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Long-Lasting Protective Effect of Posaconazole Prophylaxis in Patients with Acute Myeloid Leukemia Receiving Allogeneic Hematopoietic Stem Cell Transplantation

Alessandro Busca [1,*], Anna Candoni [2], Ernesta Audisio [3], Roberto Passera [4], Benedetto Bruno [1], Federico Monaco [5], Nicola Mordini [6], Adriana Vacca [7], Mario Delia [8], Franco Aversa [9], Livio Pagano [10]

[1] *Department of Oncology and Hematology, Stem Cell Transplant Center, AOU Citta' della Salute e della Scienza, Turin, Italy*
[2] *Division of Hematology and SCT Unit, University Hospital of Udine, Italy*
[3] *Department of Oncology and Hematology, AOU Citta' della Salute e della Scienza, Turin, Italy*
[4] *Division of Nuclear Medicine, AOU Citta' della Salute e della Scienza, Turin, Italy*
[5] *SC Ematologia, ASO SS Antonio e Biagio Alessandria, Italy*
[6] *Hematology, Azienda Ospedaliera S Croce e Carle, Cuneo, Italy*
[7] *Ematologia-CTMO Ospedale Roberto Binaghi Cagliari, Italy*
[8] *Sezione di Ematologia, Dipartimento dell'Emergenza e dei Trapianti d'Organo-Università di Bari, Italy*
[9] *Sezione di Ematologia, Università di Parma, Italy*
[10] *Istituto di Ematologia, Università Cattolica del Sacro Cuore, Roma, Italy*

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A B S T R A C T

Patients with acute myeloid leukemia (AML) during induction chemotherapy and those who receive allogeneic hematopoietic stem cell transplantation (HSCT) are at higher risk of invasive fungal infections (IFI). In the present study, we investigated whether the risk of IFI in AML patients receiving HSCT might be affected by the antifungal prophylaxis with posaconazole administered during the induction/salvage chemotherapy treatment. Between August 2001 and April 2015, 130 patients with AML received itraconazole/fluconazole (group A) and 99 received posaconazole (group B) as antifungal prophylaxis after induction/salvage chemotherapy at 7 Italian centers and all patients received fluconazole as antifungal prophylaxis after HSCT. The median duration of antifungal prophylaxis after induction/salvage chemotherapy was significantly longer for patients in group A than for those in group B (24 days versus 20 days, $P = .019$). The 1-year cumulative incidence of proven/probable IFI after HSCT was 14% and 4% in group A and group B, respectively ($P = .012$). Fungal-free survival and overall survival at 1 year after HSCT were 66% and 70% in group A, and 75% and 77% in group B ($P = .139$ and $P = .302$), respectively. Multivariate logistic analysis identified the use of alternative donors (matched unrelated donor: odds ratio [OR], 3.25; haploidentical/partially matched related donor: OR, 3.19), antifungal prophylaxis with itraconazole/fluconazole (OR, 3.82), and reduced-intensity conditioning (OR, 4.92) as independent risk factors for the development of IFI after HSCT. In summary, the present study suggests that the protective effects of posaconazole during induction/salvage chemotherapy for AML patients may have long-lasting benefits and eventually contribute to reduce the risk of IFI when patients undergo allogeneic HSCT.
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INTRODUCTION

Antifungal prophylaxis with mold-active agents has become a widely accepted strategy for patients with acute myeloid leukemia (AML) and hematopoietic stem cell transplantation (HSCT) recipients, according to the recommendations of the most recent international guidelines [1-4]. Posaconazole was shown to be effective in reducing the incidence of invasive fungal infections (IFI) in patients with AML, as compared with conventional azoles. In a large prospective randomized trial, Cornely et al. showed a significant reduction of proven and probable IFI in patients with AML and myelodysplastic syndrome who received posaconazole (9% versus 1%), which translated into better overall survival [5]. In the light of these findings, many "real-life" studies were conducted and they substantially confirmed the efficacy of posaconazole [6-9]. A consistent proportion of AML

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* Correspondence and reprint requests: Alessandro Busca, MD, Department of Oncology and Hematology, Stem Cell Transplant Center, AOU Citta' della Salute e della Scienza, Corso Bramante 88, 10126 Turin, Italy.
E-mail address: abusca@cittadellasalute.to.it (A. Busca).

