper limit of normal), a history of aspergillosis attributed to azole antifungals, documented or suspected invasive fungal infection within 10 days prior to SC transplantation, presence of uncontrolled bacteremia at time of SC transplantation, and concomitant receipt of a contraindicated drug (eg, astemizole, terfenadine, and cisapride). Randomization was stratified by factors associated with the development of GVHD and invasive fungal infections, specifically, age (\( \leq 20 \) or > 20 years) and human leukocyte antigen (HLA) matching of the stem cell graft (HLA-matched related or HLA-mismatched/unrelated). This trial was approved by the FHCRC Institutional Review Board. All subjects signed an informed consent.

From the Program of Infectious Diseases, Fred Hutchinson Cancer Research Center, Seattle, WA; the Program of Clinical Statistics, Fred Hutchinson Cancer Research Center, Seattle, WA; the Department of Medicine, University of Washington, Seattle; and the Department of Laboratory Medicine, University of Washington, Seattle.


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K.A.M. and F.C. contributed equally to this study.

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Study activities

Open-label study drugs were administered from the beginning of conditioning therapy for a minimum of 120 days. Patients who had GVHD requiring therapy with corticosteroids continued study drugs until 4 weeks after completion of corticosteroid therapy, for a maximum of 180 days. Fluconazole was administered at 400 mg daily, oral or intravenous, with doses adjusted on the basis of renal function. Itraconazole was administered as oral solution (2.5 mg/kg 3 times daily) or by way of intravenous infusion (200 mg daily). Temporary suspension (<2 weeks) of study drugs was allowed in the setting of toxicities (such as nausea), provided no other antifungal drug was administered. Study drugs were permanently discontinued when infection was suspected or confirmed (possible, probable, or proven), according to the clinical criteria described in “Infection definitions.” In the case of persistent fever during neutropenia without other signs or symptoms of IFI, study drugs were temporarily held during administration of amphotericin B products but were not permanently discontinued.

Itraconazole levels were measured by high-performance liquid chromatography (HPLC) 10 days after start or adjustment in dosing of oral drug and 3 days after start of intravenous drug. Dosages were increased by 0.5 mg/kg/d if itraconazole levels were less than 0.5 μg/mL on repeated testing. Itraconazole doses were not routinely adjusted in patients who had adequate levels (>0.5 μg/mL), unless patients had complaints of nausea or vomiting, in which case oral dosing was decreased to twice daily. In this case, levels were followed to assure they remained more than 0.5 μg/mL. Dosing was also decreased to twice daily in people who had levels that exceeded 2 μg/mL with 3 times daily administration.

Galactomannan antigenemia was included as a diagnostic variable for invasive aspergillosis, as per consensus definitions of disease. As this assay was not available for clinical use, tests were performed on sera that had been stored frozen (results were not available to the clinicians during assay was not available for clinical use, tests were performed on sera that had been stored frozen (results were not available to the clinicians during.

Infection definitions

Fungal infections were graded as possible, probable, or proven, according to the laboratory and clinical criteria described in standardized guidelines. To allow for blinded grading, patient identifiers and treatment information was masked from clinical records, and 2 investigators (M.B. and W.G.N.) reviewed the masked documents to determine grades (no infection, possible infection, probable infection, or proven infection). Inconsistencies in coding were resolved by a third investigator who was also blinded to patient identity and treatment arm (K.A.M.).

Invasive mold infections. Invasive mold infections were considered proven if histopathologic examination or culture of sterile tissue revealed the organism. Invasive mold infections were considered probable in patients who had both clinical criteria (eg, pulmonary nodules, cavitated infiltrates) and at least one microbiologic criterion, defined as growth of an organism from respiratory secretions (sputum or bronchoalveolar lavage fluid) or a positive galactomannan EIA. Invasive mold infections were considered possible in patients who had either clinical criteria or microbiologic criteria. Hence, in the absence of clinical criteria (eg, symptoms or pulmonary abnormalities), a positive galactomannan EIA was considered evidence of possible aspergillosis.

Invasive Candida infections. Growth of any Candida species from blood culture in patients with newly and symptoms of infection was considered evidence of proven candidemia. A diagnosis of organism involvement required documentation of Candida by both histologic examination and culture of sterile tissue.

