

## ORIGINAL ARTICLE

# Posaconazole vs. Fluconazole or Itraconazole Prophylaxis in Patients with Neutropenia

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## ABSTRACT

**BACKGROUND**

Patients with neutropenia resulting from chemotherapy for acute myelogenous leukemia or the myelodysplastic syndrome are at high risk for difficult-to-treat and often fatal invasive fungal infections.

**METHODS**

In this randomized, multicenter study involving evaluators who were unaware of treatment assignments, we compared the efficacy and safety of posaconazole with those of fluconazole or itraconazole as prophylaxis for patients with prolonged neutropenia. Patients received prophylaxis with each cycle of chemotherapy until recovery from neutropenia and complete remission, until occurrence of an invasive fungal infection, or for up to 12 weeks, whichever came first. We compared the incidence of proven or probable invasive fungal infections during treatment (the primary end point) between the posaconazole and fluconazole or itraconazole groups; death from any cause and time to death were secondary end points.

**RESULTS**

A total of 304 patients were randomly assigned to receive posaconazole, and 298 patients were randomly assigned to receive fluconazole (240) or itraconazole (58). Proven or probable invasive fungal infections were reported in 7 patients (2%) in the posaconazole group and 25 patients (8%) in the fluconazole or itraconazole group (absolute reduction in the posaconazole group, -6%; 95% confidence interval, -9.7 to -2.5%;  $P < 0.001$ ), fulfilling statistical criteria for superiority. Significantly fewer patients in the posaconazole group had invasive aspergillosis (2 [1%] vs. 20 [7%],  $P < 0.001$ ). Survival was significantly longer among recipients of posaconazole than among recipients of fluconazole or itraconazole ( $P = 0.04$ ). Serious adverse events possibly or probably related to treatment were reported by 19 patients (6%) in the posaconazole group and 6 patients (2%) in the fluconazole or itraconazole group ( $P = 0.01$ ). The most common treatment-related adverse events in both groups were gastrointestinal tract disturbances.

**CONCLUSIONS**

In patients undergoing chemotherapy for acute myelogenous leukemia or the myelodysplastic syndrome, posaconazole prevented invasive fungal infections more effectively than did either fluconazole or itraconazole and improved overall survival. There were more serious adverse events possibly or probably related to treatment in the posaconazole group. (ClinicalTrials.gov number, NCT00044486.)

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**I**NVASIVE FUNGAL INFECTIONS REMAIN A major cause of illness and death in patients with neutropenia who have hematologic cancers, despite the availability of new antifungal agents. The incidence of proven or probable mold and yeast infections can reach 24% among patients with leukemia.<sup>1,2</sup> Reported mortality from candidiasis or aspergillosis ranges from 40 to 50%, and mortality from fusariosis or zygomycosis is 70% or more.<sup>3-8</sup> Prophylaxis is a commonly used treatment strategy, because the diagnosis of fungal infection is often delayed or difficult to establish with certainty, and a delay in antifungal treatment increases mortality.<sup>9-11</sup>

Antifungal prophylaxis with fluconazole reduces morbidity and mortality among recipients of allogeneic hematopoietic stem-cell transplants.<sup>12,13</sup> Fluconazole prophylaxis is also used in other patient populations with neutropenia, although fewer data support its efficacy in these patients.<sup>14</sup> Fluconazole has an acceptable adverse-event profile but lacks efficacy against filamentous fungi, which have become increasingly frequent causes of infection in patients with neutropenia. Itraconazole has a wider spectrum of activity than fluconazole, including activity against aspergillus species. A meta-analysis of trials involving patients with neutropenia and hematologic cancers showed that prophylaxis with itraconazole is more effective than prophylaxis with fluconazole.<sup>15</sup> However, the clinical usefulness of itraconazole is limited by the poor tolerability of the cyclodextrin-containing oral solution and the erratic bioavailability of the oral-capsule formulation. Thus, early-generation oral azole agents have limitations related to the spectrum of antifungal activity and tolerability.

Posaconazole is a new-generation oral azole with *in vitro* activity against a wide spectrum of medically important fungi, including species of *Candida*, *Aspergillus*, *Zygomycetes*, and *Fusarium*.<sup>16,17</sup> Studies of animals and humans have shown clinical activity of posaconazole in the treatment of invasive infection with molds and yeasts.<sup>18-21</sup> We conducted a randomized trial comparing the efficacy and safety of posaconazole with those of fluconazole or itraconazole for the prevention of invasive fungal infections in patients with neutropenia who were undergoing remission-induction chemotherapy for acute myelogenous leukemia or the myelodysplastic syndrome.

