Intravenous and Oral Itraconazole versus Intravenous Amphotericin B Deoxycholate as Empirical Antifungal Therapy for Persistent Fever in Neutropenic Patients with Cancer Who Are Receiving Broad-Spectrum Antibacterial Therapy

A Randomized, Controlled Trial

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Background: **Amphotericin B deoxycholate is currently the standard empirical antifungal therapy in neutropenic patients with cancer who have persistent fever that does not respond to antibiotic therapy. However, this treatment often causes infusion-related and metabolic toxicities, which may be dose limiting.**

Objective: **To compare the efficacy and safety of itraconazole with those of amphotericin B as empirical antifungal therapy.**

Design: **An open randomized, controlled, multicenter trial, powered for equivalence.**

Setting: **60 oncology centers in 10 countries.**

Patients: **384 neutropenic patients with cancer who had persistent fever that did not respond to antibiotic therapy.**

Intervention: **Intravenous amphotericin B or intravenous itraconazole followed by oral itraconazole solution.**

Measurements: **Defervescence, breakthrough fungal infection, drug-related adverse events, and death.**

Results: **For itraconazole and amphotericin B, the median duration of therapy was 8.5 and 7 days and the median time to defervescence was 7 and 6 days, respectively. The intention-to-treat efficacy analysis of data from 360 patients showed response rates of 47% and 38% for itraconazole and amphotericin B, respectively (difference, 9.0 percentage points [95% CI, −0.8 to 19.5 percentage points]). Fewer drug-related adverse events occurred in the itraconazole group than the amphotericin B group (5% vs. 54% of patients; $P = 0.001$), and the rate of withdrawal because of toxicity was significantly lower with itraconazole (19% vs. 38%; $P = 0.001$). Significantly more amphotericin B recipients had nephrotoxicity ($P < 0.001$). Breakthrough fungal infections (5 patients in each group) and mortality rates (19 deaths in the itraconazole group and 25 deaths in the amphotericin B group) were similar. Sixty-five patients switched to oral itraconazole solution after receiving the intravenous formulation for a median of 9 days.**

Conclusions: **Itraconazole and amphotericin B have at least equivalent efficacy as empirical antifungal therapy in neutropenic patients with cancer. However, itraconazole is associated with significantly less toxicity.**

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Prolonged neutropenia is a major risk factor for invasive fungal infection (1–6). The incidence among neutropenic patients with cancer who are receiving intensive cytotoxic therapy ranges from 2% to 47%, depending on other concomitant risk factors (7). Mortality rates range from 35% to 90% (8). Fever may be the only clinical sign of infection, and definitive diagnosis is often problematic. Empirical therapy with amphotericin B deoxycholate reduces the relative risk for documented infection by 50% to 80% and overall mortality rates by 23% to 45% (1, 2, 9, 10). This practice is now standard in neutropenic patients with cancer who have persistent fever that does not respond to 3 to 7 days of treatment with broad-spectrum antibiotics (11).

Rates of clinical response to empirical amphotericin B of 43% to 72% have been reported in neutropenic patients (1–6). However, treatment is associated with significant dose-limiting toxicity in approximately 35% to 82% of patients (1–14). Consequently, less toxic alternatives have been investigated, including lipid formulations of amphotericin B and fluconazole (3–6, 13–15). Although lipid-based formulations have an efficacy similar to that of conventional amphotericin B, infusion-related side effects and nephrotoxicity remain a concern. Their high cost also prohibits routine use in most hospitals (4–6). Fluconazole is limited by its lack of activity against *Aspergillus* species and some non-*albicans Candida* species. In addition, recent reports reveal

an increasing prevalence of resistance among *Candida* species after long-term fluconazole treatment (16, 17).

In contrast, the broad-spectrum triazole itraconazole combines improved safety with activity against *Aspergillus* and *Candida* species, including many fluconazole-resistant *Candida* species (18, 19). Itraconazole is now available as an intravenous formulation and an oral solution, which is readily absorbed in neutropenic patients (20–22). Itraconazole may therefore be an alternative to amphotericin B for empirical therapy in persistently febrile neutropenic patients with suspected systemic fungal infection. We conducted an international, multicenter, randomized trial to compare the safety and efficacy of itraconazole and amphotericin B as empirical antifungal therapy in these high-risk patients.