Statistical considerations

The primary efficacy endpoint for this study was the incidence of proven or probable fungal infection analyzed in the intent-to-treat (ITT) group of patients enrolled. Initial calculations of the trial sample size used invasive fungal infection incidence estimates that were derived from the early 1990s in our institution; it was estimated that 8% of patients in the fluconazole arm would develop a proven or probable invasive mold infection. By using these numbers, it was calculated that 57% patients would be required to detect a reduction in mold infections from 8% in the fluconazole arm to 2% in the itraconazole arm (>85% power and an α of 0.05). The trial was discontinued early, after 50% of projected sample size enrollment and after review by the data and safety monitoring board. The reason for this discontinuation was that the frequency of proven and probable IFI during more recent years was actually higher (15%-22%)4,13,14; hence, only 299 patients would be required to detect a 67% reduction in IFI in the itraconazole arm (>90% power, 2-sided α = 0.05). On the basis of these projections, the trial was stopped.

Secondary efficacy endpoints included the incidence of proven or probable IMI and proven Candida infections. We also separately evaluated all invasive fungal infections, IMIs, and proven Candida infections that occurred during receipt of study drug (“on-treatment” analysis). For the latter analysis, infections were considered to have developed on-treatment if the date of first clinical signs and symptoms occurred while receiving drug, or within 2 weeks of discontinuation of study drug.

Incidence estimates for IFIs, IMIs, and proven Candida infections were evaluated by using cumulative incidence methods, treating death and second transplantation as competing risk events for the ITT analysis. For the on-treatment analysis, the time point 2 weeks after discontinuation of study drug was also considered a competing risk event. Comparisons of infection endpoints were made by using cumulative incidence and standard error estimates at the 6-month time point.

Other secondary endpoints included overall survival and survival without a proven or probable fungal infection (fungal-free survival); survival was examined early after SC transplantation (60 days) and after follow-up (250 days after SC transplantation). Overall survival and fungal-free survival were evaluated by using the method of Kaplan and Meier using time to death and death or fungal infection as endpoints, respectively. Comparisons between curves were made by using a log-rank test. Causes of death, coded by an investigator blinded to study arm (L.C.), were compared. Death in the presence of relapsed malignancy was considered to be because of relapse; however, because infection-related death was an important variable, death caused by infection in the presence of GVHD was considered to be because of infection, not GVHD.

A data and safety monitoring board (DSMB) was established at the onset of the study. Two reviews were planned; safety data were reviewed after 25% of planned enrollment, and safety and efficacy data were reviewed after 50% of the projected patient enrollment had reached 180 days of follow-up. Adverse events (AEs) examined during the first interim analysis included the incidence of acute GVHD (grades II-IV) and hepatic and renal abnormalities (tripling of baseline total bilirubin and transaminase levels). The frequency and severity of GVHD, graded according to published criteria,20,21 were also examined in patients enrolled in both study arms. The proportion of patients who were discontinued from study drugs because of suspected fungal
Findings of the interim analyses to treatment arms between March 1999 and July 2001. Two patients who received SCTs were randomly assigned to treatment arms (Table 1). Two patients in the fluconazole arm and 2 patients in the itraconazole arm never received an allogeneic SCT (3 received no transplant and one received an autologous SCT). One additional patient in the fluconazole arm was considered not evaluable because of receipt of other systemic antifungal therapy during the conditioning period, leaving 148 patients in the fluconazole arm and 151 patients in the itraconazole arm evaluable for ITT analysis (Figure 1). A modified ITT analysis was performed on-treatment, only among patients who received at least 1 day of study drug; there were 5 patients who were randomly assigned but did not receive either fluconazole or itraconazole because of evidence of pre-existing IFI, or because of protocol violation (Figure 1).

The demographic characteristics, risk categories according to underlying diseases, and transplant types were similar in the 2 treatment groups (Table 1). The median number of days until neutrophil engraftment in the fluconazole arm did not differ between itraconazole and fluconazole recipients. The median duration of follow-up among surviving fluconazole and itraconazole recipients was 23.3 and 23.6 months, respectively.

