Itraconazole Oral Solution as Prophylaxis for Fungal Infections in Neutropenic Patients with Hematologic Malignancies: A Randomized, Placebo-Controlled, Double-Blind, Multicenter Trial

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To evaluate the efficacy and safety of itraconazole oral solution for preventing fungal infections, a randomized, placebo-controlled, double-blind, multicenter trial was conducted: 405 neutropenic patients with hematologic malignancies were randomly assigned to receive either itraconazole, 2.5 mg/kg every 12 hours (201 patients), or placebo (204 patients). Proven and suspected deep fungal infection occurred in 24% of itraconazole recipients and in 33% of placebo recipients, a difference of 9 percentage points (95% confidence interval [CI], 0.6% to 22.5%; $P = .035$). Fungemia due to *Candida* species was documented in 0.5% of itraconazole recipients and in 4% of placebo recipients, a difference of 3.5 percentage points (95% CI, 0.5% to 6%; $P = .01$). Deaths due to candidemia occurred in none of the itraconazole recipients compared with 4 placebo recipients, a difference of 2 percentage points (95% CI, 0.05% to 4%; $P = .06$). Aspergillus infection was documented in four itraconazole recipients (one death) and one placebo recipient (one death). Side effects causing drug interruption occurred in 18% of itraconazole recipients and 13% of placebo recipients. Itraconazole oral solution was well-tolerated and effectively prevented proven and suspected deep fungal infection as well as systemic infection and death due to *Candida* species.

Fungal infections are an important cause of morbidity and mortality in neutropenic patients with hematologic malignancies. Because these infections are often difficult to diagnose and treat successfully, antifungal prophylaxis may be useful in institutions where fungal infections are encountered frequently. Fluconazole has been shown to significantly reduce superficial and hematogenous candidiasis and mortality in bone marrow transplant patients [1, 2] and to reduce mucosal and hematogenous candidiasis in patients with acute leukemia [3]. The efficacy of fluconazole is limited by its lack of activity against *Candida krusei,* some strains of *Candida glabrata,* and molds. Increased frequency of colonization by *C. krusei* and *C. glabrata* has been reported in a few institutions where fluconazole has been used [4]. Itraconazole has activity against *Candida* and *Aspergillus* species.

In a prospective, randomized trial of patients with hematologic malignancies, the incidence of fungal infections, duration of fever, or use of intravenous amphotericin B was essentially similar in patients treated with itraconazole capsule and in those receiving placebo in addition to oral amphotericin B [5]. This study failed to show a significant reduction in the incidence of invasive aspergillosis. Furthermore, itraconazole, in the capsule formulation, may have erratic absorption, and no preventive effect could be observed when plasma levels were <250 ng/mL [6]. Itraconazole oral solution, a formulation currently used for thrush and candidal esophagitis in patients with HIV infection [7], showed a better bioavailability both in autologous bone marrow transplant recipients [8] and in patients with acute myeloid leukemia [9]. No published evidence exists on the efficacy of itraconazole oral solution in preventing fungal infections in neutropenic patients with hematologic malignancies. However, preliminary data show that in adults receiving chemotherapy or bone marrow transplants, there were more proven systemic fungal infections and more were fatal in fluconazole recipients than in itraconazole oral solution recipients [10].

To evaluate the efficacy and tolerability of itraconazole oral solution in the setting of neutropenia, we performed a randomized, placebo-controlled, multicenter trial in patients with hematologic malignancies. The study was carried out by the GIMEMA Infection Program in several Italian hematology units.

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Informed consent was obtained from the patients or their parents or guardians, and guidelines for human experimentation of the authors' institutions were followed in the conduct of the clinical research.

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Methods

Eligible patients included consecutive adult patients who were hospitalized at participating centers and who had acute leukemia or other hematologic malignancies or were undergoing autologous bone marrow transplantation and were receiving cytotoxic therapy likely to induce neutropenia (neutrophil count, $<1000/mm^3$) within 7 days. Patients received remission-induction or reinduction therapy according to the GIMEMA protocols [11, 12]. We excluded from the study before randomization patients undergoing allogeneic bone marrow transplantation, patients <14 years old, patients with a history of hypersensitivity to triazoles, patients treated with antifungal therapy in the previous 15 days, patients with evidence of a preexisting fungal infection, and patients who had nasal colonization with *Aspergillus* species.