## METHODS

### PATIENTS

Patients 13 years of age or older were eligible if they had or were anticipated to have neutropenia, with an absolute neutrophil count of 500 cells per cubic millimeter or less, for 7 days or more, resulting from remission-induction chemotherapy for newly diagnosed, or the first relapse of, acute myelogenous leukemia or the myelodysplastic syndrome. To be eligible, patients also had to be able to take oral medications, although a brief period of intravenous therapy (less than 4 days) was permitted at entry into the trial. Exclusion criteria were an invasive fungal infection within the previous 30 days, clinically significant hepatic or renal dysfunction, an abnormal QT interval corrected for heart rate (QTc interval), a baseline Eastern Cooperative Oncology Group performance status score of more than 2 (in bed more than half of the day), a history of hypersensitivity or idiosyncratic reactions to azoles, or a requirement for medications with a potential for adverse interactions with azoles. Before enrollment, written informed consent was obtained from each patient or the patient's parent or legal guardian, and the study was approved by the institutional review board or ethics committee at each participating center.

### STUDY DESIGN

The study was designed by academic authors and employees of the sponsor, in collaboration with an independent expert panel. The sponsor analyzed the data, and the academic authors and one author who is an employee of the sponsor prepared the manuscript. The academic authors had full access to the primary data and to the results of their analyses and were given full independence in decisions concerning the reporting of results and the content of the manuscript. The academic authors vouch for the accuracy and completeness of the data and data analyses.

In this prospective, randomized trial involving evaluators who were unaware of the treatment assignments, we compared posaconazole with fluconazole or itraconazole for the prevention of invasive fungal infections. On the basis of local practices, investigators selected either fluconazole or itraconazole at the start of the study for use throughout the study. Patients were randomly assigned, in a 1:1 ratio, to receive posaconazole or

either fluconazole or itraconazole. Prophylaxis was administered with each chemotherapy cycle, starting either 24 hours after the last anthracycline dose or, in patients not receiving an anthracycline-based regimen, on the first day of chemotherapy. Prophylaxis was continued until recovery from neutropenia and complete remission, until occurrence of an invasive fungal infection, or for up to 12 weeks from randomization, whichever came first. Patients were followed for 100 days after randomization and for 30 days after the last dose of the study drug administered during the last chemotherapy cycle. An independent data review committee of infectious disease experts who were unaware of the treatment assignments reviewed and classified all cases of fungal infection as proven, probable, or possible, according to the consensus criteria of the European Organisation for the Research and Treatment of Cancer and the Mycoses Study Group.<sup>22</sup>

#### ADMINISTRATION OF THE STUDY DRUG

Study patients received 200 mg of posaconazole in an oral suspension three times daily, 400 mg of fluconazole (Diflucan, Pfizer) in an oral suspension once daily, or 200 mg of itraconazole (Sporanox, Janssen) in an oral solution twice daily. Patients who were unable to tolerate the oral study drug could receive intravenous prophylaxis at the same dose for 3 days or less per chemotherapy cycle. In the fluconazole or itraconazole group, the intravenous prophylaxis was the assigned study drug; in the posaconazole group, it was amphotericin B deoxycholate (Fungizone [Apothecon Pharmaceuticals] or a generic form, 0.3 to 0.5 mg per kilogram of body weight daily). Patients in either group were permitted to receive amphotericin B or another systemic agent as empirical antifungal therapy for a suspected invasive fungal infection.

#### ASSESSMENT OF EFFICACY

All patients underwent comprehensive evaluations for the presence of an invasive fungal infection at the beginning and the end of prophylaxis, 30 days after the last dose of the study drug had been administered, and 100 days after randomization. At any time during the treatment phase — defined as the period from randomization to 7 days after the last dose of the study drug had been adminis-

tered during the last chemotherapy cycle — if a patient had any sign or symptom of infection, including fever, a complete clinical and mycologic evaluation was performed. Surveillance blood specimens were collected twice weekly for the aspergillus galactomannan assay (Platelia aspergillus enzyme-linked immunosorbent assay, Bio-Rad Laboratories). In vitro susceptibility testing of fungal isolates was performed by staff at a central laboratory, according to the methods of the Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards).<sup>23,24</sup> We measured the steady-state plasma concentrations of the study drug and calculated the arithmetic means using liquid chromatography with a mass-spectrometric detection method for measurements of posaconazole<sup>25</sup> and fluconazole<sup>26</sup> levels and a high-performance chromatographic method for itraconazole.<sup>27</sup>

#### Primary Analysis

The primary efficacy end point was the incidence of proven or probable invasive fungal infection during the treatment phase, as adjudicated by an expert panel whose members were unaware of the treatment assignments, according to consensus criteria of the European Organisation for the Research and Treatment of Cancer and the Mycoses Study Group.