### Interim analyses

Findings of the first interim safety analysis suggested disproportionate hepatic and renal toxicities between itraconazole and fluconazole recipients early after SCT transplantation. Analysis that was performed after enrollment of 197 patients (100 itraconazole and 97 fluconazole) noted a trend to higher average daily bilirubin levels (averaged over the first 20 days after SCT transplantation) in patients in the itraconazole arm compared with patients in the fluconazole arm (median, itraconazole 1.47 versus fluconazole 1.37, *P* = .14). Also, relatively more patients who received itraconazole developed doubling of baseline serum creatinine during the first 20 days after SCT transplantation (itraconazole 30 of 100, 30% versus fluconazole 18 of 97, 19%, *P* = .07). Hepatic toxicities appeared strongest in patients who received cyclophosphamide as part of their conditioning regimen (n = 176 patients); median of average daily bilirubin levels among itraconazole (n = 89) and fluconazole (n = 87) was 1.49 (range, 0.37-10.11) and 1.29 (range, 0.43-8.53), respectively (*P* = .07). Preliminary analysis of concurrently available data on cyclophosphamide pharmacokinetics suggested that toxicities were associated with study drug interactions with cyclophosphamide metabolism.

With this concern, the protocol was amended such that drugs were initiated on the day of stem cell transfusion (day 0) rather than concurrent with conditioning therapy. The study resumed with these amendments and was discontinued after the second DSMB review.

### Results

#### Patients

A total of 304 patients who received SCTs were randomly assigned to treatment arms between March 1999 and July 2001. Two patients in the fluconazole arm and 2 patients in the itraconazole arm never received an allogeneic SCT (3 received no transplant and one received an autologous SCT). One additional patient in the fluconazole arm was considered not evaluable because of receipt of other systemic antifungal therapy during the conditioning period, leaving 148 patients in the fluconazole arm and 151 patients in the itraconazole arm evaluable for ITT analysis (Figure 1). A modified ITT analysis was performed on-treatment, only among patients who received at least 1 day of study drug; there were 5 patients who were randomly assigned but did not receive either fluconazole or itraconazole because of evidence of pre-existing IFI, or because of protocol violation (Figure 1).

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#### Table 1. Patient demographic and transplant characteristics

<table>
<thead>
<tr>
<th>Factor</th>
<th>Fluconazole; n = 148</th>
<th>Itraconazole; n = 151</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, n (%)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 y or younger</td>
<td>3 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Older than 20 y</td>
<td>145 (98)</td>
<td>149 (99)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>81 (55)</td>
<td>75 (50)</td>
</tr>
<tr>
<td>Female</td>
<td>67 (45)</td>
<td>76 (50)</td>
</tr>
<tr>
<td>Disease risk group (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>47 (32)</td>
<td>43 (28)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>74 (50)</td>
<td>74 (49)</td>
</tr>
<tr>
<td>High</td>
<td>27 (18)</td>
<td>34 (23)</td>
</tr>
<tr>
<td>Transplant type (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA MM/URD</td>
<td>82 (55)</td>
<td>79 (52)</td>
</tr>
<tr>
<td>HLA MR</td>
<td>66 (45)</td>
<td>72 (48)</td>
</tr>
<tr>
<td>Median neutrophil engraftment, d (range)†</td>
<td>19 (10-35)</td>
<td>19 (9-46)</td>
</tr>
<tr>
<td>Acute GVHD (%)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 0-I</td>
<td>22 (18)</td>
<td>30 (24)</td>
</tr>
<tr>
<td>Grades II-IV</td>
<td>99 (62)</td>
<td>93 (76)</td>
</tr>
</tbody>
</table>

HLAGM indicates human leukocyte antigen matched related; HLA MM/URD, human leukocyte antigen mismatched or unrelated donor.

†Low-risk groups include chronic myelogenous leukemia (CML, chronic phase) and aplastic anemia; intermediate disease risk groups include CML in accelerated phase and other systemic antifungal therapy during the conditioning period, leave 148 patients in the fluconazole arm and 151 patients in the itraconazole arm evaluable for ITT analysis (Figure 1). A modified ITT analysis was performed on-treatment, only among patients who received at least 1 day of study drug: there were 5 patients who were randomly assigned but did not receive either fluconazole or itraconazole because of evidence of pre-existing IFI, or because of protocol violation (Figure 1).

