

Evaluation of the Practice of Antifungal Prophylaxis Use in Patients With Newly Diagnosed Acute Myeloid Leukemia: Results From the SEIFEM 2010-B Registry

Livio Pagano,¹ Morena Caira,¹ Anna Candoni,² Franco Aversa,³ Carlo Castagnola,⁴ Cecilia Caramatti,⁵ Chiara Cattaneo,⁶ Mario Delia,⁷ Maria Rosaria De Paolis,⁸ Roberta Di Blasi,¹ Luigi Di Caprio,⁹ Rosa Fanci,¹⁰ Mariagrazia Garzia,¹¹ Bruno Martino,¹² Lorella Melillo,¹³ Maria Enza Mitra,¹⁴ Gianpaolo Nadali,¹⁵ Annamaria Nosari,¹⁶ Marco Picardi,¹⁷ Leonardo Potenza,¹⁸ Prassede Salutati,¹⁹ Enrico Maria Trecarichi,²⁰ Mario Tumbarello,²⁰ Luisa Verga,²¹ Nicola Vianelli,²² and Alessandro Busca,²³ for the SEIFEM Group^a

¹Istituto di Ematologia, Università Cattolica del Sacro Cuore, Roma; ²Clinica di Ematologia, Università di Udine; ³Istituto di Ematologia, Università di Perugia; ⁴Dipartimento Onco-Ematologico Fondazione ICRRS Policlinico San Matteo, Pavia; ⁵Sezione di Ematologia, Università di Parma; ⁶Divisione di Ematologia, Spedali Civili di Brescia; ⁷Sezione di Ematologia, Dipartimento dell’Emergenza e dei Trapianti d’Organo-Università di Bari; ⁸Dipartimento di Ematologia, Ospedale di Lecce; ⁹Istituto di Ematologia, Università di Tor Vergata, Roma; ¹⁰Unità Operativa di Ematologia, Università di Firenze; ¹¹Divisione di Ematologia, Ospedale San Camillo, Roma; ¹²Divisione di Ematologia, Azienda Ospedaliera “Bianchi Melacrino Morelli,” Reggio Calabria; ¹³Divisione di Ematologia, IRCCS Ospedale S. Giovanni Rotondo; ¹⁴Divisione di Ematologia e TMO, Policlinico di Palermo; ¹⁵UOC Ematologia, Azienda Ospedaliera Universitaria Integrata di Verona; Università di Parma; ¹⁶Divisione di Ematologia e Centro Trapianti Midollo, Ospedale Niguarda Ca’ Granda, Milan; ¹⁷Divisione di Ematologia, Dipartimento di Biochimica e Biotecnologie Mediche, Università Federico II, Napoli; ¹⁸Dipartimento di Oncologia ed Ematologia, Università di Modena e Reggio Emilia, Azienda Ospedaliera Policlinico, Modena; ¹⁹Dipartimento di Ematologia Clinica, Ospedale Santo Spirito, Pescara; ²⁰Istituto di Malattie Infettive, Università Cattolica del Sacro Cuore, Roma; ²¹Unità di Ematologia, Università di Milano, Ospedale S.Gerardo, Monza; ²²Istituto di Ematologia ed Oncologia Clinica “Lorenzo e Ariosto Seràgnoli,” Ospedale S.Orsola-Malpighi, Università di Bologna, and ²³Dipartimento di Ematologia, Ospedale S.Giovanni Battista, Torino, Italy

Background. To analyze the efficacy of antifungal prophylaxis (AFP) with posaconazole and itraconazole in a real-life setting of patients with acute myeloid leukemia (AML) during the first induction of remission.

Methods. From January 2010 to June 2011, all patients with newly diagnosed AML were consecutively registered and prospectively monitored at 30 Italian hematological centers. Our analysis focused on adult patients who received intensive chemotherapy and a mold-active AFP for at least 5 days. To determine the efficacy of prophylaxis, invasive fungal disease (IFD) incidence, IFD-attributable mortality, and overall survival were evaluated.