METHODS

Study Design

This open, multicenter, randomized, controlled clinical trial was performed at 60 oncology centers in 10 countries between March 1996 and December 1997. Patients were randomly assigned in a 1:1 ratio to receive itraconazole or amphotericin B by using a centralized computer. A contract research organization, ID^2 (Brussels, Belgium), performed central randomization on a per center basis and ensured that participants were stratified by presence of signs and symptoms attributable to deep fungal infection and underlying disease. At each center, balancing ensured that each treatment was allocated to an equal number of participants. The study was powered to demonstrate equivalency between treatments. The protocol was reviewed and approved by review boards and ethics committees of each participating institution. Written informed consent was obtained from participants before enrollment.

Patient Enrollment and Stratification

Patients 18 years of age or older who were hospitalized for treatment of hematologic cancer with intensive myelosuppressive cytotoxic therapy, with or without autologous hematopoietic stem-cell support, were eligible. Other eligibility criteria were 1) an absolute neutrophil count of 0.5×10^9 cells/L or less with an expected duration of 7 or more days and 2) body temperature greater than 38 °C that was unrelated to blood product transfusions or medications and that persisted despite 3 or more days of treatment with parenteral broad-spectrum antibiotics.

Patients were excluded if they had previously been enrolled in the trial; had been treated with other investigational drugs; or were receiving medications known to interact with itraconazole, including terfenadine, astemizole, midazolam, triazolam, cisapride, phenytoin, isoniazid, phenobarbital, and rifampicin. Other exclusion criteria were proven invasive fungal infection (positive histology or culture from a normally sterile body fluid, except urine), resident signs of an invasive fungal infection (highly suggestive chest radiograph or computed tomogram) during previous neutropenic episodes, a bacterial or viral infectious cause of fever at trial entry, and receipt of an allogeneic hematopoietic stem-cell transplant. Patients with severe liver dysfunction (aminotransferase levels $\geq$ 5 times the upper limit of normal and total bilirubin level $\geq$ 50 mmol/L), renal failure (calculated creatinine clearance $<$ 0.5 mL/s), or HIV seropositivity were excluded. Prophylactic antibacterial and antiviral therapy was permitted during the study, but prophylaxis with systemic antifungal drugs was discontinued at study entry.

Patients were stratified according to receipt or nonreceipt of an autologous hematopoietic stem-cell transplant and by the absence or presence of 1 or more signs and symptoms potentially attributable to invasive fungal infections (cough, dyspnea, chest pain, increased respiratory rate, headaches, and confusion). The four strata of signs (yes or no) and transplantation status (yes or no) were evenly distributed across the study groups (**Table 1**).

Administration of Study Medication

Intravenous itraconazole (Sporanox IV, Janssen Pharmaceutica, Beerse, Belgium), 200 mg, was administered by infusion as a 40% hydroxypropyl-β-cyclodextrin solution in water every 12 hours for the first 48 hours, followed by 200 mg daily from days 3 to 14. From day 15, oral itraconazole solution (Sporanox Oral Solution, Janssen Pharmaceutica), 400 mg/d, replaced intravenous itraconazole. However, if patients were able to tolerate oral medication, oral itraconazole could replace intravenous itraconazole as early as day 7. Amphotericin B deoxycholate (Fungizone, Bristol-Myers Squibb, Princeton, New Jersey) in 5% dextrose in water was infused intravenously over 4 to 6 hours at a daily

Table 1. **Baseline Demographic Characteristics of Patients**

Characteristic	Itraconazole Group (*n* = 192)	Amphotericin B Group (*n* = 192)
Men/women, *n/n*	119/73	110/82
Median age (range), *y*	46.5 (18–80)*	50 (18–81)*
Antifungal prophylaxis, *n (%)*		
Amphotericin B	52 (27)	60 (31)
Fluconazole	52 (27)	59 (31)
Itraconazole	16 (8)	17 (9)
Clotrimazole	26 (13)	30 (16)
Nystatin	66 (34)	68 (35)
Underlying diagnoses, *n (%)*		
Acute lymphoblastic leukemia	15 (8)	11 (6)
Acute myelogenous leukemia	107 (56)	108 (56)
Lymphoma	49 (26)	36 (19)
Myeloma	9 (5)	16 (8)
Other	12 (6)	21 (11)
Status of underlying disease, *n*†		
Induction of remission	104	103
Relapse	53	53
Refractory disease	12	11
Autologous bone marrow or peripheral stem-cell transplant recipient, *n (%)*	68 (35)	76 (39)
Median time since last chemotherapy before study entry (range), *d*	13 (4–376)	14 (0–60)
Median duration of neutropenia before study entry (range), *d*	7 (2–34)	7 (5–39)
Median duration of neutropenia during study (range), *d*	10 (0–35)	8 (0–29)
Sign/transplantation status, *n (%)*‡		
No signs, no transplantation	108 (56)	108 (56)
No signs, transplantation	57 (30)	52 (27)
Signs, no transplantation	16 (8)	18 (9)
Signs and transplantation	11 (6)	14 (7)