#### Secondary Analyses

Secondary end points included the incidence of invasive aspergillosis, the incidence of invasive fungal infection within 100 days after randomization, and treatment success (vs. failure) during the treatment phase. Treatment failure was defined as the occurrence of a proven or probable invasive fungal infection; receipt of an intravenous study drug for 4 consecutive days or more or 10 days in total; receipt of any other systemic antifungal agent for 4 days or more for suspected invasive fungal infection; the occurrence of an adverse event possibly or probably related to the study treatment, resulting in the discontinuation of treatment; or withdrawal from the study with no additional follow-up. Survival was evaluated 100 days after randomization, and analyses were conducted for overall survival, time to death from any cause, time to death related to fungal infection, and survival without proven or probable invasive

fungal infection. Time to invasive fungal infection and time to first use of empirical antifungal therapy were also assessed.

**ASSESSMENT OF SAFETY**

Adverse events were recorded from randomization until day 30 after the last dose of the study drug had been administered during the last chemotherapy cycle. These events were classified according to the Common Toxicity Criteria grading system of the National Cancer Institute.<sup>28</sup>

**STATISTICAL ANALYSIS**

The primary efficacy analysis was based on the intention-to-treat approach, with the use of data from all patients who underwent randomization. First, the noninferiority of posaconazole as compared with fluconazole or itraconazole therapy was assessed. For our study, the incidence of proven or probable invasive fungal infection was assumed to be 8% or less with fluconazole or itraconazole prophylaxis.<sup>1</sup> Therefore, using a cutoff level of significance of 4.87% for the final analysis (in order to account for the interim analysis), we calculated that if the upper bound of the 95.13% confidence interval (hereafter called the 95% CI) for the difference between the incidence of proven or probable fungal infection for posaconazole and that for fluconazole or itraconazole was less than 4%, noninferiority would be demonstrated, and the superiority of posaconazole over fluconazole or itraconazole therapy could be assessed. The superiority of posaconazole would be established if the upper bound of the same 95% CI was negative. This two-step analysis allowed for an overall type 1 error rate of 0.05. We used the Kaplan–Meier method to evaluate time to death from any cause, time to death related to fungal infection, time to proven or probable fungal infection, time to first use of empirical antifungal therapy, and survival free from proven or probable invasive fungal infection. The survival benefit was assessed with the chi-square and log-rank tests. All analyses except the noninferiority analysis were based on two-sided P values, with a two-sided P value of less than 0.05 considered to indicate statistical significance. The numbers of patients who would need to be treated to prevent one fungal infection and one death (numbers needed to treat) were calculated as described previously.<sup>29</sup>

RESULTS

**PATIENT CHARACTERISTICS**

The study was conducted from August 2002 through April 2005 at 89 centers worldwide. A total of 602 patients were randomly assigned to treatment: 304 patients to receive posaconazole and 298 patients to receive fluconazole (240) or itraconazole (58). The two groups had similar characteristics (Table 1).

**INVASIVE FUNGAL INFECTION**

Proven or probable invasive fungal infections occurred during the treatment phase in 7 of the 304 patients (2%) in the posaconazole group and in 25 of the 298 patients (8%) in the fluconazole or itraconazole group (absolute reduction in the posaconazole group, -6%; 95% CI, -9.7 to -2.5; P<0.001). The superiority of posaconazole over fluconazole was confirmed in a post hoc analysis limited to centers at which fluconazole was used as the comparison study drug (see the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org)). We estimated that 16 patients would need to be treated with posaconazole, as compared with fluconazole or itraconazole, in order to prevent one invasive fungal infection.

During the 100-day period after randomization, 14 of 304 patients (5%) in the posaconazole group had a proven or probable fungal infection, as compared with 33 of 298 patients (11%) in the fluconazole or itraconazole group (P=0.003). The mean (±SD) time to invasive fungal infection was 41±26 days in the posaconazole group and 25±26 days in the fluconazole or itraconazole group. Kaplan–Meier analysis of the time to invasive fungal infection showed a significant difference in favor of posaconazole (P=0.003) (Fig. 1A). Table 2 lists the causative pathogens of invasive fungal infections that occurred during the treatment phase; aspergillus was the most common. There were significantly fewer cases of aspergillosis associated with posaconazole prophylaxis than with fluconazole or itraconazole prophylaxis (2 [1%] vs. 20 [7%], P<0.001).