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patients are also candidates for allogeneic HSCT as part of their treatment plan after induction/consolidation chemotherapy. In this study, we hypothesized that the efficacy of antifungal prophylaxis with posaconazole during induction of AML patients may have had a favorable impact on the incidence of IFI after the allograft. We retrospectively analyzed the incidence of IFI after HSCT in a group of AML patients who received antifungal prophylaxis with either posaconazole or conventional azoles (namely, itraconazole/fluconazole) during induction/salvage chemotherapy.

PATIENTS AND METHODS

Eligibility Criteria

The study was conducted at 7 divisions of hematology at tertiary care centers or university hospitals in Italy. Between August 2001 and April 2015, adult patients with AML who received antifungal prophylaxis with itraconazole (200 mg twice daily), fluconazole (200 mg twice daily), or posaconazole oral suspension (200 mg 3 times daily) during up-front induction chemotherapy or salvage treatments and who then proceeded to allogeneic HSCT were included in the study. Antifungal prophylaxis started on the first day of chemotherapy or 1 to 2 days later and continued until the neutrophil count was higher than 500×10^9/L or until proven or suspected diagnosis of IFI, whichever occurred first. When possible, posaconazole was administered with fatty food or nutritional supplements and without proton pump inhibitors, if gastric hyperacid symptoms were not present. Patients who developed proven or probable IFI during induction or salvage chemotherapies or at any time before allogeneic HSCT were excluded from the analysis. Further exclusion criteria were a time interval from diagnosis of AML to HSCT longer than 365 days and/or antifungal prophylaxis other than fluconazole after HSCT. The study was approved by the ethics committees of each participating center.

Patient Monitoring

Throughout the treatment plan, patients with febrile neutropenia underwent similar diagnostic work-up at all participating centers, which included urine and blood cultures and chest X-ray. Empiric broad-spectrum antibiotic treatment was invariably started on the first day of neutropenic fever. A chest computed tomography (CT) scan was scheduled for persistent unexplained fever or at the onset of any clinical signs or symptoms at the discretion of the attending physician. When radiological chest abnormalities were detected without evidence of any microbiologically documented infection, bronchoscopy with bronchoalveolar lavage was scheduled for microbiological testing and galactomannan antigen detection whenever possible. Moreover, abdominal ultrasound or other CT scans (ie, sinus or brain CT) were scheduled according to patient symptoms. Aspergillus galactomannan antigen was tested on serum samples twice each week by using the double-sandwich ELISA Platelia Aspergillus. Additional blood, sputum, or other relevant samples were cultured from potential sites of infection when clinically indicated.

Study Design

This study was retrospective and noninterventional. The primary endpoint was the occurrence of proven and probable IFI within 180 days from HSCT. IFI were classified according to the 2008 European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria [10]. Secondary endpoints included the use of empirical antifungal therapies and clinical outcome. Mortality was considered attributable to IFI when patients died within 12 weeks from the onset of fever with microbiological, histological, or clinical evidence of active IFI, and other potential causes of death could be ruled out by the attending physician. All causes of death within 12 weeks were recorded.