* $P = 0.02$.
† More that one category may apply to a given patient.
‡ Signs or symptoms of invasive fungal infection were cough, dyspnea, chest pain, increased respiratory rate, headaches, or confusion. Transplantation was hematopoietic stem-cell transplantation.

dose of 0.7 to 1.0 mg/kg of body weight for up to 28 days. Infusion-related toxicities were treated with hydrocortisone, antihistamines, or antipyretics at the investigators' discretion. Participants received therapy until defervescence and recovery from neutropenia (absolute neutrophil count $> 0.5 \times 10^9$ cells/L on ≥ 2 successive days).

Pharmacokinetic Evaluation of Itraconazole

To determine plasma levels of itraconazole and its active metabolite, hydroxyitraconazole, venous blood was sampled before administration of itraconazole on days 0, 3 (before the fifth infusion), and 8 (before intravenous or, where applicable, oral administration) and on days 15, 22, and 28 (during oral treatment). Each 10-mL sample was drawn from the arm opposite the administration site, or from a central intravenous line, into heparinized tubes and was separated by centrifugation (1000 *g* for 10 minutes). The lines were flushed before and after administration of the study drug to reduce the chance that residual drug remained in the tubing. Plasma samples were stored at −20 °C until assay by using high-performance liquid chromatography. Patients who had received previous itraconazole prophylaxis before the study were excluded from pharmacokinetic analysis.

Evaluation Criteria and Definitions

The primary efficacy measurement was a favorable response at the end of treatment. Patients were evaluable for response if they had received study medication for 3 or more days. A favorable treatment response was defined as a patient who became afebrile (daily oral peak temperature < 38 °C) and recovered from neutropenia (absolute neutrophil count $> 0.5 \times 10^9$ cells/L on ≥ 2 successive days). Patients who became afebrile but were

still neutropenic were considered nonresponders, unless they had received study medication for 10 days or longer and remained afebrile for 3 consecutive days after treatment discontinuation.

Failure of treatment was defined as the presence of any of the following conditions: documented breakthrough invasive fungal infection, death from any cause after 3 days of treatment with study drug, failure to defervesce by the time of marrow recovery or by day 28, persistent fever requiring a change in therapy, or treatment discontinuation due to intolerance.

Patients who received the study drug for fewer than 3 days or in whom a viral, bacterial, or fungal cause of persistent fever was identified at study entry were considered nonevaluable. Nonevaluable patients who received at least one dose of study medication were included in the safety analysis.

The response rate in the intention-to-treat analysis was defined as the number of responders divided by the total number of patients (those who responded, those who had treatment failure, and nonevaluable patients). An additional outcome analysis was performed by using the composite end points described by Walsh and colleagues (5), in which treatment success was defined as survival for 7 days after start of treatment, defervescence during neutropenia, absence of breakthrough invasive fungal infection during drug administration or within 7 days of study completion, and no premature withdrawal of study medication because of intolerance or lack of efficacy.

Subgroup Analysis

Further planned analyses were performed in patient subgroups for the primary efficacy end point (defervescence and recovery from neutropenia) according to the following criteria: fever of less than 5 days' or 5 or more days' duration before study entry, duration of neutropenia since study initiation of less than 7 days or 7 or more days, and receipt of antifungal prophylaxis before enrollment.

Monitoring of Adverse Events

All patients receiving study medication were evaluated for safety. Adverse events were monitored prospectively. Nephrotoxicity was defined as a creatinine concentration greater than twice the baseline value. Creatinine clearance was calculated from serum creatinine concentration, age, body weight, and sex by using the formula of Cockroft and Gault (23).

Statistical Analysis

Sample size calculations were done for a trial designed to show equivalency. The efficacy of itraconazole was considered clinically equivalent to the efficacy of amphotericin B if the difference in response rates for the treatment was not greater than 15%. Assuming a 65% response rate in both groups (1–6, 13–15, 24, 25), a sample size of 348 patients (174 patients per group) was required to achieve a power of 90% at a one-sided significance level of 5% and a power of 80% at a two-sided significance level of 5%. To account for a 10% dropout rate, we enrolled 390 patients.

