A Single Center Experience for Antifungal Prophylaxis in Patients with Acute Myelogenous Leukemia

Gökhan Metan · Zeynep Türe · Çiğdem Pala ·
Leylagül Kaynar · Afra Yıldırım · Ferhan Elmalı ·
Nuri Tutar · Nuran Yozgat · Bülent Eser

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Abstract We aimed to provide real-life information about the effectivity of different types of primary antifungal prophylaxis (AFP) in patients with acute myeloid leukemia (AML). Records of AML patients who received remission-induction chemotherapy between June 2010 and February 2013 were retrospectively reviewed. A total of 85 AML remission-induction chemotherapy cycles were identified in 80 patients. Fluconazole prophylaxis (FP) was administered in 29 cycles, and posaconazole prophylaxis was given in 56 cycles. Failure in the AFP was observed in 45 (57.9 %) out of 85 cycles. Any type of invasive fungal diseases were detected in 15 (26.8 %) out of 56 cycles receiving posaconazole and 15 (51.7 %) out of 29 cycles receiving fluconazole ($p = 0.023$). Relapsing or refractory AML, longer duration of neutropenia and FP were more

common in patients with AFP failure. Multivariate logistic regression analysis showed that type of AFP (odds ratio (OR) 3.63; 95 % confidence interval (CI) 1.19–11.07), presence of neutropenia longer than 21 days (OR 3.96; 95 % CI 1.36–11.46), and refractory or relapsing AML (OR 6.09; 95 % CI 2.09–17.73) were independent factors associated with failure of AFP. We observed superiority of posaconazole on fluconazole in the prophylaxis of AML patients receiving remission-induction chemotherapy.

Keywords Posaconazole · Fluconazole · Antifungal prophylaxis · Invasive fungal disease · Acute myelogenous leukemia

Introduction

Patients receiving remission-induction chemotherapy for acute myelogenous leukemia (AML) are at high for invasive fungal diseases (IFDs). As the response to antifungal treatment is usually poor and the cost of treatment of IFDs is high, antifungal prophylaxis (AFP) has become the standard of care in such kind of high risk patients. Fluconazole prophylaxis (FP) was used to prevent IFDs for a long time, however, the increasing rate of fluconazole resistant *Candida* spp. and lack of activity against *Aspergillus* species cause concern about the effectivity of FP [1, 2]. Posaconazole is a new azole agent which provides broad-spectrum coverage against several yeasts and moulds, including fluconazole-resistant *Candida* spp. and *Aspergillus* [3]. The randomized clinical trial conducted by Cornelly and colleagues [4], showed superior efficacy of posaconazole prophylaxis (PP) compared with fluconazole/itraconazole in preventing proven and probable IFDs (occurrence in 2 vs. 8 % of patients, respectively) and

G. Metan (✉) · Z. Türe
Department of Infectious Diseases and Clinical Microbiology,
Gevher Nesibe Hastanesi, Enfeksiyon Hastalıkları Kliniği,
Erciyes Üniversitesi Tıp Fakültesi, Kat:10 Talas Yolu,
38039 Kayseri, Turkey
e-mail: gokhanmetan@gmail.com; gmetan@erciyes.edu.tr

Ç. Pala · L. Kaynar · B. Eser
Department of Hematology, Erciyes University, Kayseri, Turkey

A. Yıldırım
Department of Radiology, Erciyes University, Kayseri, Turkey

F. Elmalı
Department of Biostatistics, Erciyes University, Kayseri, Turkey

N. Tutar
Department of Chest Diseases, Erciyes University, Kayseri,
Turkey

N. Yozgat
Hospital Pharmacy Unit, Faculty of Medicine, Erciyes
University, Kayseri, Turkey

reducing overall mortality in patients with AML or myelodysplastic syndrome. After then, posaconazole has become the standard of care for the AFP in AML patients receiving remission-induction chemotherapy [5]. However, factors such as epidemiologic features of the center, duration of neutropenia or response to the treatment for AML can influence the incidence of IFDs along with the type of the antifungal prophylaxis. Recently, a prospective observational study reported no difference in the incidence of IFDs in AML patients receiving remission-induction or consolidation therapy regarding to the type of AFP contrast to numerous studies in this field [6–10]. Also, a study from Turkey which included 50 patients with AML did not find any difference between posaconazole and fluconazole in terms of AFP failure [11].