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With this concern, the protocol was amended such that drugs were initiated on the day of stem cell transfusion (day 0) rather than concurrent with conditioning therapy. The study resumed with these amendments and was discontinued after the second DSMB review.

Review of safety and efficacy after 50% of projected enrollment triggered discontinuation of the trial. At this time, there were concerns of persistent differences in safety parameters and overall survival, and the trial was considered to be sufficiently powered to evaluate relative efficacy of the drugs, given updated incidence estimates. In the following sections, efficacy analyses are presented for all patients evaluable (n = 299), and safety analyses are presented for patients who received both study drug schedules (209 patients who were enrolled prior to and 90 patients who were enrolled after the protocol amendment).

#### Study drug administration and safety

When considering all patients enrolled in the study, fluconazole was administered for a median of 120 days after transplantation (range, 1-183 days), and itraconazole was administered for a median of 89 days after transplantation (range, 1-189 days, *P* = .001). More patients were discontinued from itraconazole compared with fluconazole because of toxicities deemed related to the study drug (36% versus 16%, *P* < .001); the majority of itraconazole discontinuations were due to gastrointestinal complaints (eg, nausea, vomiting, or diarrhea, 23.8% versus 4.7%, *P* < .001).
Among all patients evaluable at the end of the study, there was a trend to more renal toxicities (doubling of baseline serum creatinine) in the itraconazole arm (11 [7%] of 151) compared with the fluconazole arm (4 [3%] of 148, \( P = .07 \)). However, this difference was not apparent among patients who were enrolled after the protocol was amended to administer study drug after conditioning therapy; during the latter time period, 3 (7%) of 46 patients in the itraconazole arm and 4 (9%) of 44 patients in the fluconazole arm developed renal toxicities (\( P = .68 \)).

Among all patients, there were also more patients in the itraconazole arm who had at least tripling of baseline total bilirubin level (143 [95%] of 151 itraconazole versus 128 [86%] of 143 fluconazole, \( P = .02 \)). A trend to increased hepatic toxicities was still apparent among patients who received itraconazole after the protocol was amended (41 [89%] of 46 itraconazole versus 34 [77%] of 44 fluconazole, \( P = .13 \)).

**Efficacy of study drugs for prevention of fungal infections**

There was not a significant difference in the probability of proven or probable IFIs that occurred in patients who were randomly assigned to receive fluconazole or itraconazole (intent-to-treat analysis, \( P = .46 \); Figure 2; Table 2). However, significantly more patients developed proven or probable IFIs while receiving fluconazole compared with patients receiving itraconazole (on-treatment analysis, \( P = .03 \); Figure 3). This difference was due to fewer mold infections in itraconazole recipients (12% versus 5%, \( P = .03 \); Table 3). There was not a significant difference in the incidence of candidiasis in patients receiving either fluconazole or itraconazole.

**Use of other antifungals for suspected fungal infection**

The number of patients who received antifungal agents for suspected fungal infection while on-treatment or within 2 weeks of discontinuation of study drugs (SD) is shown. The number of patients at risk (alive) at each interval is indicated. The \( P \) value shown was calculated from tests comparing the incidences at 6 months.

**Itraconazole levels and antimicrobial susceptibilities**

The majority (> 95%) of fluconazole and itraconazole recipients required intravenous study drug prior to engraftment. Itraconazole levels were examined both before engraftment, in patients receiving the intravenous formulation, and after engraftment, in patients arms. During the posttransplantation period, 25 (16.9%) of 148 fluconazole recipients and 19 (12.6%) of 151 itraconazole recipients received alternative antifungals (amphotericin B formulations, caspofungin, and/or voriconazole) in the absence of a confirmed IFI. Of these patients, 10 fluconazole recipients (6.8%) and 8 itraconazole recipients (5.3%) were considered to have met clinical criteria for possible IFI according to signs or symptoms. The remaining patients were treated with alternative antifungals because of clinical suspicion, although they did not meet criteria for possible IFI. Retrospective measurement of circulating galactomannan in patients who had fever during neutropenia upgraded the diagnoses to possible in one patient in each treatment arm.