All statistical tests were interpreted at the 5% significance level. Two-sided 95% CIs were calculated where appropriate. The chi-square test or Fisher exact test was used to compare differences in the proportions. A logistic regression model including study drug and covariates that may determine treatment response was used to perform multivariate analysis of the probability of response. Covariates were age, sex, underlying diagnosis, status of underlying disease (induction of remission, relapse, or refractory disease), antifungal prophylaxis before study, number of days since last chemotherapy, number of days of neutropenia before study, sign/transplantation stratum, creatinine clearance at baseline, colonization with fungus at baseline, and presence of an indwelling central catheter. These covariates and their interactions with treatment were also included in a multivariate analysis investigating treatment effect in the subgroups. For safety analysis, dichotomous variables were compared by using the chi-square test. The Wilcoxon rank-sum test was used to compare creatinine concentrations. Effect of treatment center on outcome was evaluated by using conditional logistic regression in which center was the conditioning variable and treatment was the unique covariate.

Role of the Funding Source

The funding source played no role in the design of the study. The Itraconazole Study Group guided the conduct of the study with the help of the independent contract organization ID2 (for randomization and strat-

ification) and Janssen Pharma (for distribution of drugs and pharmacokinetic analysis of serum samples). Each investigator was responsible for the conduct of the study at his or her center. The Study Group was responsible for reporting the study and the decision to publish.

RESULTS

Patients

A total of 394 patients were enrolled. Of the patients who were randomly allocated, 384 received at least one dose of study medication and were included for safety analysis (192 patients in each group). The efficacy evaluation was based on the intention-to-treat sample of 360 patients who underwent randomization and met the inclusion and exclusion criteria: hematologic cancer, neutropenia, and persistent fever of unknown origin (179 patients in the itraconazole group and 181 patients in the amphotericin B group). With the exception of age ($P = 0.02$), groups did not significantly differ in baseline demographic characteristics (**Table 1**). Most patients had received previous antifungal prophylaxis (132 [74%] and 139 [77%] of itraconazole and amphotericin B recipients, respectively). The agents used as antifungal prophylaxis were oral amphotericin B, oral itraconazole (8% and 9% of itraconazole and amphotericin B recipients, respectively), oral fluconazole, topical nystatin, or combinations of these drugs. The most common diagnosis was acute myelogenous leukemia (56% of patients). Autologous bone marrow or peripheral blood stem-cell transplantation was performed in 68 (35%) itraconazole recipients and 76 (39%) amphotericin B recipients.

The median duration of neutropenia during the study was 10 days in the itraconazole group and 8 days in the amphotericin B group; the median duration of treatment was 8.5 days and 7 days, respectively. Sixty-five patients switched from intravenous to oral itraconazole. Among these patients, the median duration of intravenous treatment was 9 days (range, 7 to 15 days) and the median duration of oral treatment was 7 days (range, 1 to 24 days). The mean maximum daily dose of amphotericin B was 0.85 mg/kg (range, 0.79 to 0.90 mg/kg); the mean daily dose was 0.71 mg/kg (range, 0.68 to 0.74 mg/kg).

Twenty-four itraconazole recipients and 44 amphotericin B recipients were nonevaluable because study therapy was given for fewer than 3 days or a positive microbial culture before entry documented an infectious cause. Documented baseline fungal infections were noted in 2 itraconazole recipients (1 with candidemia and 1 with *Aspergillus* pneumonia) and 4 amphotericin B recipients (3 with candidemia and 1 with *Aspergillus* pneumonia). Documented baseline systemic bacterial infections were noted in 6 itraconazole recipients and 10 amphotericin B recipients, and 1 patient in each group had documented systemic viral infection. Fifteen itraconazole recipients and 31 amphotericin B recipients had had fewer than 3 days of therapy.

Efficacy

Overall response rates and response rates by sign/transplantation stratum are shown in **Table 2**. The overall response rate in the intention-to-treat sample of 360 patients (179 itraconazole recipients and 181 amphotericin B recipients) was 47% in the itraconazole group and 38% in the amphotericin B group (difference, 9 percentage points [95% CI, −0.8 to 19.5 percentage points]). This difference corresponds to an overall odds ratio of 1.47 (CI, 0.96 to 2.23) in favor of itraconazole. In the multivariate analysis, the odds ratio for study drug (itraconazole or amphotericin B) was 1.62 (CI, 0.99 to 2.64). In the conditional logistic regression model, with center as the conditioning variable and treatment as the only covariate, the odds ratio was 1.40 (CI, 0.90 to 2.17). This value was indistinguishable from the overall odds ratio, indicating that center did not affect the probability of response to treatment.