Results. In total, 515 patients were included in the present analysis. Posaconazole was the most frequently prescribed drug (260 patients [50%]) followed by fluconazole (148 [29%]) and itraconazole (93 [18%]). When comparing the groups taking posaconazole and itraconazole, there were no significant differences in the baseline clinical characteristics, whereas there were significant differences in the percentage of breakthrough IFDs (18.9% with posaconazole and 38.7% with itraconazole, $P < .001$). The same trend was observed when only proven/probable mold infections were considered (posaconazole, 2.7% vs itraconazole, 10.7%, $P = .02$). There were no significant differences in the IFD-associated mortality rate, while posaconazole prophylaxis had a significant impact on overall survival at day 90 ($P = .002$).

Conclusions. During the last years, the use of posaconazole prophylaxis in high-risk patients has significantly increased. Although our study was not randomized, it demonstrates in a real-life setting that posaconazole prophylaxis confers an advantage in terms of both breakthrough IFDs and overall survival compared to itraconazole prophylaxis.

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^aThe members of the SEIFEM Group are listed in the Acknowledgments.

Correspondence: Livio Pagano, MD, Istituto di Ematologia, Università Cattolica del Sacro Cuore, Largo Francesco Vito 1, Roma I-00168, Italia (lpagano@rm.unicatt.it).

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Invasive fungal diseases (IFDs) are a leading cause of morbidity and mortality in severely neutropenic patients, especially in patients with acute myeloid leukemia (AML) and allogeneic hematopoietic stem cell transplant (allo-HSCT) recipients [1–6]. In particular, first induction chemotherapy may be considered the highest risk phase of treatment for development of IFDs in patients with AML [7, 8].

To reduce the incidence of IFDs, various strategies have been investigated and various results have been obtained. Previous meta-analytic studies support the use of antifungal prophylaxis in allo-HSCT patients and suggest possible benefits in other patients, particularly those that have a high risk of developing IFDs [9, 10].

In the last few years, posaconazole has been demonstrated to significantly impact the current use of antifungal prophylaxis. Two randomized clinical trials demonstrated that posaconazole prophylaxis was superior to fluconazole or itraconazole in reducing the incidence of IFDs in high-risk patients, namely, AML patients and allo-HSCT recipients with severe graft-versus-host disease [11, 12]. Accordingly, international guidelines highly recommend the use of posaconazole prophylaxis in AML patients [13–15]. To confirm these results, some studies in real-life settings evaluating the potential benefits of posaconazole have been reported [16–21].

The aim of the present study was to describe the use of antifungal prophylaxis in current clinical practice and to investigate the impact in terms of IFD incidence and clinical outcome. In particular, we focused on posaconazole and itraconazole because these agents have antimold activity, and invasive aspergillosis is the most frequent IFD in AML patients.

PATIENTS AND METHODS

The present prospective study was conducted in 30 hematology wards of tertiary care centers or university hospitals located throughout Italy from January 2010 to June 2011. All adult patients with newly diagnosed AML undergoing first remission-induction chemotherapy who received antifungal prophylaxis were included in the registry and followed up. Prophylaxis, which consisted of 400 mg of fluconazole daily, a 2.5 mg/kg oral itraconazole solution twice daily, or 200 mg of posaconazole thrice daily, was started 1–3 days prior to chemotherapy and continued until neutrophil recovery reached $>0.5 \times 10^9$ neutrophils/L or when therapy was interrupted because of a suspected or confirmed IFD.

The data were entered prospectively into case report forms. The ethics committee of each participating site approved the use of the Epidemiological Survey on Invasive Fungal Infections in Hematological Malignancies (SEIFEM) registry.

This was a noninterventional study. Accordingly, the enrollment of a patient had no impact on the standard clinical

practice of the hematology units that were involved. The last patient was recorded on 30 June 2011 and follow-up was completed on 30 September 2011. A minimum follow-up of 90 days after completion of chemotherapy was requested.

For each patient, baseline data were recorded at the time of admission including age, sex, weight, occupation, AML subtype, and comorbidities. The following additional information was also collected: risk factors (eg, central venous catheter, level and duration of neutropenia), performance status (according to World Health Organization [WHO] grading), AML treatment, and antifungal prophylaxis (administered drug and duration).