**CLINICAL SUCCESS OR FAILURE**

Rates of clinical success or failure and the reasons for clinical failure are listed in Table 3. Of the 304 patients in the posaconazole group, 81 (27%) received an empirical antifungal agent during the

**Table 1. Characteristics of the Intention-to-Treat Population at Baseline and during the Treatment Phase.\***

Characteristic	Posaconazole (N=304)	Fluconazole or Itraconazole (N=298)	Fluconazole (N=240)	Itraconazole (N=58)	P Value
Age — yr					
Mean	49±17	50±16	50±17	52±14	0.30
Median	53	53	52	54	
Range	13–82	13–81	13–79	20–81	
Race or ethnic group — no. (%)†					
White	220 (72)	231 (78)	182 (76)	49 (84)	0.16
Nonwhite	84 (28)	67 (22)	58 (24)	9 (16)	
Black	16 (5)	9 (3)	7 (3)	2 (3)	
Asian	13 (4)	9 (3)	3 (1)	6 (10)	
Hispanic	51 (17)	47 (16)	46 (19)	1 (2)	
Other	4 (1)	2 (1)	2 (1)	0	
Male sex — no. (%)	158 (52)	160 (54)	128 (53)	32 (55)	0.68
Region — no. (%)					
United States	81 (27)	78 (26)	70 (29)	8 (14)	0.93
Europe	125 (41)	127 (43)	92 (38)	35 (60)	
Canada	14 (5)	14 (5)	14 (6)	0	
Far East	18 (6)	21 (7)	9 (4)	12 (21)	
Latin America	66 (22)	58 (19)	55 (23)	3 (5)	
Primary diagnosis — no. (%)					
Acute myelogenous leukemia					
New diagnosis	213 (70)	222 (74)	181 (75)	41 (71)	0.24
First relapse	42 (14)	38 (13)	31 (13)	7 (12)	0.72
Myelodysplastic syndrome	49 (16)	38 (13)	28 (12)	10 (17)	0.25
Nadir ANC during treatment phase — no. (%)					
≤500 cells/mm <sup>3</sup>	298 (98)	290 (97)	234 (98)	56 (97)	0.60
≤100 cells/mm <sup>3</sup>	264 (87)	261 (88)	213 (89)	48 (83)	0.81
Total no. of days of neutropenia during treatment phase					
0–7 — no. (%)	21 (7)	21 (7)	17 (7)	4 (7)	
8–21 — no. (%)	141 (46)	143 (48)	118 (49)	25 (43)	
>21 — no. (%)	142 (47)	134 (45)	105 (44)	29 (50)	
Mean	25±17	23±13	23±13	24±14	0.046
Yeast-colonization status in stool or throat at baseline — no. (%)					
Positive	133 (44)	121 (41)	107 (45)	14 (24)	0.67
Negative	147 (48)	144 (48)	107 (45)	37 (64)	
Missing or unknown	24 (8)	33 (11)	26 (11)	7 (12)	

treatment phase, as did 112 of the 298 patients (38%) in the fluconazole or itraconazole group ( $P=0.004$ ). The analysis of the time to first use of empirical antifungal therapy during the 100-day period revealed a significant difference in favor of posaconazole over fluconazole or itraconazole ( $P=0.02$ ).

#### MORTALITY

Of the 304 patients in the posaconazole group, 49 (16%) died during the study period, as did 67 of 298 patients (22%) in the fluconazole or itraconazole group ( $P=0.048$ ); 44 patients (14%) and 64 patients (21%), respectively, died within 100 days. Kaplan–Meier analysis of the time to death from

Table 1. (Continued.)					
Characteristic	Posaconazole (N=304)	Fluconazole or Itraconazole (N=298)	Fluconazole (N=240)	Itraconazole (N=58)	P Value
Use of systemic antifungal agents as prophylaxis before randomization					
Patients — no. (%)	42 (14)	42 (14)	28 (12)	14 (24)	1.0
No. of days					
Mean	4±7	3±5	3±6	3±5	
Median	1	1	1	1	
Range	1–45	1–31	1–31	1–17	
No. of days from randomization to last contact	93±33	90±33	87±33	99±34	0.31
No. of days of prophylaxis with study drug	29±21	25±17	24±16	29±21	0.008
Total no. of chemotherapy cycles during treatment phase — no. (%)					
1	174 (57)	182 (61)	146 (61)	36 (62)	0.36
≥2	130 (43)	116 (39)	94 (39)	22 (38)	
Use of growth factors during treatment phase					
Patients — no. (%)	143 (47)	147 (49)	111 (46)	36 (62)	0.62
Days — no. (%)	14±12	12±10	12±10	13±11	0.08
Use of intravenous study drug as substitute for oral prophylaxis during treatment phase‡					
Patients — no. (%)	17 (6)§	30 (10)	25 (10)	5 (9)	0.048
Days — no. (%)					
1–3	11 (4)	18 (6)	17 (7)	1 (2)	
4–7	4 (1)	8 (3)	6 (3)	2 (3)	
>7	2 (1)	4 (1)	2 (1)	2 (3)	
Mean	4±4	4±4	4±4	6±4	
Treatment with systemic amphotericin B					
Patients — no. (%)	68 (22)	82 (28)			0.16
No. of days	1±3	2±3			0.29