In the subgroup analysis, the response rate in patients in whom fever persisted despite 5 or more days of treatment with broad-spectrum antibiotics was higher among itraconazole recipients (52 of 109 [48%]) than amphotericin B recipients (34 of 110 [31%]) (difference, 17.0 percentage points [CI, 4.0 to 29.5 percentage points]). Response rates were similar among patients with persistent fever who received fewer than 5 days of antibiotic therapy (32 of 70 [46%] itraconazole recipients vs. 34 of 70 [49%] amphotericin B recipients; difference, −3.0 percentage points [CI, −19.4 to 13.7 percentage points]). Among patients who had previously received antifungal prophylaxis, the response rate was higher in the itraconazole group than the amphotericin B group (63 of 132 patients [48%] vs. 48 of 139 patients [35%]; difference, 13.0 percentage points [CI, 1.6 to 24.8 percentage points]). No treatment effect was

Table 2. **Response to Empirical Antifungal Therapy**

Response	Itraconazole Group (*n* = 179)*	Amphotericin B Group (*n* = 181)*	Difference (95% CI)†
Overall, *n/n* (%)	84/179 (47)	68/181 (38)	9.0 (−0.8 to 19.5)
By sign/transplantation status, *n/n (%)*‡			
No signs, no transplantation	51/103 (49)	34/105 (32)	17.0 (−4.0 to 30.3)
No signs, transplantation	24/52 (46)	22/48 (46)	0 (−19.2 to 19.9)
Signs, no transplantation	4/14 (29)	6/18 (33)	−4.0 (−36.9 to 27.4)
Signs and transplantation	5/10 (50)	6/10 (60)	−10.0 (−53.4 to 33.4)
Defervescence, *n/n (%)*	131/179 (73)	127/181 (70)	3.0 (−6.3 to 12.3)
Median time to defervescence (range), *d*	7 (1–26)	6 (1–22)	
By previous antifungal prophylaxis, *n/n (%)*			
Yes	63/132 (48)	48/139 (35)	13.0 (1.6 to 24.8)
No	21/47 (45)	20/42 (48)	−3.0 (−23.7 to 17.8)
By duration of fever that did not respond to antibiotic therapy, *n/n (%)*			
<5 d	32/70 (46)	34/70 (49)	−3.0 (−19.4 to 13.7)
≥5 d	52/109 (45)	34/110 (31)	6.0 (4.0 to 29.5)
By duration of neutropenia, *n/n (%)*			
<7 d	27/60 (45)	23/58 (40)	5.0 (−12.5 to 23.1)
≥7 d	56/107 (52)	44/108 (41)	11.0 (−1.6 to 24.8)
Breakthrough fungal infections, *n*	5	5	
Candidemia	2§	2‖	
Filamentous fungal pneumonia	3¶	3**	

* Four patients (3 in the itraconazole group and 1 in the amphotericin B group) had no global evaluation.
† Differences are expressed as percentage points.
‡ Signs or symptoms of invasive fungal infection were cough, dyspnea, chest pain, increased respiratory rate, headaches, or confusion. Transplantation was hematopoietic stem-cell transplantation.
§ *Candida krusei* in 1 patient and *C. guillermondii* in 1 patient.
‖ *Candida albicans*.
¶ *Aspergillus fumigatus* in 1 patient, *A. sydowi* in 1 patient, and *Geotrichum capitatum* in 1 patient.
** *Aspergillus fumigatus*.

observed among patients who had not received antifungal prophylaxis, regardless of allocation (21 of 47 [45%] itraconazole recipients vs. 20 of 42 [48%] amphotericin B recipients; difference, −3.0 percentage points [CI, −23.7 to 17.8 percentage points]).

Groups did not differ substantially in response rates according to duration of neutropenia. Response rates were 45% in the itraconazole group and 40% in the amphotericin B group (difference, 5.0 percentage points [CI, −12.5 to 23.1 percentage points]) in patients with neutropenia for fewer than 7 days; the corresponding response rates in patients with neutropenia for 7 or more days were 52% and 41% (difference, 11 percentage points [CI, −1.6 to 24.8 percentage points]). The change in magnitude of the difference between response rates for itraconazole and amphotericin B recipients for each of the subgroup analyses was not significant in a multivariate analysis performed by using a logistic regression model, which included interactions of these covariates and other important clinical covariates with treatment.

In the intention-to-treat sample (360 patients), 95 (53%) itraconazole recipients and 113 (62%) amphotericin B recipients had treatment failure. Treatment failed in the itraconazole and amphotericin B groups for the following reasons: discontinuation of therapy because of poor tolerance (12 and 38 patients; $P = 0.001$), persistent fever after resolution of neutropenia (20 and 10 patients; $P = 0.06$), fever requiring a change in antifungal regimen (19 and 1 patient; $P = 0.001$), breakthrough invasive fungal infection (5 and 5 patients), and death after 3 or more days of therapy with the study drug (15 and 15 patients). Treatment was also considered to have failed in patients who were nonevaluable because they received the study drug for fewer than 3 days and those who had a microbiologically documented infection at baseline (24 itraconazole recipients and 44 amphotericin B recipients). Susceptibility testing of the organisms that caused breakthrough fungal infections was not performed.