Statistical Analysis

Categorical variables were expressed as proportions and continuous variables as the median with the respective range. Comparisons were performed with the chi-square and the Mann-Whitney test for categorical and continuous variables, respectively. Probabilities of overall survival (OS) were estimated by the Kaplan-Meier method, using the log-rank test for univariate comparisons [11]. Cumulative incidence of IFI was estimated by the Gray test [12], where relapse/death without IFI were considered competing events. Risk factors for the development of IFI were then investigated by the univariate/multivariate competing risks regression model and the Fine-Gray test. Finally, the odds of an IFI occurrence (dependent categorical variable) was tested by the univariate/multivariate binary logistic regression model, considering as risk factors the previously reported covariates (independent categorical variables). Probability of fungal-free survival (FFS) was estimated using the Kaplan-Meier product limit estimate. FFS was a survival estimate and the events were either death or IFI (probable or proven). Patients who did not experience an event were censored at the time of last follow-up. All reported *P* values are 2-sided and were accepted as statistically significant if <.05. Potential risk factors for the occurrence of IFI were considered age (>50 versus ≤50 years), gender, disease phase (induction versus salvage), prophylaxis during chemotherapy treatment (itraconazole/fluconazole versus posaconazole), duration of neutropenia after chemotherapy treatment, days from diagnosis to HSCT, disease status at HSCT, type of donor (matched sibling versus matched unrelated donor [MUD] versus haploidentical/partially matched related donor [PMRD]), graft source (bone marrow versus peripheral blood stem cell versus umbilical cord blood), conditioning regimen (myeloablative versus reduced-intensity conditioning), use of antithymocyte globulin, and time to neutrophil engraftment after HSCT. Relationships between baseline characteristics, including the use of antifungal prophylaxis during induction/salvage treatment, and IFI were tested in univariate analysis by analysis of variance and chi-square test. Data were analyzed as of June 2016 by R 3.2.3 (R Foundation for Statistical Computing, Vienna-A, http://www.R-project.org).

RESULTS

Patient Characteristics

Overall, 284 AML patients who received up-front induction or salvage chemotherapy were screened. Ninety (32%) underwent antifungal prophylaxis with itraconazole, 80 (28%) with fluconazole, and 114 (40%) with posaconazole. Seventeen patients in the itraconazole/fluconazole group (group A) and 5 in the posaconazole group (group B) who developed probable or proven IFI during induction/salvage chemotherapy were excluded from the analysis. Of the remaining 262 patients who proceeded to allogeneic HSCT, 229 (87%) received post-transplantation antifungal prophylaxis with fluconazole and were eligible for data analysis, while 33 patients were excluded as they received different antifungal prophylaxes (Figure 1). The 2 treatment groups were similar with respect to age, gender, induction/salvage chemotherapy treatments, and median time to neutrophil recovery after chemotherapy (Table 1). Similarly, consolidation chemotherapy treatments, including anthracycline and cytarabine in the majority of the patients (162 of 229, 71%), were equally distributed between group A (n = 89) and group B (n = 73) (*P* = .470); purine analogues were administered to 41 patients (group A, n = 28; group B, n = 13), whereas 26 patients received other consolidation treatments. By contrast, most patients (84%) who received itraconazole/fluconazole were treated between 2001 and 2010 and 65% had received chemotherapy as salvage treatment whereas after 2010, most patients (60%) had received posaconazole and 82% received induction chemotherapy. The median duration of antifungal prophylaxis was significantly longer in

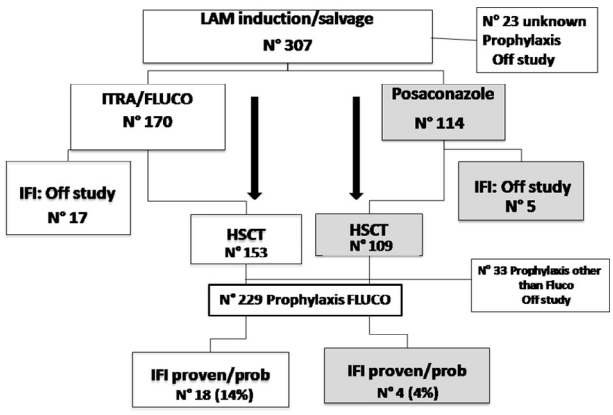


Figure 1. Flow diagram outlining patients' enrollment into the study protocol.