\* Plus–minus values are means ±SD. The treatment phase was defined as the period from randomization to 7 days after the last dose of the study drug had been administered during the last cycle of chemotherapy. P values are for the posaconazole group as compared with the pooled fluconazole and itraconazole groups. ANC denotes absolute neutrophil count.

† Race or ethnic group was reported by physicians.

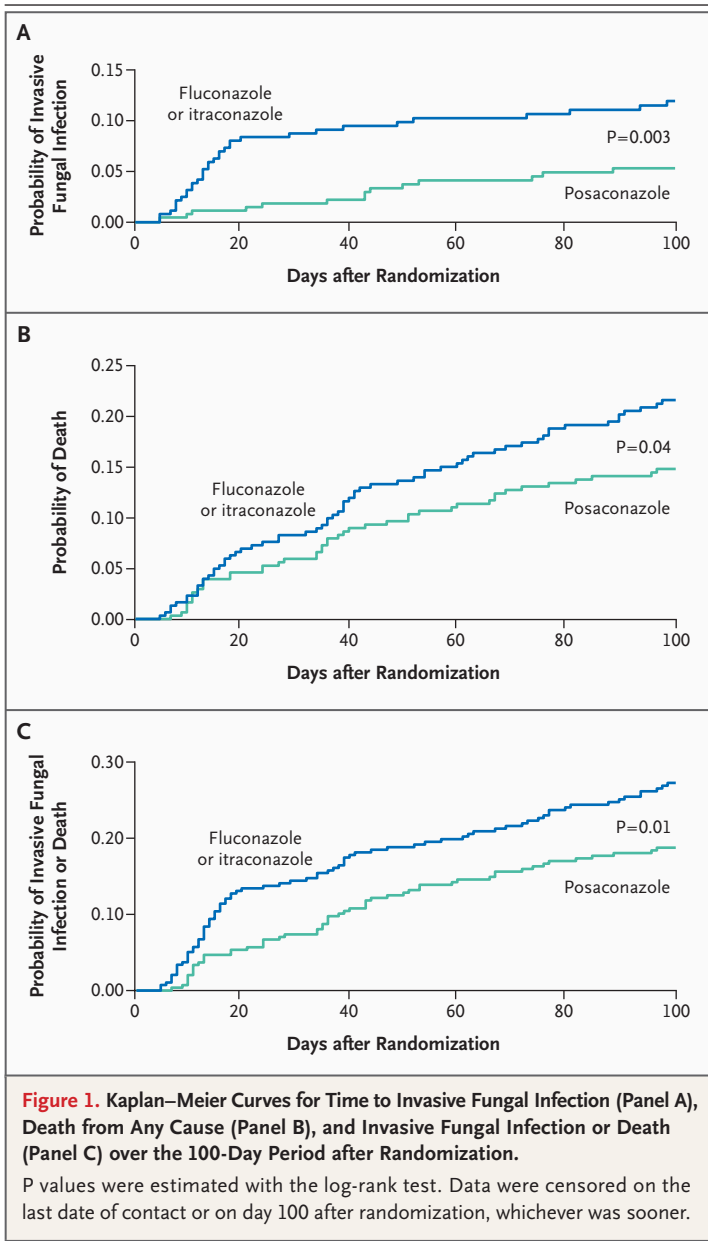
‡ The intravenous study drug used was amphotericin B deoxycholate for patients in the posaconazole group and an intravenous formulation of the study drug for patients in the fluconazole and itraconazole groups.

§ These patients include the six who received amphotericin B as the intravenous alternative study drug for 4 consecutive days or more or for 10 days in total (see Table 3).

any cause at the end of the 100-day period after randomization showed a significant survival benefit in favor of posaconazole over fluconazole or itraconazole ( $P=0.04$ ) (Fig. 1B). The relative reduction in mortality at day 100 in the posaconazole group, as compared with the fluconazole or itraconazole group, was 33%. The estimated number needed to treat with posaconazole, as compared with fluconazole or itraconazole, to prevent one death was 14 patients.