Study protocol. After informed consent was obtained, the patients were randomly assigned to receive either itraconazole oral solution, 2.5 mg/kg twice daily, or placebo. Itraconazole and placebo medication were provided as solution containing 400 mg/mL of hydroxypropyl-β-cyclodextrin. Itraconazole solution contained 100 mg of itraconazole per 10 mL of cyclodextrin.

Itraconazole and placebo were provided in identical, unmarked bottles, and they tasted similar because of the presence of cyclodextrin. Patients were randomly assigned to treatment groups by use of random permuted blocks of 10, containing different and balanced sequences of the two regimens. Antifungal prophylaxis was started 1–3 days before the administration of cytotoxic chemotherapy and continued until the neutrophil count returned to 1,000/μL or a systemic fungal infection was proved or suspected, with a maximum of 8 weeks. All patients received nystatin suspension, 500,000 U four times a day, and oral ciprofloxacin, 500 mg twice daily [13]; antiviral prophylaxis and central venous catheters were used, according to autonomous decisions made at each participating center. The patients were treated under conventional ward conditions or in single rooms, depending on the center.

All patients were examined daily for clinical signs of fungal infection. When the axillary temperature increased to >38°C or infection was suspected, samples for microbiological cultures, including at least three separate blood specimens, were obtained, prophylactic therapy with ciprofloxacin was stopped, and treatment with amikacin and ceftazidime plus a glycopeptide antibiotic (teicoplanin or vancomycin) was started; if fever persisted despite 4–6 days of systemic antibiotics, empirical intravenous amphotericin B was started.

Proven deep fungal infections were treated with systemic antifungal agents (mainly intravenous amphotericin B), and superficial fungal infections were treated with topical antifungal agents without interrupting the blinded prophylactic regimen.

To compare the efficacy and tolerability of the two prophylactic regimens, the following variables were measured: proven deep fungal infection, suspected deep fungal infection, superficial fungal infection, compliance, treatment interruption due to side effects, and mortality.

Definition of fungal infection. Superficial fungal infection was defined as clinically apparent infection of the oropharynx or skin along with positive cultures. A suspected case of deep fungal infection was defined as any episode of fever that persisted despite 4–6 days of empirical antibiotics or any relapsing fever after initial response to antibiotics for which empirical intravenous amphotericin B was started. Proven deep fungal infection was defined as one in which there was both clinical evidence of blood or tissue infection and a culture or biopsy specimen from the involved site demonstrating a pathogenic fungal organism [14].

Compliance. Compliance was monitored by the nurse who measured the volume of itraconazole oral solution or placebo each day and recorded these data on the case report form. Compliance was defined as good if the patient missed <3 consecutive doses or took >90% of the total number of doses, as moderate if the patient missed 3–5 consecutive doses or took 50%–90% of the total number of doses, and as poor if the patient missed >5 consecutive doses or took <50% of the total number of doses.

Statistical analysis. Statistical analysis was done at the Janssen Research Foundation and confirmed by the GIMEMA Infection Program Data Center with the SAS package (SAS Institute, Cary, NC). Results are reported for all patients enrolled in the study (intention-to-treat analysis).

Three hundred eight evaluable cases (154 for each group) were needed to demonstrate a 10% absolute reduction of proven and suspected deep fungal infection in itraconazole recipients (β error, .2; α error, .05, one-sided), taking into account that in the previous GIMEMA study [14], these infections accounted for 20% of the total evaluable cases.

The χ^2 test with a correction for continuity or Fisher's exact test, when appropriate, were used to compare differences in proportions between the two groups. The logrank test was used to compare the Kaplan-Meier curves of survival. Student's unpaired t test was used to compare the means. CIs of 95% are given where appropriate.

Results

A total of 405 patients with hematologic malignancies from 39 centers were studied; 201 were randomly assigned to receive itraconazole and 204 to receive placebo. The two groups of patients were similar in sex, age, underlying diseases, protective environment, use of central venous catheters, and duration and severity of neutropenia (table 1). Itraconazole oral solution significantly reduced the incidence of proven and suspected deep fungal infection, which occurred in 24% of itraconazole recipients compared with 33% of placebo recipients, a difference of 9 percentage points (95% CI, 0.6% to 22.5%; $P = .035$). The odds ratio calculated on data combin-

Table 1. Characteristics of neutropenic patients with hematologic malignancies receiving prophylaxis with either itraconazole oral solution or placebo.