Erciyes University Hospital is a 1,300-bed tertiary center serving with 38-bed hematology clinics and 27-bed stem cell transplantation hospital. In a recent study from our center, proven or probable invasive aspergillosis was detected in 19 out of 20 patients with AML under FP or empirical antifungal therapy [12]. Posaconazole was introduced to the market in 2010 in Turkey and replaced fluconazole for the primary AFP in AML patients during remission-induction chemotherapy in our center. Here, we aimed to provide real-life information about the effectivity of different types of primary antifungal prophylaxis, also share our experience in the diagnosis and treatment of breakthrough IFDs after failure of antifungal prophylaxis.

Patients and Methods

This retrospective observational study was conducted on patients with AML who received fluconazole or posaconazole prophylaxis between June 2010 and February 2013. The study was approved by the Erciyes University Faculty of Medicine Ethics Committee. The patients were identified from the hospital pharmacy databases. Since there were heavy constructions around the hospital until January 2010, we did not include the AML patients who received cytotoxic chemotherapy before June 2010 in order not to cause a selection bias against fluconazole. Only the patients older than 18-years, and received remission-induction chemotherapy for AML were included. All relevant data was extracted from the charts and electronic records from the time of hospital registration until 120 days after remission-induction chemotherapy. Survival was evaluated 100 days after AFP was started, and analyses were conducted for overall survival, death from any cause.

During the observation period, patients received 200 mg of posaconazole in an oral suspension three times daily or 200 mg of fluconazole in an oral suspension twice daily. AFP was initiated on the first day after the end of cytotoxic

chemotherapy and continued until recovery from neutropenia or start of another systemic antifungal agent. Posaconazole was given with a fatty meal for better absorption. All patients received proton pump inhibitors or h2 receptor-blockers for stress ulcer prophylaxis. Antibacterial prophylaxis consisted of levofloxacin 500 mg daily or moxifloxacin 400 mg daily. Patients were hospitalized in single bedrooms without high-efficiency particulate air filtration and positive pressure until recovery from neutropenia or resolution of all clinical symptoms if any source of infection was detected. Galactomannan (GM) antigen (Platelia™ *Aspergillus* EIA, Bio-Rad) and 1,3-beta-D-glucan (BDG) (Fungitell™, Associates of Cape Cod) tests were scheduled twice weekly when neutrophil count was <500 cells/μl until recovery from neutropenia.

In the case of neutropenic fever (neutrophil count <500 cells/μl, temperature >38 °C for >1 h or >38.3 °C recorded once), imipenem or meropenem was started after two sets of blood cultures were obtained, and vancomycin was added in case of suspicion of Gram-positive infection or septic shock. Thoracic computed tomography (CT) was performed if the fever does not resolve in 72–96 h or fever relapsing after 48 h of defervescence, presence of any respiratory symptoms, and GM > 0.5 (or BDG > 80 pg/mL when available). Additional examinations such as abdominal ultrasound scan, sinus or brain CT, or bronchoalveolar lavage (BAL) were performed when required.

Prophylaxis failure was defined as; (1) the occurrence of IFDs based on European Organization for Research and Treatment of Cancer and the Mycoses Study Group (EORTC/MSG) criteria, (2) receipt of any other systemic antifungal agent for 4 days or more during febrile neutropenia episode without any identified IFDs, (3) the occurrence of an adverse event related to the fluconazole or posaconazole resulting in the discontinuation of antifungal prophylaxis. According to EORTC/MSG criteria; possible pulmonary fungal disease was defined as persistent neutropenia plus radiological findings (dense, well-circumscribed nodular lesion(s) with or without a halo sign, air-crescent sign, and cavitory lesion) concordant with IFDs without microbiological evidence. Probable pulmonary fungal disease was defined as persistent neutropenia plus radiological finding concordant with IFDs and serum GM < 0.7 and BDG > 80 pg/mL, and probable invasive aspergillosis (IA) was diagnosed based on persistent neutropenia plus radiological evidence of the disease and serum GM > 0.7 or BAL fluid GM > 1, or isolation of *Aspergillus* species from respiratory samples [13].