The diagnostic workup was similar among all participating centers and included the following tests: nasal, pharyngeal, and rectal swabs at the time of admission; blood cultures and chest radiography at onset of fever; galactomannan assays twice weekly; and a chest computed tomography (CT) scan on the fourth to seventh day of fever. Additional examinations (eg, abdominal ultrasound scan, sinus or brain CT, skin biopsy, bronchoalveolar lavage, or fundus examination) were performed as required.

The IFD incidence was assessed within the first 30 days after chemotherapy had ended. Invasive fungal diseases were classified according to the 2008 EORTC/MSG (European Organization for Research and Treatment of Cancer/Mycoses Study Group) criteria [22].

The registry also included the following data regarding antifungal therapy: employed drugs, dosage, and approach (eg, empirical, preemptive, or target treatment) [23].

Mortality was considered attributable to the IFD (IFD-attributable mortality) when patients died within 12 weeks from the onset of a fever with microbiological, histological, or clinical evidence of an active IFD and if other potential causes of death could be excluded by the responsible physician [24]. All causes of death within 12 weeks were recorded (overall mortality).

STATISTICAL ANALYSIS

Continuous variables were compared using Student *t* test (normally distributed variables) or the Mann-Whitney *U* test (nonnormally distributed variables). Categorical variables were evaluated using the χ^2 test or 2-tailed Fisher exact test. Values are expressed as the mean \pm standard deviation (SD) or median (range; continuous variables) or as a percentage of the group from which they were derived (categorical variables). The effect of type of drug used for prophylaxis (posaconazole or itraconazole) on survival of the patients was first analyzed with the Kaplan-Meier method and, in addition, with a Cox proportional hazard model that was not adjusted for any variable because no statistically significant differences among

Table 1. Clinical Characteristics of the Patients Treated in the 2 Study Arms

	Itraconazole (n = 93)	Posaconazole (n = 260)	P Value
Age, median (IQR)	60 (49–67)	56 (44–65)	.08
Male	48 (52.2%)	117 (45.0%)	.23
Duration of prophylaxis	21 (15–26)	21 (16–28)	.70
Deep neutropenia (PMN < 500/ μ L >7 d)	87 (93.5%)	240 (92.3%)	.69
Duration of neutropenia, d, median (IQR)	22 (16–27.5)	23 (18–29)	.25
CVC	75 (80.6%)	200 (76.9%)	.45
Performance status ^a			
0–1	72 (77.4%)	204 (78.5%)	.83
2–4	21 (22.6%)	56 (21.5%)	
Anthracycline-based chemotherapy	81 (87.1%)	242 (93.1%)	.08
Primary AML	68 (73.1%)	198 (76.2%)	.56

Data are presented as No. (%) unless otherwise specified.

Abbreviations: AML, acute myeloid leukemia; CVC, central venous catheter; IQR, interquartile range; PMN, polymorphonuclear cells.

^a According to World Health Organization grading.

clinical and demographic variables analyzed were observed between the 2 groups (see Table 1).

Two-tailed tests were used to determine statistical significance; a *P* value of <.05 was considered significant. All statistical analyses were performed with the Intercooled Stata software program, version 11 for Windows (StataCorp, College Station, Texas).

RESULTS

Over an 18-month period, 703 adult patients with newly diagnosed AML were enrolled in the study. In total, 127 patients received only supportive care or palliative treatments and were excluded from the present analysis. The remaining 576 AML patients received conventional intensive chemotherapy. Patients who did not receive prophylaxis (33 cases), those who received topical polyenes (16 cases), or those who received <5 days of systemic prophylaxis due to early interruption (7 posaconazole, 3 fluconazole, or 2 itraconazole) were considered not eligible and were excluded from the present analysis (61 patients; Figure 1).

Among the 515 evaluable patients who were treated with systemic prophylaxis, 260 received posaconazole prophylaxis (50.4%), 148 fluconazole (28.7%), and 93 itraconazole (18%); 14 patients received other antifungal agents (5 voriconazole, 1 caspofungin, and 8 liposomal amphotericin B). An overall progressive increase in the use of posaconazole prophylaxis

was observed during the 18 months of the study, while a fairly constant use of itraconazole and a marked reduction in the fluconazole prophylaxis was observed (Figure 2).