Defervescence, defined as remaining afebrile for 2 consecutive days at the end of therapy, was achieved in a similar proportion of itraconazole (73%) and amphotericin B (70%) recipients; the median times to defervescence were 7 and 6 days, respectively.

A further outcome analysis used the composite end point of survival for 7 days after start of treatment, defervescence during neutropenia, absence of breakthrough invasive fungal infection during drug administration or within 7 days of study completion, and no premature withdrawal of study medication because of intolerance or lack of efficacy. By these criteria, treatment was successful in 53% of itraconazole recipients and 46% of amphotericin B recipients (difference, 7.0 percentage points [CI, −17.5 to 3.1 percentage points]).

Nineteen (11%) itraconazole recipients and 25 (14%) amphotericin B recipients died. Breakthrough invasive fungal infection caused 2 deaths in itraconazole recipients (both from pulmonary aspergillosis) and 4 deaths in amphotericin B recipients (1 due to pulmonary aspergillosis and 3 due to candidemia). Clinically documented pneumonia and respiratory failure caused 12 deaths in itraconazole recipients and 11 deaths in amphotericin B recipients, multiple organ failure caused 2 and 3 deaths, and progressive underlying cancer caused 12 and 11 deaths.

Safety and Toxicity

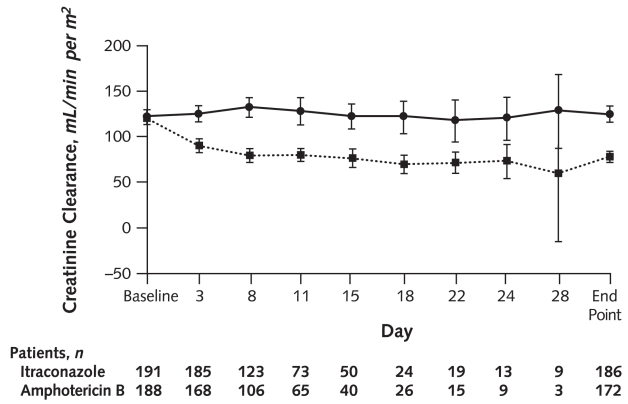
Safety and toxicity analysis was done for 192 patients in each treatment group (**Table 3**). Overall, patients tolerated itraconazole significantly better than amphotericin B. Fewer itraconazole recipients had drug-related adverse events ($P = 0.001$), required treatment withdrawal because of toxicity ($P = 0.001$), or experienced severe adverse events ($P = 0.001$). The most common reasons for withdrawal from amphotericin B therapy were nephrotoxicity (21% vs. 0.5% for itraconazole; $P < 0.001$) and rigors (4% vs. 0%; $P = 0.004$). The most frequently reported causes of withdrawal from itraconazole therapy were nausea and vomiting (5% vs. 0.5% for amphotericin B; $P = 0.01$), rash (3% vs. 0%; $P = 0.03$) and bilirubinemia or transaminasemia (3% vs. 0%; $P = 0.014$). Nineteen (10%) itraconazole recipients and 9 (5%) amphotericin B recipients had bilirubinemia ($P = 0.01$); however, liver enzyme levels did not differ significantly between the groups. Twenty-one (11%) itraconazole recipients and 15 (8%) amphotericin B recipients had liver toxicity. The incidence of

Table 3. **Safety and Toxicity of Empirical Treatment with Itraconazole and Amphotericin B**

Event	Itraconazole Group (*n* = 192)	Amphotericin B Group (*n* = 192)
	n (%)	
Drug-related adverse event	9 (5)	103 (54)*
Adverse event leading to treatment withdrawal	36 (19)	73 (38)*
Severe adverse event	37 (19)	65 (34)*
Infusion-related toxicity		
Fever	12 (6)	20 (10)
Chills or rigors	19 (10)†	77 (40)†
Nausea	46 (24)	45 (23)
Vomiting	37 (19)	40 (21)
Dyspnea	17 (9)	21 (11)
Tachycardia	6 (3)	12 (6)
Hypotension	13 (7)	21 (11)
Metabolic toxicity		
Nephrotoxicity‡	10 (5)†	46 (24)†
Hypokalemia	34 (18)§	59 (31)§
Hypomagnesemia	14 (7)	17 (9)
Bilirubinemia	19 (10)†	9 (5)†
Increased serum alanine aminotransferase level	5 (3)	3 (2)
Increased serum aspartate aminotransferase level	4 (2)	1 (1)
Increased γ-glutamyltransferase level	4 (2)	3 (2)
Premedication to support study drug administration		
Analgesics	8 (4)†	82 (43)†
Antihistamines	6 (3)†	69 (36)†
Corticosteroids	1 (0.5)†	50 (26)†