In patients with failure of prophylaxis, responses to switch antifungal treatment was assessed based on European Organization for Research and Treatment of Cancer and Mycoses Study Group (EORTC/MSG) consensus

criteria at the end of therapy. Success was defined as radiological stabilization (defined as 0–25 % reduction in the diameter of the lesion), resolution of all attributable symptoms and signs of fungal disease. Failure was defined as a deterioration of attributable clinical or radiographic abnormalities necessitating alternative antifungal therapy or death during the treatment period regardless of attribution [14]. In patients with neutropenic fever without any identified source; response to the empirical antifungal therapy was considered favorable in the absence of breakthrough IFDs up to 7 days and survival for 7 days after discontinuation of antifungal therapy, no discontinuation because of antifungal drug toxicity, and resolution of fever for 48 h during period of neutropenia [15].

Antifungal treatment decisions were given by the attending physicians of the infectious diseases and hematology departments in case of prophylaxis failure. Liposomal amphotericin B (3 mg/kg/day), caspofungin (70 mg/day loading dose, 50 mg/day as maintenance dose), and voriconazole (12 mg/kg/day loading dose and 8 mg/kg/day maintenance dose) were used for the suspected or radiological/microbiological evidenced IFDs.

For statistical analysis, we divided the patients into two groups according to the success of antifungal prophylaxis. All statistical analyses were performed with SPSS software for Windows (version 15.0; SPSS, Chicago, IL). Continuous variables were expressed as median values, first and third quartiles, categorical variables were expressed as the frequencies and percentages of the patients analysed. Groups were compared with the use of Chi square and Fisher's exact tests for categorical variables, and the Mann–Whitney U test for continuous variables. In order to identify the independent risk factors failure of antifungal prophylaxis, multivariate logistic regression analysis was used to control for the effects of confounding variables. Odds ratios (ORs) and their 95 % confidential intervals (CIs) were calculated. All risk factors with potential association with failure of AFP (whether they were statistically significant or not) and statistically significant variables were included in the multivariate logistic model, and backward stepwise selection was performed at a stringency level of $p < 0.10$ to determine the independent risk factors for failure of antifungal prophylaxis. Measures of the goodness-of-fit were obtained to assess the performance of the models. All p values were two-tailed, and $p < 0.05$ was considered statistically significant.

Results

A total of 85 AML remission-induction chemotherapy cycles were identified in 80 patients. The median age of the patients were 44 (range 18–71)-years, and 45 of them were

male. Median duration of AFP was 21 days. Fluconazole was administered in 29 cycles between June 2010 and May 2011, and posaconazole was given in 56 cycles between February 2011 and February 2013. None of the patients had a previous history of IFDs. The demographic and clinical characteristics of fluconazole and posaconazole groups were similar, except, higher rate of presence of neutropenia >21 days in fluconazole group (Table 1). A total of 39 intensive chemotherapy cycles were initiated in patients with relapsing/refractory AML. Two patients were de nova cases whose AML relapsed over the study period while the other patients had refractory/relapsed disease when they were included in the analysis. The number of relapsing/refractory AML was 26 in posaconazole group, and 13 in fluconazole group (Table 1). Failure in the AFP was observed in 45 (57.9 %) out of 85 cycles. AFP with posaconazole failed in 16 (61.5 %) out of 26 patients with refractory/relapsed AML and fluconazole failure was detected in 12 (92.3 %) out of 13 patients with refractory/relapsed AML.

When we compared the patients based on the success of the antifungal prophylaxis; relapsing or refractory AML, longer duration of neutropenia and FP were more common in patients with failure (Table 2). Multivariate logistic regression analysis showed that type of AFP (OR 3.63; 95 % CI 1.19–11.07, $p = 0.023$), presence of neutropenia longer than 21 days (OR 3.96; 95 % CI 1.36–11.46, $p = 0.011$), and refractory or relapsing AML (OR 6.09; 95 % CI 2.09–17.73, $p = 0.001$) were independent factors associated with failure of antifungal prophylaxis. Because patients were distributed unevenly in terms of duration of neutropenia and refractory of relapsing AML, a complementary statistical analysis adjusting for these variables was performed. The results from this analysis indicated a trend toward the superiority of PP (Table 3).