Of the 116 deaths that occurred during the study, 21 were considered to be related to fungal

infection: 5 (2%) that occurred in the posaconazole group and 16 (5%) in the fluconazole or itraconazole group ( $P=0.01$ ). Other causes of death were intercurrent illnesses in 20 patients (7%) in the posaconazole group and 30 patients (10%) in the fluconazole or itraconazole group and leukemia-related complications in 24 patients (8%) and 21 patients (7%), respectively. The analysis of the time to invasive fungal infection or death also showed a significant benefit in favor of posaconazole ( $P=0.01$ ) (Fig. 1C).



#### SAFETY ANALYSIS

All 602 patients in the intention-to-treat population were included in the safety evaluation. The incidence of treatment-related adverse events was similar among the treatment groups (Table 4 and the Supplementary Appendix). Treatment-related prolongation of the QT or QTc interval was reported in 12 of the 304 patients (4%) receiving posaconazole, 5 of the 240 patients (2%) receiving fluconazole, and 4 of the 58 patients (7%) receiving itraconazole; the prolongation was considered to be serious in 1 patient in the posaconazole

group. Other serious treatment-related cardiac events included atrial fibrillation, a decreased ejection fraction, and torsades de pointes, each occurring in one patient receiving posaconazole. Serious adverse events possibly or probably related to treatment were reported by 19 patients (6%) in the posaconazole group and 6 patients (2%) in the fluconazole or itraconazole group ( $P=0.01$ ).

#### PHARMACOKINETIC ANALYSES

Among patients from whom blood was collected for pharmacokinetic analysis, the mean plasma concentration of the study drug was  $583\pm 381$  ng per milliliter in 215 patients receiving posaconazole,  $13,577\pm 7104$  ng per milliliter in 172 patients receiving fluconazole, and  $785\pm 429$  ng per milliliter in 33 patients receiving itraconazole.

#### DISCUSSION

Our randomized clinical trial involving more than 600 high-risk patients showed that, as compared with fluconazole or itraconazole prophylaxis, posaconazole effectively prevented invasive fungal infections during successive cycles of chemotherapy for acute myelogenous leukemia or the myelodysplastic syndrome. Furthermore, mortality from any cause was significantly lower in the posaconazole group than in the fluconazole or itraconazole group, indicating that the survival of patients with acute leukemia can be improved with the use of antifungal prophylaxis during remission-induction chemotherapy.

Before our study, significant reductions in the incidence of invasive fungal infections and in mortality from any cause had been shown with fluconazole prophylaxis only in patients undergoing hematopoietic stem-cell transplantation.<sup>13</sup> Fluconazole prophylaxis has become the standard of care in this setting<sup>14</sup> and has been used in patients undergoing remission induction for acute leukemia, even though advantages with respect to morbidity or mortality have not been proved and there is no consensus among clinicians regarding its use in these high-risk patients.<sup>30</sup> Although the use of itraconazole seems to reduce the incidence of proven invasive fungal infections,<sup>31</sup> it does not confer a significant survival benefit over fluconazole in large trials, and it has been associated with greater toxicity.<sup>32,33</sup>

When we designed our trial, both fluconazole and itraconazole had been shown to be more ef-

**Table 2. Proven or Probable Invasive Fungal Infection during the Treatment Phase.\***

Invasive Fungal Infection	Posaconazole (N=304)	Fluconazole or Itraconazole (N=298)	Fluconazole (N=240)	Itraconazole (N=58)	P Value	95% CI
Proven or probable†	7 (2)	25 (8)	19 (8)	6 (10)	<0.001	-9.7 to -2.5
Mold						
Invasive aspergillosis	2 (1)	20 (7)	15 (6)	5 (9)	<0.001	-9.1 to -3.1
<i>Aspergillus fumigatus</i>	0	2	1	1		
<i>A. flavus</i>	0	2	2	0		
Aspergillus species‡	2	16	12	4		
Rhizopus species	0	1	1	0		
<i>Pseudallescheria boydii</i>	0	1	1	0		
Mold, not otherwise specified	1	0	0	0		
Yeast						
Invasive candidiasis	3 (1)	2 (<1)	2 (<1)	0		
<i>Candida glabrata</i>	2	1	1	0		
<i>C. krusei</i>	0	1§	1§	0		
<i>C. parapsilosis</i>	0	1§	1§	0		
<i>C. tropicalis</i>	1	0	0	0		
Other						
<i>Pneumocystis jirovecii</i> ¶	1	1	0	1		

\* The treatment phase was defined as the period from randomization to 7 days after the last dose of the study drug had been administered during the last cycle of chemotherapy. P values were calculated with the use of the chi-square test. P values and 95% confidence intervals (CIs) are reported for the posaconazole group as compared with the pooled fluconazole and itraconazole groups.