* $P = 0.001$.
† $P < 0.001$.
‡ Defined as a serum creatinine concentration of more than twice the baseline value.
§ $P = 0.004$.

Figure. **Creatinine clearance as a function of time on study in itraconazole recipients (*circles*) and amphotericin B recipients (*squares*).**



Creatinine clearance was calculated from serum creatinine concentration, age, body weight, and sex by using the formula of Cockcroft and Gault (23). Error bars represent 95% CIs. To convert creatinine clearance to mL/s, multiply by 0.0167.

chills and rigors was significantly lower among itraconazole recipients than amphotericin B recipients (10% vs. 40%; $P < 0.001$). Rigors in itraconazole recipients were always related to simultaneous infusion of blood products and not to infusion of study drug. Use of concomitant medication to support study drug administration was reported more frequently in amphotericin B recipients (**Table 3**). Nephrotoxicity and hypokalemia were less frequently reported in itraconazole recipients.

Mean calculated creatinine clearance was significantly reduced in amphotericin B recipients compared with itraconazole recipients at all time points after baseline (**Figure**). Nephrotoxicity (defined as doubling of baseline creatinine concentration) occurred in 10 (5%) itraconazole recipients and 46 (24%) amphotericin B recipients ($P < 0.001$).

Sixty-five (35%) of the 184 itraconazole recipients switched to oral therapy after a median of 9 days of therapy. In general, most adverse events, including gastrointestinal events, started during intravenous itraconazole therapy. During intravenous itraconazole therapy, 20% of patients had nausea, 17% had diarrhea, and 18% had vomiting; the corresponding values during oral itraconazole therapy were 14%, 12%, and 9%. Six (9%) of the 65 patients discontinued oral itraconazole therapy because of gastrointestinal side effects. The incidence of gastrointestinal side effects in intravenous amphotericin B recipients was similar: Twenty-three percent had nausea, 28% had diarrhea, and 21% had vomiting.

Pharmacokinetic Studies

Plasma concentrations of itraconazole and hydroxyitraconazole were measured in 599 blood samples from 137 patients who had not previously received prophylactic itraconazole (**Table 4**). On day 3 of treatment, plasma itraconazole concentrations greater than 250 ng/mL were attained in 97% of patients. These levels were maintained after substituting oral itraconazole for intravenous itraconazole.

DISCUSSION

This trial demonstrates that the efficacy of itraconazole is similar to that of amphotericin B as empirical antifungal therapy in persistently febrile neutropenic patients with hematologic cancer. The overall response rate was 47% for empirical itraconazole compared with 38% for amphotericin B. The number of breakthrough fungal infections and overall mortality was similar in both groups. Adverse events, however, were much less frequent with itraconazole.

Although rates of defervescence were similar in both groups, 19 itraconazole recipients were switched to alternative systemic antifungal therapy because of persistent fever; treatment was considered to have failed in these patients. In contrast, only 1 amphotericin B recipient had treatment failure due to a change of therapy. Since the participating physicians were not blinded to

Table 4. **Predose plasma concentrations of itraconazole and hydroxyitraconazole***

Treatment Day	Itraconazole	Hydroxyitraconazole
	ng/mL	
Intravenous administration		
Day 0 (n = 99)	0 ± 0	0 ± 0
Day 3 (n = 88)	779 ± 638	809 ± 327
Day 8 (n = 54/55)	878 ± 647	1338 ± 524
Day 15 (n = 11)	1391 ± 648	2091 ± 821
Oral administration		
Day 15 (n = 10)	1133 ± 568	1918 ± 534
Day 22 (n = 6)	695 ± 453	1351 ± 912

* Data are given as the mean ± SD. Clinically effective itraconazole plasma concentrations (>250 ng/mL) (20, 27) were attained in 97% of patients by day 3 and were maintained after patients were switched from intravenous itraconazole to the oral formulation.

the study drug, the more frequent changes in therapy with itraconazole may have reflected some inexperience and discomfort with a new, previously untested approach to empirical therapy. In contrast, among unevaluable patients receiving treatment for fewer than 3 days, 21 amphotericin B recipients but only 5 itraconazole recipients were switched to alternative systemic antifungal therapy because of drug-related adverse events.