Table 1
Demographic and Clinical Characteristics of 229 Patients with AML Receiving either Fluconazole/Itraconazole or Posaconazole as Antifungal Prophylaxis during Induction/Salvage Chemotherapy Treatment

Characteristic	Antifungal Prophylaxis		*P* Value
	Itraconazole (n = 73) Fluconazole (n = 57)	Posaconazole (n = 99)	
Age, median (range), yr	48 (20-69)	49 (17-66)	.909
Gender			.505
Male	71	49	
Female	59	50	
Disease phase			.005
First induction	84 (65%)	81 (82%)	
Salvage	46 (35%)	18 (18%)	
Chemotherapy treatment			.276
Anthracycline-based	102 (78%)	74 (75%)	
Fludarabine-based	10 (8%)	11 (11%)	
High-dose cytarabine	14 (11%)	12 (12%)	
Other	4 (3%)	2 (2%)	
Duration of neutropenia, median (range), d	20 (9-50)	20 (8-50)	.513
Duration of antifungal prophylaxis, median (range), d	24 (3-55)	20 (5-60)	.019
EAT, n (%)	26 (20%)	15 (15%)	.494
Duration of EAT, median (range), d	12 (3-27)	13 (3-20)	.787

EAT indicates empirical antifungal treatment.

the itraconazole/fluconazole group (24 days versus 20 days, $P = .019$) and the median duration of empirical antifungal therapy was similar in both groups (Table 1). Patients in the itraconazole/fluconazole group were empirically treated with lipid formulation of amphotericin B (n = 15), echinocandins (n = 6), mold-active azoles (n = 4), and with combination therapy (n = 1), while in the posaconazole group, patients were administered liposomal amphotericin B (n = 10) and echinocandins (n = 5).

Patient and Transplantation Characteristics

Table 2 shows HSCT characteristics and clinical outcomes by antifungal prophylaxis; patients are divided into group A (itraconazole/fluconazole) and group B (posaconazole). Median time from the start of chemotherapy (induction/salvage treatment) to HSCT was significantly longer in group B than in group A (152 days versus 123 days, $P = .002$). More patients in group A had advanced disease (second complete remission/third complete remission/relapse) at transplantation, whereas more patients in group B received HSCT from alternative donors. Though marginally significant in difference, 55 and 46 patients in group A and B, respectively, received grafts from a MUD, 7 and 10 patients, respectively, from a haploidentical donor, and 1 and 4 patients, respectively, from a 1-antigen–mismatched related donor. More patients in group B received peripheral blood stem cells and the only 9 umbilical cord blood transplantations were in group A. Myeloablative conditioning was employed in 76% and 91% of the patients in groups A and B, respectively. The median time to neutrophil engraftment was not significantly different between the 2 groups. Graft failure was reported in 3 patients in group A and 1 in group B.

Impact of Azoles Prophylaxis on Post-HSCT Fungal Infections

Overall cumulative incidences of proven-probable IFI at 6 months and 1 year after HSCT for the entire study cohort were 8% and 10%, respectively. The cumulative incidences of IFI (proven or probable) were 13% at 6 months and 14% at 1 year in group A and 2% and 4%, respectively, in group B ($P = .012$) (Figure 2). The median time of onset of the 18 IFI in group A was day 35 as compared with day 209 in group B ($P = .195$). Seven IFI in the group A and 1 IFI in group B occurred before engraftment. All mold infections were caused by Aspergillus spp, whereas yeast infections were caused by C. albicans (n = 1) and Torulopsis glabrata (n = 1). Six-month and 1-year FFS rates were similar: 71% and 66% for group A and 84% and 75% for group B, respectively ($P = .139$) (Figure 3). Likewise, 6-month and 1-year OS rates were not significantly different between group A, 79% and 70%, and group B, 87% and 77%, in respectively ($P = .302$).

Risk Factors for Proven and Probable IFIs

Table 3 illustrates risk factors for proven and probable IFI in HSCT recipients. By multivariate analysis, the use of alternative donors (MUD: odds ratio [OR], 3.25; 95% confidence interval [CI], 1.13 to 9.39; haploidentical/PMRD: OR, 3.19; 95% CI, .70 to 14.48), previous antifungal prophylaxis with itraconazole/fluconazole (OR, 3.82; 95% CI, 1.25 to 11.67), and reduced-intensity conditioning (OR, 4.92; 95% CI, 1.95 to 12.39) were independent risk factors for the development of IFI after