† The global distribution of invasive fungal infection was as follows: United States, 7 patients (posaconazole group, 1 of 81; fluconazole or itraconazole group, 6 of 78), Europe, 15 patients (posaconazole, 3 of 125; fluconazole or itraconazole, 12 of 127), Canada, 0 patients, Far East, 5 patients (posaconazole, 2 of 18; fluconazole or itraconazole, 3 of 21), and Latin America, 5 patients (posaconazole, 1 of 66; fluconazole or itraconazole, 4 of 58).

‡ Microbiologic criteria for proven or probable infection with aspergillus species included a positive test for aspergillus galactomannan antigen (≥0.5 on the galactomannan index), not necessarily a positive culture, or compatible histopathological findings.

§ Two infections were in one patient; therefore, they are counted as a single infection.

¶ *Pneumocystis pneumonia* was included even though there is no evidence that azoles, including the study drugs, act against *P. jirovecii*.

fective than placebo in preventing fungal infections, so they had been routinely used as the standards of care. However, no benefit of one azole over the other had been clearly established,<sup>32,33</sup> nor has one been revealed by more recent data.<sup>34</sup> Therefore, given the increased risk of invasive fungal infection among patients undergoing cytotoxic chemotherapy and the benefit seen among those undergoing hematopoietic stem-cell transplantation,<sup>13</sup> we believed that a placebo-controlled trial was not feasible. In our study, the investigators used their preferred standard azole as the comparison drug. The different dosing schedules of the three study drugs and the logistics of their intravenous alternatives precluded a double-blind design. To minimize the possibility of bias, an

independent data review committee, whose members were unaware of the treatment assignments, examined all suspected potential invasive fungal infections in order to adjudicate them as proven or probable, according to international consensus criteria.<sup>22</sup>

A patient's ability to swallow is rarely compromised immediately after induction chemotherapy, but oral intake may decrease owing to mucositis later in the course of treatment. Few patients in this trial were unable to tolerate oral medications at entry or during the course of treatment (Table 1). The study is therefore limited in its ability to provide data on the usefulness of azole prophylaxis in patients who have severe mucositis and are unable to eat or take oral medication.

**Table 3. Clinical Response and Reasons for Failure during the Treatment Phase.\***

Clinical Response	Posaconazole (N=304)	Fluconazole or Itraconazole (N=298)	P Value	95% CI
	no. (%)			
Clinical success	195 (64)	160 (54)		
Clinical failure†	109 (36)	138 (46)	0.009	−18.3 to −2.6
Proven or probable invasive fungal infection	7 (2)	25 (8)	<0.001	−9.7 to −2.5
Use of systemic antifungal agent for ≥4 consecutive days for a suspected fungal infection‡	68 (22)	101 (34)	0.002	−18.7 to −4.3
Adverse event possibly or probably related to study treatment, resulting in discontinuation	25 (8)	25 (8)	0.94	
Use of intravenous study drug for ≥4 consecutive days or for 10 days in total	6 (2)§	12 (4)	0.14	
Withdrawal for any reason and loss to follow-up	8 (3)	1 (<1)	0.02	0.0 to 4.2

\* The treatment phase was defined as the period from randomization to 7 days after the last dose of the study drug had been administered during the last cycle of chemotherapy. P values were calculated with the use of the chi-square test. P values are reported for the posaconazole group as compared with the pooled fluconazole and itraconazole groups; related 95% confidence intervals (CIs) are provided when significance was achieved.

† Clinical failure was also defined as randomization without subsequent treatment, which accounted for 7 of the 304 patients (2%) in the posaconazole group and 6 of the 298 patients (2%) in the fluconazole or itraconazole group. Numbers of patients in each subcategory do not sum to the total because some patients had more than one type of clinical failure.

‡ Amphotericin B was the systemic antifungal agent most frequently administered to patients in both groups.

§ Seventeen patients in the posaconazole group received amphotericin B intravenously as an alternative to posaconazole; however, only six of them received it for 4 consecutive days or more or for 10 days in total.