Characteristic	Itraconazole	Placebo
Patients with neutropenia	201	204
Males/females	116/85	110/94
Mean age (range), y	44 (17–79)	44 (17–75)
Acute leukemia	149 (74)	157 (76)
Other hematologic malignancies	15 (7)	10 (5)
Autologous bone marrow transplantation	37 (18)	37 (18)
First-induction therapy	132 (66)	127 (62)
Protective environment	98 (49)	102 (50)
Central venous catheter	101 (50)	110 (54)
Mean duration of prophylaxis (range), d	20 (1–56)	19 (1–56)
Mean duration of neutropenia (range), d	15 (0–56)	14 (0–56)
Neutropenia (d)		
$<100/mm^3$	9	8
$100–499/mm^3$	4	4
$500–999/mm^3$	2	2
Patients with granulocyte count		
$<100/mm^3$, %	85.8	82.2

NOTE. Data are no. or no. (%) of patients unless stated otherwise.

ing proven and suspected fungal infections was 0.63 (95% CI, 0.40 to 0.99).

Proven deep fungal infection. Proven deep fungal infection occurred in 5 itraconazole recipients (2.5%) and in 9 placebo recipients (4.4%), a difference of 1.9 percentage points (95% CI, −1.6% to 5%; $P > .2$). All but one of these infections occurred in patients with acute leukemia.

Fungemia due to *Candida* species or other yeasts was documented in one itraconazole recipient (0.5%) and in eight placebo recipients (4%), a difference of 3.5 percentage points (95% CI for difference, 0.5% to 6%; $P = .01$). *Candida parapsilosis* was isolated from itraconazole recipients, while *Candida albicans* (3), *Candida tropicalis* (3), *C. parapsilosis* (1), and *Trichosporon capitatum* (1) were isolated from placebo recipients.

No death due to candidal infection occurred in itraconazole recipients, while four deaths (2%) occurred in placebo recipients, a difference of 2 percentage points (95% CI for difference, 0.05% to 4%; $P = .06$). In placebo recipients, deaths occurred in two patients with *C. albicans* infection, one patient with *C. tropicalis* infection, and one patient with *T. capitatum* infection (table 2).

Infections due to *Aspergillus* species were documented in four itraconazole recipients (2%) and in one placebo recipient (0.5%), a difference of 1.5 percentage points (95% CI, −3% to 0.6%; $P > .2$). In itraconazole recipients, *Aspergillus* species were responsible for pneumonia in one patient and sinusitis in two patients; the other patient had double infection (pneumonia caused by *Aspergillus flavus* and sinusitis due to *Fusarium* species), which caused the patient's death. In placebo recipients, a single case of aspergillus pneumonia was documented, which caused the patient's death (table 3).

Itraconazole blood level measurements were available for three of five patients who developed proven deep fungal infection. The patient with *C. parapsilosis* fungemia had adequate blood levels (>500 ng/mL), as did one patient with *A. flavus* sinusitis (>900 ng/mL); one patient with *Aspergillus fumigatus* pneumonia had inadequate blood levels (<150 ng/mL).

Suspected deep fungal infection. A lower rate of suspected deep fungal infections requiring empirical intravenous antifungal therapy occurred in itraconazole recipients (43 of 201, 21.4%) than in placebo recipients (59 of 204, 28.9%), but this difference did not reach statistical significance (a difference of 7 percentage points; CI for difference, −0.8% to 15%; $P = .081$). The time interval to the use of amphotericin B was 22 days for itraconazole recipients and 17 days for placebo recipients ($P = .089$).

Superficial fungal infection. Superficial fungal infection was reported in 11 patients receiving itraconazole (5.4%) and in 13 of those receiving placebo (6.3%). The prevalent site of superficial infection was the oral cavity, and the most common fungal isolate was *C. albicans* (table 4).

Patients with acute leukemia receiving first-induction chemotherapy. A separate analysis of the subgroup of 259 patients with neutropenia who were receiving first-induction chemotherapy showed that they did not differ from the other patients in demographic characteristics, use of protective environment, use of central venous catheters, and mean duration of neutropenia. Furthermore, no difference was found in this subgroup of patients between the two treatment arms for any of the following variables: proven deep fungal infections, suspected deep fungal infections requiring the empirical use of intravenous amphotericin B, superficial infections, or deaths related to fungal infections.