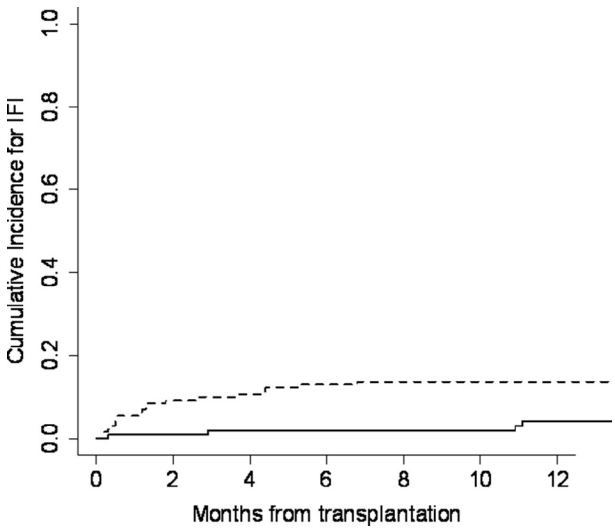


Figure 2. Cumulative incidence of IFI in AML patients submitted to allogeneic HSCT after receiving fluconazole/itraconazole (dashed line) or posaconazole (solid line) prophylaxis during induction/salvage chemotherapy ($P = .012$).

Table 2
Transplantation Characteristics and Outcomes according to the Antifungal Prophylaxis Received during AML Induction/Salvage Chemotherapy Treatment

Characteristic/Outcome	Group A n = 130	Group B n = 99	*P* Value
Interval between induction/salvage chemotherapy and HSCT, median (range), d	123 (32-368)	152 (22-369)	.002
Disease phase at transplantation			.056
CR1	85 (66%)	79 (80%)	
CR2-CR3	20 (15%)	8 (8%)	
PIF/relapse	25 (19%)	12 (12%)	
Type of HSCT			.057
Matched related	67 (52%)	39 (39%)	
Matched unrelated	55 (42%)	46 (47%)	
Mismatched related donor	8 (6%)	14 (14%)	
Graft source			.002
PBSC	89 (68%)	84 (85%)	
BM	32 (25%)	15 (15%)	
Cord blood	9 (7%)	—	
Preparative regimen			.005
MAC	99 (76%)	90 (91%)	
RIC	31 (24%)	9 (9%)	
Use of ATG	58 (45%)	61 (62%)	.560
Time to engraftment*, median (range)	17 (9-56)	15 (4-29)	.560
IFI			.043
Total	21 (16%)	7 (7%)	
Possible	3 (2%)	3 (3%)	
Probable	14 (11%)	3 (3%)	
Proven	4 (3%)	1 (1%)	
Time from HSCT to IFI, median (range), d	35 (7-208)	209 (8-337)	.195
Fungal species			1.000
Mold	16	4	
Yeast	2	—	
Site of infection			.445
Lung	13†	3	
CNS	2	—	
Blood	2	—	
Sinus	1	—	
Other	—	1	
Outcome			.060
Alive	66 (51%)	63 (64%)	
Died	64 (49%)	36 (36%)	

Group A received itraconazole/fluconazole and group B received posaconazole.
CR indicates complete remission; PIF, primary induction failure; PBSC, peripheral blood stem cells; BM, bone marrow; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; ATG, antithymocyte globulin; CNS, central nervous system.
* Engraftment (neutrophils > $.5 \times 10^9$/L).
† In 1 case combined with CNS involvement.

HSCT. Patients prepared for HSCT with a reduced-intensity conditioning were, however, significantly older (median age, 60 years) and mostly received itraconazole/fluconazole prophylaxis (31 of 40, 77%).

The potential synergistic effect of antifungal prophylaxis and empirical antifungal treatment (EAT) after induction/salvage chemotherapy on the occurrence of IFI after HSCT was also investigated. In the whole study cohort, the cumulative incidences of proven/probable IFI at 1 year after HSCT for patients who received or did not receive EAT were 8% and 14%, respectively ($P = .226$). In a patient subgroup analysis of group A, itraconazole/fluconazole did not show any cumulative effect with EAT on post-HSCT incidence of IFI: 13% versus 15%, respectively, in patients who received and did not receive EAT ($P = .774$). However, in group B, posaconazole and EAT showed a marginal statistical significance with a cumulative incidence of IFI of 2% and 13%, respectively, for patients who received or did not receive EAT ($P = .057$).