**Table 3. Organisms that caused IFIs that occurred while on-treatment**

<table>
<thead>
<tr>
<th>Infection*</th>
<th>Fluconazole</th>
<th>Itraconazole†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillosis–total</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>( A ) fumigatus</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>( A ) species–NOS</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>( A ) terreus</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>( A ) niger</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Multiple‡</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other mold infections–total</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Fusarium species</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Candida–total§</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>( C ) glabrata</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>( C ) krusei</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>( C ) parapsilosis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>( C ) albicans</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

NOS indicates not otherwise specified (organism detected by histopathology only).

*Only organisms that caused proven or probable IFIs are listed.
†One patient developed both aspergillosis and candidemia.
‡One patient in the itraconazole arm developed a mixed infection with \( A \) niger and \( C \) krusei, and one fluconazole recipient developed a mixed infection with \( A \) fumigatus and \( A \) niger.
§All Candida species were resistant to fluconazole and itraconazole (data not shown).
Table 4. Cause of death in all patients

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Fluconazole (%)</th>
<th>Itraconazole (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsed malignancy</td>
<td>9 (6)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Idiopathic pneumonitis*</td>
<td>8 (5)</td>
<td>12 (8)</td>
</tr>
<tr>
<td>Bacterial sepsis or pneumonia</td>
<td>5 (3)</td>
<td>14 (9)</td>
</tr>
<tr>
<td>Fungal infections†</td>
<td>11 (7)</td>
<td>12 (8)</td>
</tr>
<tr>
<td>Viral infections†</td>
<td>4 (3)</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Other‡</td>
<td>7 (5)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

*Includes idiopathic pneumonitis, bronchiolitis obliterans–organizing pneumonia, and diffuse alveolar damage/bronchiolitis.

†Viral infections included diseases caused by cytomegalovirus (n = 7), human herpes virus 6 (n = 3), respiratory viruses (n = 2), and Epstein-Barr virus (n = 1).

‡Other causes of death included multiorgan failure (n = 3), regimen-related toxicity/venoocclusive disease (n = 2), pulmonary embolism (n = 1), encephalopathy (n = 1), meningitis of unknown etiology (n = 1), and trauma (n = 1).

Survival early after SC transplantation (at day 60) was also analyzed among patients enrolled before and after the protocol amendment. The probability of survival was lower among itraconazole recipients enrolled before the protocol was amended (Figure 4A). Although there was limited power to detect small differences in early survival in patients enrolled after the study amendment, there was no apparent survival difference in patients who received the altered study drug schedule (Figure 4B).

There were fewer itraconazole recipients who were alive and still receiving study drug 2 months after SC transplantation (83 itraconazole versus 123 fluconazole), the period during which patients were at highest risk of infection (Figures 3-4). It is possible that an unequal distribution of deaths and withdrawal from study drug may have led to bias in intent-to-treat and on-treatment analyses of the probability of infections. We evaluated this possibility by analyzing features of the patients remaining in the 2 groups and compared fungal-free survival in patients enrolled before and after the protocol amendment was enacted. The latter composite endpoint minimizes bias by treating death because of any cause as an important efficacy endpoint. Patients remaining on each study drug at 2 months after SC transplantation did not differ with regard to age, underlying disease risk, transplant type, or severity of acute GVHD (data not shown). Among all patients enrolled in the study, there was no difference in overall fungal-free survival after 6 months (Figure 5A). Among patients who were enrolled during the early phase of the study (before the protocol amendment), there was a trend to superior fungal-free survival in the fluconazole arm (fluconazole 69% versus itraconazole 63%, P = .23; Figure 5B). However, after the protocol amendment, there was a trend to improved fungal-free survival among itraconazole recipients (fluconazole 67% versus itraconazole 75%, P = .30; Figure 5C). The primary difference between these groups was an improved fungal-free survival in itraconazole recipients enrolled after the protocol amendment (75%) relative to those patients who received itraconazole during conditioning therapy (63%, P = .11). These data suggest that overall fungal-free survival was at least in part affected by early toxicities that developed in patients who received concurrent itraconazole and conditioning therapy.

Discussion

Both fluconazole and itraconazole prevent candidal infections, resulting in fewer candidiasis-related deaths, and in the highest-risk patients, improved overall survival.1-3,9,10,12 In this large randomized trial of high-risk patients, we have shown that itraconazole prevented mold infections better than fluconazole; however, the overall success of this prophylaxis strategy was limited by poor tolerability of the drug and toxicities early after SC transplantation.