Mortality. The comparison of the survival curves showed no difference between the two treatment groups ($P > .6$). The overall mortality was similar: 15 (7%) of 201 itraconazole recipients died and 18 (9%) of 204 placebo recipients died. Death was attributed to proven fungal infection in one itracona-

Table 2. Fungemia due to *Candida* and other yeasts according to treatment group among neutropenic patients with hematologic malignancies.

	Itraconazole		Placebo	
Infection	No. of patients	No. of deaths	No. of patients	No. of deaths
Candida albicans	. . .	. . .	3	2
Candida tropicalis	. . .	. . .	3	1
Candida parapsilosis	1	0	1	0
Trichosporon capitatum	. . .	. . .	1	1
Total infections	1*		8*	
Fungal deaths		0†		4†

* One (0.5%) of 201 compared with eight (4%) of 204; $P = .01$.
† Zero of 201 compared with four (2%) of 204; $P = .06$.

Table 3. Systemic infections due to *Aspergillus* species among neutropenic patients with hematologic malignancies receiving prophylaxis with itraconazole oral solution or placebo.

		Itraconazole		Placebo	
Manifestation	Infection	No. of patients	No. of deaths	No. of patients	No. of deaths
Pneumonia	*Aspergillus fumigatus*	1	0	. . .	. . .
	Aspergillus species	. . .	. . .	1	1
Sinusitis	*Aspergillus flavus*	1	0	. . .	. . .
	Aspergillus species	1	0	. . .	. . .
Pneumonia and sinusitis	*A. flavus, Fusarium* species	1	1	. . .	. . .
Total infections		4*		1*	
Fungal deaths			1†		1†

* Four (2%) of 201 compared with one (0.5%) of 204; $P > .2$.
† One (0.5%) of 201 compared with 1 (0.5%) of 204; $P > .2$.

zole recipient and in five placebo recipients, a difference of 2 percentage points (95% CI, −0.3% to 4%; $P = .11$). Nonfungal infective causes of death and noninfective causes of death were equally distributed in both groups.

Compliance and adverse reactions. Compliance was classified as good for 83% of itraconazole recipients and 72% of placebo recipients; as moderate for 14% of itraconazole recipients and 21% of placebo recipients; and as poor for 3% of itraconazole recipients and 7% of placebo recipients.

Blood level determinations were available for 144 patients (438 determinations), documenting plasma concentrations of itraconazole of >250 mg/L for 53% of the samples drawn before 12 days of prophylaxis and for 86%–100% of the samples drawn after 12 days of treatment.

Side effects definitely or probably related to the study drug that caused drug interruption occurred in 37 (18%) of 201 itraconazole recipients and 27 (13%) of 204 placebo recipients, a difference of 5 percentage points (95% CI for difference, −12% to 1%; $P = .19$). Gastrointestinal disturbances (nausea, vomiting, diarrhea, and/or abdominal pain) caused drug interruption in 26 itraconazole recipients (13%) and 21 placebo recipients (10%). A reversible increase in aminotransferase levels occurred in 5 itraconazole recipients (2%) and in 3 placebo recipients (1.5%).

Table 4. Superficial fungal infections among neutropenic patients with hematologic malignancies receiving prophylaxis with itraconazole oral solution or placebo.

Site	Isolate	Itraconazole	Placebo
Oral cavity	*Candida albicans*	7	8
	Non–*albicans Candida*	2	3
	Torulopsis glabrata	1	. . .
Vagina	*C. albicans*	1	. . .
	Non–*albicans Candida*	. . .	1
	T. glabrata	. . .	1
Total		11*	13*

* Eleven (5.4%) of 201 compared with 13 (6.3%) of 204; $P > .2$.

Discussion

Four main findings of our study require attention. First, our study showed that antifungal prophylaxis with itraconazole oral solution effectively reduces proven and suspected deep fungal infections in neutropenic patients with hematologic malignancies. Treatment of 11 patients should prevent a single primary efficacy end point (proven and suspected fungal event), and this may compare favorably with the cost needed to treat an important fungal infection.

Second, results of our study compare favorably with those obtained in neutropenic patients treated with itraconazole capsules [6] because of the better bioavailability of the oral solution preparation [8, 9], as is also documented by the blood levels measured in our study.

Third, in our study itraconazole provided effective prophylaxis for infection and death due to *Candida* species. The prophylactic efficacy of itraconazole oral solution against candidal infections is similar to that of fluconazole. In a comparative study of neutropenic patients with hematologic malignancies, infections due to *Candida* species occurred in 1 itraconazole recipient (0.3%) and in 2 fluconazole recipients (0.7%) [10]. It is noteworthy that in both studies, the prophylactic use of itraconazole did not seem to be associated with the selection and emergence of resistant *Candida* organisms otherwise observed with fluconazole [4].