Finally, the cumulative incidence of developing IFI was investigated by the Fine and Gray competing risk regression model to identify the effect of prognostic factors on the cumulative incidence function for competing risks data. Multivariate analysis showed that main determinants associated with higher risk of developing IFI were the use of alternative donors (MUD/haploidentical/PMRD versus sibling: (subdistribution hazard ratio [SDHR], 2.40; 95% CI, 1.41 to 4.09), antifungal prophylaxis with itraconazole/fluconazole before HSCT (SDHR, 3.52; 95% CI 1.19 to 10.39), and reduced-intensity conditioning (SDHR, 3.80; 95% CI, 1.72 to 8.41).

Transplantation Clinical Outcomes

After a median follow-up of 63 months (range, 5 to 160 months) after HSCT, 129 patients were alive: 66 in group A and 63 in group B. Overall, 64 patients in group A died, 38 with progressive disease and 26 from transplantation-related complications, whereas 36 patients in group B died, 28 with progressive disease and 8 of transplantation-related complications. Five of the 18 patients (28%) with IFI in group A and 1 of the 4 patients (25%) with IFI in group B died of fungal infection. The Kaplan-Meier estimate of OS at 5 years after HSCT was 55% for the entire study population, and it was significantly worse for patients who developed IFI after HSCT (9% versus 60%, $P < .001$) and for patients who underwent HSCT after salvage chemotherapy (34% versus 63%, $P < .001$).

DISCUSSION

It is widely assumed that induction and salvage chemotherapy represent the treatment phases with the highest risk of developing IFI for patients with AML. Thus, antifungal

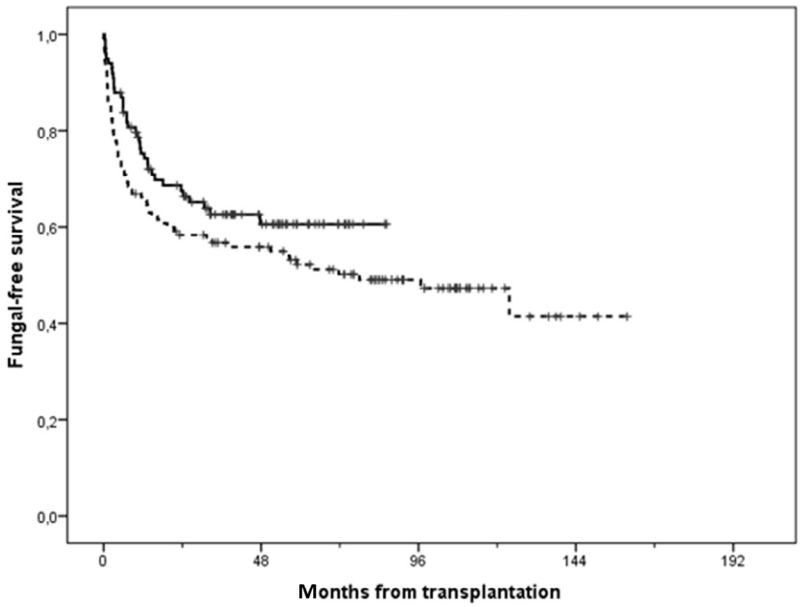


Figure 3. Fungal-free survival of AML patients submitted to allogeneic HSCT after receiving fluconazole/itraconazole (dashed line) or posaconazole (solid line) prophylaxis during induction/salvage chemotherapy ($P = .139$).

prophylaxis with a mold-active agents is of upmost importance [13]. A consistent number of studies have documented that posaconazole is highly effective in preventing IFI in AML. We then hypothesized that this protective effect may have translated into a long-lasting benefit in later phases of the disease, including the post-transplantation period. To address this issue, a study cohort of 229 adult AML patients were divided into 2 groups. Before HSCT, group A received conventional azoles (fluconazole/itraconazole) and group B received posaconazole during induction/salvage chemotherapy. Both groups received prophylactic conventional azoles after HSCT.