While the reason for failure was persistent neutropenic fever in 15 patients, breakthrough IFDs were detected in 30 patients. Although there was no statistically significant difference, neutropenic fever without any identified source were more common in patients receiving fluconazole than patients receiving posaconazole (Table 1). In patients with neutropenic fever longer than 5 days; posaconazole was switched to caspofungin in 5 patients (2 of whom failed), liposomal amphotericin B in 2 patients (none of them failed), and voriconazole in 2 patients (2 of whom failed). Fluconazole was switched to caspofungin in 4 patients (1 of whom failed), and voriconazole in 2 patients (2 of whom failed). Failure reason for empirical caspofungin therapy was *Candida albicans* and *Candida krusei* fungemia in two patients each group. The reason for failure was death under antifungal treatment in other patients who received empirical antifungal therapy. The median duration of empirical antifungal therapy was 15 days (range 5–46).

Table 1 Demographic and clinical characteristics of the patients based on the type of antifungal prophylaxis

	Posaconazole (n = 56) (%)	Fluconazole (n = 29) (%)	p value
Age median (Interquartile range) years	45.5 (33–53)	42 (28–54.5)	0.707
Male	32 (57.1)	17 (58.9)	0.896
Relapsing or refractory acute myeloid leukemia	26 (46.4)	13 (44.8)	0.888
Vomiting	5 (8.9)	0	0.97
Diarrhea	2 (3.6)	0	0.303
Duration of neutropenia median (Interquartile range) days	23.5 (16–33.8)	28 (19–43.5)	0.123
Neutropenia longer than 21 days	30 (53.6)	22 (75.9)	0.046
Duration of antifungal prophylaxis, median (Interquartile range) days	22 (15–27)	20 (14–27.5)	0.458
Failure criteria			
Neutropenic fever without any identified source	9 (16.1)	6 (20.7)	0.596
Invasive fungal diseases	15 (26.8)	15 (51.7)	0.023
Possible IFD	8	8	
Probable IFD	4	1	
Probable IA	2	6	
Fungemia	1	0	
Success of first switch antifungal therapy after failure of prophylaxis	12 (50)	12 (57)	0.632
Duration of antifungal therapy median (Interquartile range), days	17 (9–27)	13 (15–27.5)	0.860
Serum galactomannan >0.7	2 (3.6)	6 (20.7)	0.017
Serum beta-D-glucan >80 pg/ml ^a	3 (5.4)	5 (17.2)	NA
Bronchoalvolar lavage fluid galactomannan >1	3	2	NA
Overall mortality	10 (17.9)	6 (20.7)	0.751

^a Serum 1,3-beta-D-glucan test was not available in 27 out of 56 patients receiving posaconazole and 5 out of 29 cycles receiving fluconazole. NA not available

Table 2 Demographic and clinical characteristics of the patients based on the outcome of the antifungal prophylaxis

	Total (n = 85) (%)	Success (n = 40) (%)	Failure (n = 45) (%)	p value
Relapsing or refractory acute myeloid leukemia	39 (45.9)	11 (27.5)	28 (62.2)	0.001
Duration of neutropenia median (Interquartile range) days	26 (16.5–35.5)	20.5 (15–31.5)	29 (21–42)	0.003
Neutropenia longer than 21 days	52 (61.2)	18 (45.0)	34 (75.6)	0.004
Type of antifungal prophylaxis				0.01
Posaconazole	56 (65.9)	32 (80.0)	24 (53.3)	
Fluconazole	29 (34.1)	8 (20.0)	21 (46.7)	
Duration of antifungal prophylaxis, Median (Interquartile range) days	21 (15–27)	22 (20–27.5)	17 (13–27)	0.026
Overall mortality	16 (18.8)	1 (2.5)	15 (33.3)	<0.001