The overall IFD incidence (possible, probable, and proven) observed in this cohort of patients was 22.3% (115 cases over 515 patients). Sixty percent of observed IFDs (62 cases) were considered possible cases.

The aim of present study was to compare the 353 patients who received the antimold prophylaxis posaconazole (n = 260) to those who received itraconazole (n = 93).

Among the participating centers, no differences emerged in the distribution of patients treated with either posaconazole or itraconazole.

The primary characteristics of the 2 groups of patients are shown in Table 1. No statistically significant differences emerged in terms of performance, sex, percentage of deep neutropenic patients (neutrophils <0.5 $\times 10^9$ /L), duration of neutropenia >7 days, prophylaxis duration, or the use of central venous catheter. The posaconazole arm included younger subjects and more patients who were treated with anthracycline-based chemotherapy protocols. The 2 populations also had a comparable distribution of AML morphological and biological characteristics (eg, promyelocytic morphology and cytogenetic patterns).

Overall, the IFD incidence in the itraconazole arm was 38.7% (36/93 patients), which is significantly higher than that observed in the posaconazole arm (18.9% [49/260 patients], *P* < .001; Table 2). Excluding possible cases in both groups, the same trend was observed in terms of proven/probable mold infections, which were 10.7% in the itraconazole group and 2.7% in the posaconazole group (*P* = .02).

In both groups, all proven/probable mold infections were caused by *Aspergillus* strains, except for 1 case of *Fusarium* species infection in the itraconazole group. Among the 6 proven yeast infections, 4 were caused by *Candida* strains (2 in each arm, respectively), 1 by *Trichosporon* (posaconazole arm), and 1 by *Geotrichum* (itraconazole arm).

Despite antifungal prophylaxis, 110 of 353 patients (31.2%) required a subsequent antifungal treatment; a significantly reduced use of frontline antifungal therapy was observed in the posaconazole arm (69 patients [26.6%] in the posaconazole group vs 41 patients [45.1%] in the itraconazole group; *P* = .001). Although there were no differences in the use of empirical therapy, both preemptive and target approaches were more frequently used in the itraconazole arm (14% in the itraconazole arm vs 4.6% in the posaconazole arm, *P* = .003; and 7% in the itraconazole arm vs 1.5% in the posaconazole arm, *P* = .004, respectively).

Forty-nine of the 74 patients who started with a frontline empirical approach (21 in the itraconazole arm and 53 in the posaconazole arm) had a subsequent IFD diagnosis (16 in

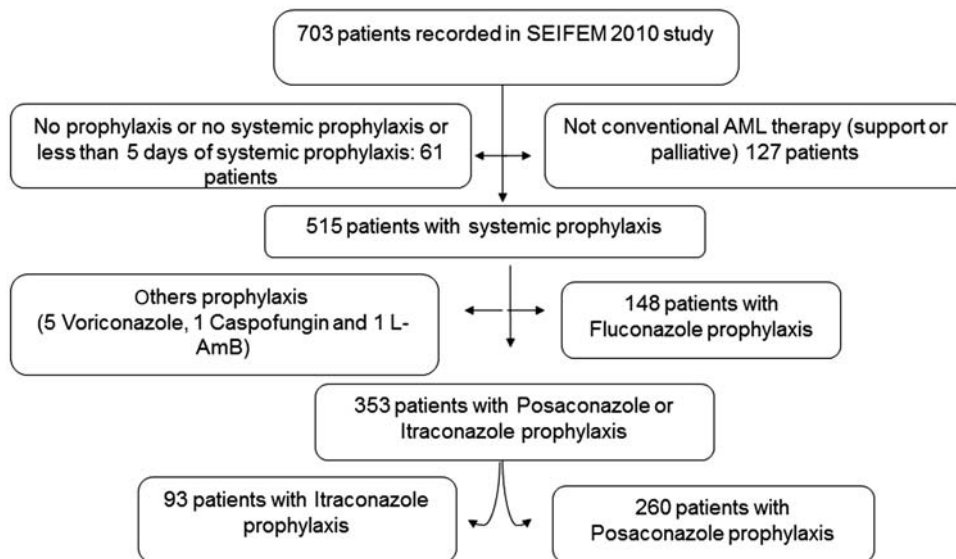


Figure 1. Flow chart of the study patients. Abbreviations: AML, acute myeloid leukemia; L-AmB, liposomal amphotericin B.