In this study, there was not a significant difference in fungal infections in the 2 study arms when incidence was compared by
Prophylactic antifungal drugs targeted against invasive mold infections in patients who receive allogeneic SCTs require long-term administration, given the late onset of infection during GVHD. We found that itraconazole effectively prevented infection in patients who were tolerating the drug; however, almost one quarter of patients were withdrawn from this drug because of GI complaints. This frequency is high, but not outside the range reported in prior studies. Three large studies performed in patients with hematologic malignancies noted that GI intolerance occurs frequently, with complaints of nausea, vomiting, and diarrhea in 15% to 57% of patients who receive itraconazole oral solution.

The itraconazole dosing regimen (2.5 mg/kg twice daily) used in prior prophylaxis trials was based on the observation that twice daily dosing yields serum levels that typically exceed 0.25 μg/mL, the target cutoff for efficacy suggested in prior studies. Because the results of more recent analyses suggest a higher target cutoff for efficacy (0.5 μg/mL), we used a high-frequency dosing schedule (3 times daily). Our results confirm that 3 times daily dosing yields levels more than 0.5 μg/mL in most patients. Although these high levels may have increased the antimicrobial efficacy of the drug, the frequent dosing schedule may have also encouraged more GI complaints, because the hydroxypropyl-β-cyclodextrin vehicle is known to cause diarrhea. The step-down strategy to twice daily dosing was effective, because most patients maintained target levels more than 0.5 μg/mL after decreased dosing. Breakthrough infections did not appear to be related to either inadequate drug levels or antimicrobial resistance, suggesting that future studies should use well-tolerated doses of drug.

Although this trial was not powered to measure differences in overall survival as an endpoint to define success, results emphasize the importance in comparing deaths to identify unexpected study drug toxicities. In this study, there was a trend to better survival in patients who received fluconazole, despite the efficacy of itraconazole in preventing invasive fungal infections. The timing of death (coincident with hepatic and renal toxicities) and improved outcomes after altering the study drug administration schedule suggest that the overall survival of itraconazole recipients was adversely affected by the differential toxicities encountered during conditioning therapy. We are currently investigating the hypothesis that hepatic and renal toxicities may be related to the effect of the study drugs on cytochrome P450-mediated metabolism of cyclophosphamide.

The high frequency of patient withdrawal from itraconazole and disproportionate number of deaths can lead to bias in both intent-to-treat and on-treatment analyses of drug efficacy, because of a resultant imbalance in competing risk events (death and discontinuation of study drug). It has been suggested that composites variables such as fungal-free survival be used to minimize such bias, especially in the setting in which the cause of patient drop-out (drug-related toxicities or death) may be outcomes of interest. Analysis of fungal-free survival before and after the protocol was amended suggested improvement in outcomes among itraconazole recipients, likely related to fewer toxicities early after SCT transplantation. In this study, successful prevention of fungal infections may well have had a more dramatic effect on overall survival had the drugs not been administered with conditioning therapy in the early phase of the study. Because safety is a major component of effectiveness, especially when measuring the effect of long-term administration of drugs that have complex and unpredictable toxicities, future antifungal prophylaxis studies could be constructed using endpoints that capture survival and infection within a composite variable.

The results of this trial demonstrate the importance of considering risk-benefit ratios in formulating preventative strategies, because the therapeutic benefits of antifungal coverage may be
outweighed by negative outcomes associated with drug toxicities or interactions. These negative effects may be particularly apparent in patients who require long-term prophylaxis, especially in patients who have only small or moderate risks of infection. Future studies should determine whether “pre-emptive” antifungal therapy guided by early infection monitoring (eg, antigenemia, polymerase chain reaction [PCR]) would provide equivalent, or better overall outcomes.

In summary, the results of this large randomized trial suggest that antifungal prophylaxis might effectively prevent invasive mold infections when administered long term in patients who received allogeneic SCTs. For selected patients, itraconazole, initiated after completion of conditioning therapy, might be useful; however, tolerability and toxicities associated with the drug limit the overall success of the strategy. Future studies should be undertaken to identify an optimal strategy to prevent mold infections after allogeneic stem cell transplantation, using drugs with fewer toxicities and/or the use of early diagnostic tests.

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References

Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants

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