Any type of IFDs were detected in 15 (26.8 %) out of 56 cycles receiving PP and 15 (51.7 %) out of 29 cycles receiving FP ($p = 0.023$) (Table 2). Caspofungin was the drug of choice in 11 out of 29 patients with pulmonary fungal disease (3 of whom failed in posaconazole group and 4 of whom failed in fluconazole group). Voriconazole was initiated in 12 patients with pulmonary fungal disease (1 of whom failed in posaconazole group and 4 of whom failed in fluconazole group). Liposomal amphotericin B

was used in the treatment of 6 patients with pulmonary fungal disease (1 of whom failed in posaconazole group, and 2 of whom failed in fluconazole group). Since the number of the patients were low, we were not able to analyze the outcome of the patients with IFDs based on treatment with different classes of antifungal agents, and also based on EORTC/MSG classification. The median duration of parenteral antifungal therapy in patients with IFDs was 15 days (range 5–51 days). *Blastoschizomyces*

Table 3 The influence of the type of the prophylactic agent in the success of antifungal prophylaxis with or without adjusting the factors related to failure of antifungal prophylaxis

	Odds ratios (ORs) and their 95 % confidential intervals (CIs)
Without any adjustment	OR 3.63; 95 % CI 1.19–11.07, $p = 0.023$
Adjusted for duration of neutropenia	OR 3.01; 95 % CI 1.09–8.34, $p = 0.034$
Adjusted for relapsing or refractory AML	OR 4.39; 95 % CI 1.51–12.76, $p = 0.007$
Adjusted for duration of neutropenia and relapsing or refractory AML	OR 3.90; 95 % CI 1.26–12.05, $p = 0.018$

capitatus fungemia was detected in a patient who received PP for 3 weeks. This patient was switched to liposomal amphotericin B, although the blood cultures became negative, fever persisted and resolved after a second switch to voriconazole.

The retrospective nature of the study that limited our ability to systemically monitor the adverse effects of antifungal prophylaxis, however, no adverse effects related to interruption of AFP was recorded. Nevertheless, PP failed in seven patients with vomiting or diarrhea (Table 2). The reason for failure was persistent fever in 5 patients, probable IA in 1 patient, and fungemia in 1 patient. Further systemic antifungal therapy was successful in 3 patients. The other four patients were died under antifungal therapy without any documented breakthrough IFDs.

The diagnosis of breakthrough IFDs under AFP is a challenge, so, we evaluated the role of GM and BDG detection in the diagnosis of breakthrough IFDs in patients with prophylaxis failure. Serum GM was positive in six patients received fluconazole and in two patients received posaconazole ($p = 0.017$). Bronchoscopy was available in 6 out of 29 patients who had pulmonary lesions concordant with IFDs. While serum GM index was >0.7 in only 1 of these 6 patients, GM index in BAL fluid was >1 in 5 patients, and *Aspergillus fumigatus* was isolated from one of the patient's BAL fluid who was under PP for 15 days. This patient was successfully treated with liposomal amphotericin B, and then switched to oral voriconazole after documentation of in vitro susceptibility.

Discussion

In our study, the risk of failure was three times higher for FP when compared with PP. However, a greater proportion of patients in the fluconazole group had prolonged neutropenia fluconazole is unlikely to cause prolonged neutropenia but a prolonged neutropenia is a risk factor for

fungal infection. Because of the retrospective nature of our study, we were not able to define why the patients who received fluconazole has a longer duration of neutropenia. The cytotoxic therapy regimes were similar in both groups. Receipt of other drugs such as beta-lactam antibiotics, glycopeptides, non-steroid anti-inflamatuary drugs, or the granulocyte colony stimulation factors can influence the duration of neutropenia and it is difficult to comment about these factors in a retrospective study. However, we believe that the major discussion in our study is not the causes of longer duration of neutropenia in fluconazole group, the main question is if longer duration of neutropenia in one fluconazole group caused the bias against fluconazole. To solve this problem, we performed a complementary statistical analysis adjusting for the variables as duration of neutropenia and relapsing/refractory disease. After adjustment posaconazole still has an advantage in terms of AFP (Table 3). However, despite the fact posaconazole seems to work better than fluconazole in terms of antifungal prophylaxis, it is obvious that the rates of failure even with posaconazole is high (24 out of 56, 42.8 %) in our study, and IFDs are still of concern in AML patients receiving intensive chemotherapy.