Fourth, we did not observe a reduction in the rate of aspergillus infection with use of itraconazole oral solution. This result is similar to that observed in the trial comparing itraconazole oral solution with fluconazole suspension [10]. The lack of a statistically significant difference favoring itraconazole oral solution with respect to aspergillus infection observed in these trials can be explained by the very low rate of mold infections

in treated patients. The risk of aspergillus infection is higher in patients undergoing allogeneic bone marrow transplantation if they had unrelated donors, advanced age, acute myelogenous leukemia in second relapse, or graft-versus-host disease treated with high-dose steroids and if they were cared for outside a laminar airflow room with high-efficiency particulate air filtration. The risk is higher in patients with acute myelogenous leukemia or other hematologic malignancies if they receive high-dose cytarabine or any other gut-damaging high-dose chemotherapy or steroids [15]. This is not the case for our trial. Patients undergoing allogeneic bone marrow transplantation were excluded from the study, and patients with acute leukemia or other hematologic malignancies did not receive high-dose cytarabine.

The rate of superficial fungal infection observed in itraconazole recipients (5.4%) and in the placebo arm (6.3%) is similar. A possible explanation for this unexpected result is that both treatment groups received oral nystatin as a topical antifungal agent. The oral, non-absorbable agent nystatin (as well as clotrimazole troches and oral miconazole), although unable to prevent systemic candidiasis, is effective in preventing thrush.

In our study, the use of itraconazole oral solution did not influence the rate of overall mortality. Mortality in neutropenic patients is influenced by several factors that are unrelated to the type of prophylaxis used, such as the response to antibiotic and antifungal therapy, the severity of underlying disease, and complications other than infection. A meta-analysis of prophylactic antifungal treatment vs. placebo or no treatment in patients with cancer and neutropenia showed that there seems to be no survival benefit from antifungal agents [16]. However, in our study, deaths due to proven deep candidal infection occurred less frequently in itraconazole recipients than in placebo recipients (0 vs. 4 deaths; $P = .06$). Similarly, fluconazole prophylaxis has been shown to reduce mortality associated with systemic fungal infections in bone marrow transplant patients in a prospective randomized trial [1].

Compliance was similar for itraconazole and placebo recipients, and this seems to be related to the similar rate of gastrointestinal side effects that occurred in both groups. Gastrointestinal disturbances were the most frequently encountered side effects for both treatment groups, because itraconazole and placebo medication were provided in a solution containing 400 mg/mL hydroxypropyl-β-cyclodextrin. The contribution of cyclodextrin to the toxicity of itraconazole did not seem to be relevant, as predicted in toxicology studies. Because of an osmotic effect, cyclodextrin may be responsible for diarrhea. Moreover, the role of cancer chemotherapy in gastrointestinal side effects should be considered. No relationship was found between gastrointestinal upset and documented deep fungal infection.

The question as to whether azole prophylaxis prolongs the duration of neutropenia has been a concern raised by some investigators, who also noted a higher incidence of bacteremias in the azole-treated patients [17]. In our study, the mean duration of neutropenia was similar in both treatment groups, but interestingly, a statistically significant higher rate of bacteremias occurred in itraconazole recipients than in placebo recipients (47 [23%] of 201 vs. 31 [15%] of 204; $P = .037$). In another study of ketoconazole prophylaxis, a higher incidence of bacteremias in leukemia patients receiving ketoconazole was observed (74% vs. 37% in controls; $P = .004$). Also in that study, the higher incidence of bacteremia could not be explained by the prolongation of neutropenia in the ketoconazole-treated patients [18].

In conclusion, itraconazole oral solution reduced proven and suspected deep fungal infections in neutropenic patients with hematologic malignancies not undergoing bone marrow transplantation and effectively prevented infection and death due to *Candida* species. Itraconazole oral solution was well-tolerated.

The results of our study suggest that itraconazole oral solution may be a useful option for antifungal prophylaxis in neutropenic patients with hematologic malignancies with acute leukemia or autologous bone marrow transplantation, in particular for candidal infection prophylaxis. Further studies are warranted to clarify the role of itraconazole prophylaxis in aspergillus infection and in allogeneic bone marrow transplant patients.

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