the itraconazole arm and 33 in the posaconazole arm). In 25 patients (5 in the itraconazole arm and 20 in the posaconazole arm), diagnostic tests did not reveal any fungal disease, and these patients were registered as FUO (fever of unidentified origin; 7.3%).

There was a trend toward a reduced duration of antifungal treatment (empirical, preemptive, and target) in the posaconazole arm ($P = .05$). A significant increase in the use of AmB lipid compounds (eg, L-AmB or lipid complex amphotericin B)

was observed after prophylaxis failure in the posaconazole arm.

Overall, mortality was significantly reduced in the posaconazole arm (3.5% vs 9.7%, $P = .02$; Table 2). Kaplan-Meier survival estimates at 90 days confirmed the lower risks of mortality associated with posaconazole prophylaxis ($P = .002$; Figure 3). The Cox proportional hazards model demonstrates that the mortality risk for the posaconazole group is 0.37 times the risk estimated for the itraconazole group ($P = .003$).

The overall and IFD attributable mortality rates were both higher in the itraconazole arm (Table 2).

Nine patients (7 in posaconazole arm, 2.5% and 2 in itraconazole arm, 2.1%) were not considered eligible for the study because they received <5 days of prophylaxis due to side effects. No severe adverse events were observed (WHO grade > 3) that were attributable to posaconazole or itraconazole toxicity. No cases of increased cardiotoxicity for concomitant anthracycline-based chemotherapy were observed.

DISCUSSION

Two recent randomized trials demonstrated that posaconazole prophylaxis has a higher efficacy and an excellent safety profile in high-risk patients such as those with AML and allo-HSCT recipients with graft-versus-host disease [11, 12]. Particularly in AML patients, posaconazole prophylaxis significantly impacted both the IFD incidence and the patients' overall survival. Thus, it may be a valid alternative to old prophylactic regimens. Additionally, international guidelines recommend this approach because of the high level of evidence [13–15].

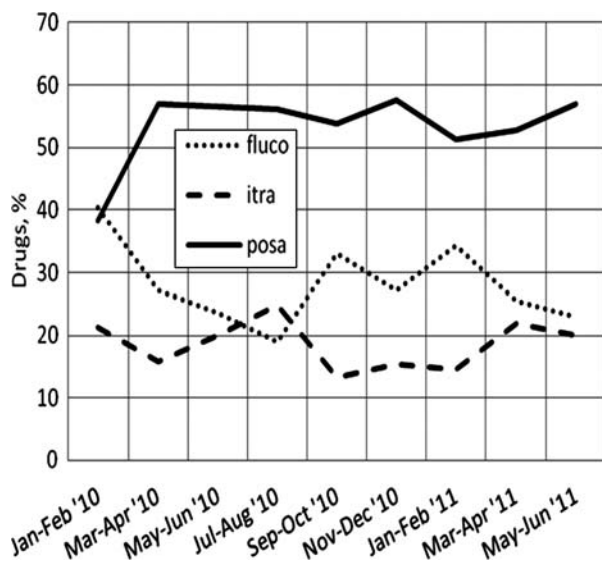


Figure 2. Trends in the use of different antifungal drugs used as prophylaxis during the study period. Abbreviations: fluco, fluconazole; itra, itraconazole; posa, posaconazole.