Although there was no statistically significant difference for the overall mortality rates in patients receiving posaconazole and fluconazole (Table 1), the overall mortality was lower in patients with successful prophylaxis (2.5 vs. 33.3 %, $p < 0.001$). This finding underscores the importance of the prevention of IFDs in patients with AML. Unfortunately, the number of the patients in our study was low to compare the survival in two different prophylactic regimens, but a significant survival benefit in favor of posaconazole over fluconazole or itraconazole was reported in a large randomized controlled study [4].

One of the important goals of the effective AFP is decreasing the rate of empirical systemic antifungal therapy. As contrast to posaconazole, fluconazole does not have any activity against molds, and this situation can trigger the use of mold active agents empirically based on persisting fever and neutropenia without any clinical or microbiological evidence of IFDs. In our study, the rate of empirical antifungal therapy was similar in patients receiving fluconazole or posaconazole prophylaxis. This can be due to no access of therapeutic drug monitoring for posaconazole. Seven of the patients receiving posaconazole had severe diarrhea or vomiting in our cohort. Posaconazole has a highly variable bioavailability and the association between prophylaxis failure and posaconazole serum levels was reported [16]. A recent multicenter study from Italy showed that posaconazole was switched to empirical systemic antifungal therapy in 102 (20 %) out of 510 AML patients with persistent neutropenia and fever [17]. This finding shows that there are still concerns about

the effectivity of prophylaxis with oral posaconazole in a large group of well-trained hematology physicians.

Although there was not a significant reduction in the rate of initiation of empirical antifungal treatment during febrile neutropenia after prophylaxis policy was changed to posaconazole, the number of the IFDs were significantly lower in patients receiving posaconazole compared to fluconazole in our center (Table 1). The guidelines recommend a different class of antifungal agent after mold active AFP failure due to the concerns about cross-resistance [5]. However, voriconazole treatment was successful in 4 out of 5 patients diagnosed as PFD after posaconazole failure in our cohort. *Blastoschizomyces capitatus* and *A. fumigatus* isolated from patients with posaconazole failure, were reported as susceptible to voriconazole, and maintenance therapy with voriconazole was also successful. A recent study reported a good outcome in five out of six AML patients with possible or probable IA treated with voriconazole after failure of posaconazole [17]. In patients with severe diarrhea or vomiting, optimal exposure to posaconazole is minimum, so intravenous voriconazole can be an alternative for such kind of patients based on the reports which showed that majority of fungus causing breakthrough IFDs under PP were found to be susceptible to posaconazole. But, these findings (with very low number of patients) need to be applied cautiously in daily practice, and optimal management of breakthrough infections after mould active prophylaxis still remains to be determined [18].

Fungal biomarkers such as GM and BDG are considered as important tools as the early and accurate diagnosis of IFDs. A reduction in the sensitivity of GM was reported in patients receiving mould active prophylaxis [19]. Our findings were concordant with this finding, and the rate of serum GM positivity was higher in patients receiving fluconazole than posaconazole (17.2 vs. 5.1 %, $p = 0.017$). Four patients with failure of posaconazole underwent BAL examinations, and three were found to have a positive GM antigenemia in BAL fluid, and *A. fumigatus* was isolated from BAL fluid of one patient. This finding underscores the impact of fiberoptic bronchoscopy in patients with negative serum GM suspected for IA based on radiological findings. Five of out 15 patients with pulmonary fungal disease had positive BDG contrast to negative GM antigenemia (Table 1). Concurrent use of fungal biomarkers can improve the diagnostic certainty.

As a conclusion, despite several limitations of the study such as no access to plasma levels of posaconazole and a higher rate of patients with longer duration of neutropenia in fluconazole group, we observed superiority of posaconazole on fluconazole for the AFP of patients with AML receiving remission-induction chemotherapy. This finding might guide to centers sharing similar features with our clinic to decide on AFP strategy.

Conflict of interest G.M. has received honorarium for speaking at symposia and lecture organized by Gilead, financial compensation from Pfizer for the time and expenses for a meeting organised to discuss the content of a review paper, received research support from Associates of Cape Cod, and received travel grants from MSD, Pfizer, and Gilead to participate conferences. L.K has received honorarium for speaking at a lecture organized by Gilead. The other authors declared to have any completing interest. No funding was received for this study.

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