Our study showed that 1-year cumulative incidence of proven/probable IFI after HSCT was significantly lower in group B (4%) than in group A (14%). The incidence of IFI in group B was superimposable to those reported by Cornely et al. (2%) [5] and Pagano et al. (2.7%) [6] with posaconazole prophylaxis in AML patients and by Winston et al. in HSCT recipients (7.5%) [14]. Multivariate analysis confirmed that patients receiving conventional azoles had a 4-fold greater risk of IFI after HSCT compared with those who received posaconazole during induction/salvage treatments. These findings suggest that posaconazole prophylaxis before HSCT may significantly reduce the fungal burden, thereby limiting the development of overt infection in the post-transplantation follow-up period. Furthermore, we also observed a possible synergistic effect of posaconazole with EAT during induction/salvage chemotherapy. This finding may reinforce the hypothesis that better control of fungal growth during the phases of higher risk of developing IFI may also effectively contribute to lowering it during subsequent treatments, including HSCT.

Interestingly, we reported a late onset of IFI (median day +209 after HSCT) in group B even though the very low number of events (n = 4) may have influenced our findings. However, the reduced incidence of IFI in group B was not associated

Table 3
Univariate and Multivariate Analysis of Risk Factors for Proven/Probable IFI among 229 Patients with AML Receiving Allogeneic HSCT

Variable	Univariate		Multivariate	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Time interval from chemotherapy to HSCT	.54 (.22-1.35)	.191		
Disease phase of AML				
Salvage versus induction	1.54 (.61-3.87)	.358		
Donor type				
MUD versus MSD	3.25 (1.13-9.39)	**.029**	3.76 (1.25-11.36)	**.019**
Haplo/PMRD versus MSD	3.19 (.70-14.48)	.133	5.52 (1.07-28.38)	**.041**
Status at HSCT				
Relapse versus CR	1.61 (.55-4.67)	.382		
Stem cell source				
PBSC versus BM	.52 (.17-1.59)	.248		
Conditioning				
RIC versus MAC	4.92 (1.95-12.39)	**.001**	4.16 (1.56-11.09)	**.004**
Antifungal prophylaxis				
Itra/fluco versus posa	3.82 (1.25-11.67)	**.019**	3.72 (1.15-12.01)	**.028**

Bold indicates statistical significance.
MSD indicates matched sibling donor; Haplo, haploidentical; MSD, matched sibling donor; Itra, itraconazole; fluco, fluconazole; posa, posaconazole.

with better clinical outcome after HSCT. This undoubtedly may have been partly due to potential confounding factors, including the more frequent use of alternative donors (in two-thirds of the patients) in group B. Most importantly, overall, our study showed that the occurrence of IFI remains an adverse variable for the clinical outcome of allogeneic HSCT. Therefore, efforts to maximize preventive measures of fungal infections appear of paramount importance.

Limitations of our study should be acknowledged. Given its retrospective nature, some heterogeneities between the 2 patient groups were inevitable. The year of AML diagnosis significantly differed over the 14-year study period. Sixty percent of the patients in group B were enrolled during the past 5 years (2011 to 2015) whereas the vast majority (84%) of the patients (84%) in group A were diagnosed between 2001 and 2010. This difference may have been clinically relevant given the recent remarkable improvements in supportive care and diagnostic options including, noninvasive serological tests combined with high-resolution CT scans. More patients in group A were evaluated after salvage chemotherapy than in group B (35% versus 18%, $P = .005$). The potential effect of disease phase on the risk of IFI after HSCT was, however, excluded by univariate analysis.

In conclusion, the present study showed that the effects of antifungal prophylaxis with posaconazole during induction/salvage chemotherapy in AML patients may lead to long-lasting benefits, including a reduced risk of IFI in patients who proceed to allogeneic HSCT. Prospective randomized large trials are warranted to confirm our findings.

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