Although empirical amphotericin B therapy for suspected unproved invasive fungal infection in neutropenic fever has become common practice (11), well-controlled trials supporting this approach remain limited (1, 2). Recent large empirical trials comparing lipid-based formulations with conventional amphotericin B have shown response rates of 46% (4), 49% (5), and 43% (6) to conventional amphotericin B; 64% (4) and 50% (5) to liposomal amphotericin B (4); and 50% to amphotericin B colloidal dispersion (6). The response rate to amphotericin B in our study was lower (38%) than the rates reported in previous studies (43% to 73%) (1–6). However, the response rate to itraconazole therapy (47%) was similar to the range of 50% to 64% reported for lipid-based formulations of amphotericin B (4–6). Furthermore, exploratory outcome analysis using a composite end point of success defined in a study comparing liposomal with conventional amphotericin B (5) demonstrated response rates of 53% and 46% for itraconazole and amphotericin B, respectively. In contrast to previous comparative trials, in which response was defined as defervescence, frequency of breakthrough fungal infections, and change to other systemic antifungal therapy, we included resolution of neutropenia among the response criteria and a minimum administration period of 3 days for inclusion in the intention-to-treat group. These additional criteria for response and patient evaluability may have contributed to the somewhat lower response rates in our study.

Conventional amphotericin B is associated with infusion-related toxicity, including chills or rigors (54%), fever (44%), and cardiorespiratory events (46%) (5). Increased serum creatinine concentration indicative of renal damage has been reported in an average of 31% of patients (range, 11% to 52%) (2–6, 13, 14, 24), and hypokalemia occurs in approximately 7% to 48% of patients (2, 3, 5, 13, 14). Development of serious metabolic toxicities may prevent effective dosing and necessitate treatment withdrawal altogether. Such toxic events are less frequent, but not eliminated, when lipid-based formulations of amphotericin B are used. Overall, in our study, amphotericin B therapy was discontinued because of adverse events more often than itraconazole therapy; nephrotoxicity (21%), hypotension (3%), and chills (4%) were the most common reasons for discontinuation. The reduced potential for nephrotoxicity with itraconazole is especially beneficial among patients with hematologic cancers. A relatively high proportion of these patients are likely to require concomitant treatment with other nephrotoxic agents (aminoglycosides, cyclosporine, and certain chemotherapeutic agents) that may augment amphotericin B–induced renal damage. The reduction in infusion-related events should also improve comfort in patients who experience toxicity from anticancer therapy.

Plasma itraconazole concentrations greater than 250 ng/mL are active against most itraconazole-susceptible fungi (26). Itraconazole oral solution produces plasma concentrations of 250 ng/mL in neutropenic patients with cancer, which correlate with effective prophylaxis (20, 27). Maintenance of plasma concentrations higher than the effective level after oral dosing in our trial provides a rationale for changing from intravenous to oral antifungal therapy in selected patients who are clinically stable and can tolerate oral medications. The replacement of intravenous itraconazole with oral itraconazole can improve quality of life, allow ambulatory treatment, and reduce drug administration costs in patients who need prolonged antifungal therapy. Both oral and intravenous itraconazole are considerably less expensive than lipid-based formulations of amphotericin B.

Patients were observed for up to 7 days after completion of treatment with the study drug for clinical or microbiological evidence of fungal infection. However, because of additional chemotherapy, underlying cancer that is refractory to treatment, or other risk factors, new or relapsed signs and symptoms of fungal infection may develop after longer periods of observation. Thus, continued surveillance for evidence of fungal infection is warranted after empirical antifungal therapy with itraconazole or amphotericin B in patients who remain at high risk for infection.

A limitation of our trial is that neither physicians nor patients were blinded to the empirical antifungal therapy being administered. Consequently, despite well-defined prestudy criteria for evaluating efficacy and tox-

icity, evaluation of the treatment response and the relationship of adverse events to the study drugs may have been somewhat biased. We also did not evaluate the response to treatment in patients with documented fungal infections. Thus, no conclusions can be made about the relative efficacy of itraconazole and amphotericin B for treatment of documented fungal infections in neutropenic patients.

In conclusion, we found that itraconazole is safe and effective as empirical antifungal therapy for suspected invasive fungal infection in neutropenic patients with persistent fever despite broad-spectrum antibacterial therapy. Itraconazole has potential advantages over amphotericin B in terms of toxicity and the flexibility to change to oral therapy in certain patients.

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