Table 2. Invasive Fungal Disease Incidence, Treatment, and Outcome in the 2 Study Groups

	Itraconazole (n = 93)	Posaconazole (n = 260)	P Value
All IFDs	36 (38.7%)	49 (18.9%)	<.001
Possible mold IFDs	23 (24.7%)	39 (15.0%)	.03
Probable and proven mold IFDs	10 (10.7%)	7 (2.7%)	.02
Proven yeast IFDs	3 (3.2%)	3 (1.1%)	.18
FUO who received antifungal therapy	5 (5.4%)	20 (7.6%)	.45
Frontline antifungal approach of IFD			.001
Empirical	21 (22.6%)	53 (20.3%)	.49
Preemptive	13 (14.0%)	12 (4.6%)	.003
Target	7 (7.0%)	4 (1.5%)	.004
Median duration of antifungal treatment, d (IQR)			.05
Empirical	12 (8.5–19)	11 (7–14)	.27
Preemptive	15 (9.5–24)	14 (10–26)	.62
Target	18 (5–20)	12.5 (10–18)	.46
Antifungal drugs employed			
Lipid AmB (L-AmB, ABLC)	17/41 (41.5%)	42/69 (60.9%)	.05 ^c
Caspofungin	12/41 (29.0%)	18/69 (26.1%)	.72 ^c
Voriconazole	9/41 (22.0%)	8/69 (11.6%)	.15 ^c
Other	3 ^a /41 (7.3%)	1 ^b /69 (1.4%)	.14 ^d
Overall mortality	9/93 (9.7%)	9/260 (3.5%)	.02
Attributable mortality			.04
For molds	4/93 (4.3%)	0/260 (0%)	.005
For yeasts	0/93 (0%)	2/260 (0.8%)	.54

Abbreviations: ABLC, lipid complex amphotericin B; FUO, fever of unidentified origin; IFD, invasive fungal disease; IQR, interquartile range; L-AmB, liposomal amphotericin B.

^a Anidulafungin, posaconazole (from prophylactic to therapeutic doses 400 mg twice a day), itraconazole.

^b Posaconazole (from prophylactic to therapeutic doses 400 mg twice a day).

^c χ^2 test.

^d Fisher exact test.

In the last few years, some retrospective studies conducted in real-life settings have been published to confirm the results obtained in the 2 prospective clinical trials [16–20]. In these studies, the reported incidence of proven/probable IFDs ranges from 0% to 5%, which confirms the efficacy of posaconazole prophylaxis. However, these studies consisted of small case series, and the patients were almost always compared to historical controls or to patients receiving drugs without antimold activity (ie, fluconazole or oral polyenes).

One of the criticisms raised by the study performed by Cornely et al was the lack of a direct comparison between

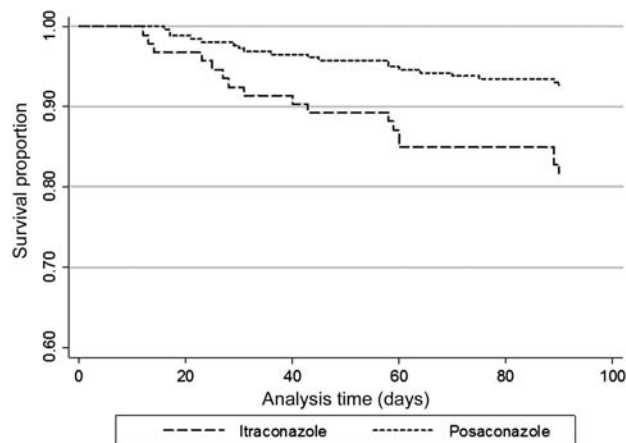


Figure 3. Survival functions among patients treated with posaconazole or itraconazole prophylaxis.

posaconazole and itraconazole [25]. In our study, we focused our attention on 2 antifungal agents with known efficiencies against molds in a homogeneous cohort of patients who were newly diagnosed with AML and who received standard chemotherapy.

Our data confirm the previous results of both randomized trials and real-life studies that posaconazole prophylaxis reduces the overall incidence of IFDs. Furthermore, posaconazole significantly reduced the number of febrile episodes requiring intravenous antifungal treatment. This may also result in an economical advantage. It is unknown whether the patients who developed breakthrough IFDs were those who did not achieve adequate posaconazole plasma levels because therapeutic drug monitoring in clinical practice is unavailable in the majority of the participating centers.