The difference in the incidence of breakthrough fungal infections during the treatment phase resulted predominantly from the significantly lower incidence of invasive aspergillosis in the posaconazole group than in the fluconazole or itraconazole group, which was consistent with the superior antifungal activity of posaconazole against aspergillus species. However, the incidence of aspergillosis among patients who had received itraconazole prophylaxis was unexpectedly high and was similar to that in the fluconazole group.

In our trial, throat and stool surveillance cultures were collected on a weekly basis. The reduction in the incidence of fungal colonization after prophylaxis was similar for the three study drugs. Furthermore, there was no apparent trend toward selection of azole-resistant colonizing yeast strains, although further observation is warranted.

The value of less rigorous end points — such as the time to antifungal treatment or mortality attributable to fungal infection — remains an issue of debate.<sup>14</sup> As compared with fluconazole or itraconazole, however, posaconazole prophylaxis resulted in a significant delay of empirical antifungal treatment and a significantly improved rate of survival without proven or probable inva-

sive fungal infection. Since the numbers of patients needed to treat to prevent one invasive fungal infection or one death are low (16 and 14, respectively), the benefit of posaconazole prophylaxis seems to outweigh the risks of toxic effects and selection of resistant organisms, which are inherent in prophylactic drug regimens, and to justify the cost.

Adverse events during treatment were similar with posaconazole and fluconazole. As expected, patients treated with itraconazole had gastrointestinal symptoms more frequently than did patients receiving fluconazole or posaconazole. Although certain serious adverse events — including a decreased ejection fraction, prolongation of the QT or QTc interval, and torsades de pointes — were each reported in one patient receiving posaconazole, the open nature of our study and the prevailing perception of fluconazole as a safe drug cannot be ruled out as an influence in determining any possible relation with posaconazole.

In summary, prophylaxis with posaconazole was superior to prophylaxis with fluconazole or itraconazole in the prevention of proven or probable invasive fungal infection and resulted in lower mortality from any cause and longer survival free

**Table 4. Summary of Serious Adverse Events.\***

Event	Posaconazole (N = 304)	Fluconazole or Itraconazole (N = 298)		
		Fluconazole (N = 240)	Itraconazole (N = 58)	
<i>number of patients (percent)</i>				
Any event†				
Total	159 (52)	175 (59)	143 (60)	32 (55)
Neutropenia	22 (7)	23 (8)	18 (8)	5 (9)
Gastrointestinal hemorrhage	8 (3)	3 (1)	2 (1)	1 (2)
Bilirubinemia	7 (2)	5 (2)	4 (2)	1 (2)
Hypotension	10 (3)	21 (7)	17 (7)	4 (7)
Cardiac failure	6 (2)	3 (1)	3 (1)	0
Cardiac arrest	4 (1)	6 (2)	5 (2)	1 (2)
Cardiorespiratory arrest	4 (1)	5 (2)	4 (2)	1 (2)
Atrial fibrillation	2 (1)	6 (2)	5 (2)	1 (2)
Event possibly or probably related to treatment				
Total	19 (6)	6 (2)	4 (2)	2 (3)
Bilirubinemia	5 (2)	3 (1)	2 (1)	1 (2)
Increased hepatic enzymes	3 (1)	1 (<1)	1 (<1)	0
Increased alanine aminotransferase	1 (<1)	1 (<1)	0	1 (2)
Hepatic failure	1 (<1)	0	0	0
Hepatitis	1 (<1)	0	0	0
Hepatocellular damage	1 (<1)	0	0	0
Jaundice	1 (<1)	0	0	0
Diarrhea	1 (<1)	0	0	0
Atrial fibrillation	1 (<1)	0	0	0
Syncope	2 (1)	0	0	0
Decreased ejection fraction	1 (<1)	0	0	0
QT or QTc prolongation‡	1 (<1)	0	0	0
Torsades de pointes	1 (<1)	0	0	0
Diplopia	0	1 (<1)	1 (<1)	0

\* Events are listed for the period from randomization until 30 days after the last dose of the study drug had been administered. For a complete listing, see the Supplementary Appendix. Numbers for subentries may not sum to the total numbers because patients could have more than 1 event. QTc denotes the QT interval corrected for heart rate.

† Events listed are those with a 2% or greater incidence in the posaconazole group or in the fluconazole or itraconazole group.

‡ Prolongation was defined as a period of more than 450 msec for men and more than 470 msec for women.

from proven or probable invasive fungal infection. Thus, posaconazole prophylaxis may be a useful addition to the standard of care for patients with acute myelogenous leukemia or myelodysplastic syndromes who are undergoing remission-induction chemotherapy.

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APPENDIX

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