Recent literature has debated whether the positive results observed with posaconazole reflect a true reduction in the number of IFD cases or rather the ability of posaconazole to suppress galactomannan expression [26, 27]. The latter would translate to an increased proportion of possible cases (with radiological signs only) [28]. In our experience, the number of possible cases was reduced, and this observation supports the idea that posaconazole efficiently prevents IFDs.

However, the preemptive approach (based either on a galactomannan test or on CT scan positivity) was less frequently used in the posaconazole arm. Furthermore, it is worth noting that posaconazole prophylaxis did not reduce the use of the empirical approach. Twenty patients in the posaconazole arm received an empirically administered antifungal therapy but were classified as FUO.

The different prophylactic approaches did not impact the spectrum of infection nor the response to treatment. Notably, the overall IFD-attributable mortality rate was comparable

between the 2 groups, while the number of deaths attributable to molds was significantly lower after posaconazole therapy. This is in contrast to a previous observation that reported a higher mortality rate due to breakthrough IFDs after posaconazole prophylaxis [29]. It is worth noting that few rare fungal agents were isolated and no cases of Mucorales were observed in both prophylactic arms.

The most frequently used antifungal agents after azole prophylaxis failure were lipid AmB compounds; a significantly higher percentage was used in the posaconazole arm. This could be due to the higher percentage of the use of an empirical approach that was observed in our series. It is also possible that voriconazole is not considered the best frontline approach for invasive aspergillosis after the failure of a highly efficacious azole prophylaxis by some physicians (ie, with posaconazole). This hypothesis should be confirmed by an additional study.

Similarly to Cornely and colleagues [11], we found that posaconazole prophylaxis was able to lower overall mortality, and the mortality risk was 0.37 times the risk estimated for the itraconazole group in a homogeneous cohort of AML patients. It has recently been proven that IFDs may continue to affect a patient's outcome despite survival of the initial infection because of its influence on subsequent chemotherapy regimens [30, 31].

This survey analyzed the use of different prophylactic regimens utilized in a real-life pattern. It is remarkable that posaconazole, which is considered the drug of choice for AML, was utilized in only 50% of our patients. However, there was an increasing trend in use from 20% to 65% during the study period (from January 2010 to June 2011). On the other hand, approximately 7% of patients did not receive systemic prophylaxis (no prophylaxis or topic polyenes). This could be justified by the fact that the group with no prophylaxis included many patients with acute promyelocytic leukemia, which is a form treated with chemotherapy that does not usually induce deep and prolonged neutropenia.

Conversely, the exact reason for the use of the different azoles for prophylaxis in the same center is unclear. No significant differences in the clinical characteristics emerged between cases treated with posaconazole and those with itraconazole. The only trend observed was that patients treated with itraconazole were older. Therefore, it can be speculated that physicians prefer to use newer triazoles in younger patients undergoing more aggressive chemotherapies to reduce infectious risks and possible negative effects on their treatment schedule. It is not possible to exclude the possibility that this patchy use of azoles could also be due to economic issues.

Despite the limitations of the study design (observational, not interventional and unequal sample sizes in the posaconazole and itraconazole groups), our prospectively collected data support the use of posaconazole prophylaxis in AML patients

during induction chemotherapy because the drug appeared to provide advantages in terms of both IFD prevention and survival. The optimal management of breakthrough infections remains to be determined as well as the usefulness and reliability of diagnostic tools in this context [25].

Notes

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Potential conflicts of interest. L. Pagano has received honoraria from Gilead Sciences, Schering-Plough, Astellas Pharma, Merck, and Pfizer Pharmaceuticals. M. C. has received honoraria from Gilead Sciences, Merck, Pfizer Pharmaceuticals, and Schering-Plough. F. A. has received honoraria from Gilead Sciences, Schering-Plough-Merck and Pfizer Pharmaceuticals and has been a speaker for Gilead Sciences, Schering-Plough-Merck, Pfizer Pharmaceuticals, and Cephalon. M. D. has received honoraria from Gilead Sciences and Merck. L. Potenza has received honoraria from Gilead Sciences and Merck. R. F. has received honoraria from Schering-Plough and Merck. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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