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Systemic antifungal treatment after posaconazole prophylaxis: results from the SEIFEM 2010-C survey

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Objectives: To investigate the incidence, treatment and outcome of breakthrough invasive fungal infections (IFIs) in adult acute myeloid leukaemia (AML) patients after posaconazole prophylaxis.

Methods: From January 2010 to April 2012, all consecutive patients with newly diagnosed AML were prospectively registered at 33 participating Italian centres. All cases of IFIs occurring within 30 days after the end of the first induction chemotherapy were recorded. The strategy of antifungal treatment (empirical, pre-emptive or targeted) and the drugs used were analysed. ClinicalTrials.gov code: NCT01315925.

Results: In total, 1192 patients with newly diagnosed AML were enrolled in the study, of whom 510 received posaconazole prophylaxis and were included in the present analysis. Of these patients, 140 (27%) needed systemic antifungal treatment. Among the 127 evaluable cases, an empirical approach was utilized in 102 patients (80%), a pre-emptive approach in 19 patients (15%) and targeted therapy in 6 patients (5%). Only five patients died of IFIs (three in the empirical group and two in the targeted group; 4%). A critical review of IFI diagnoses at 30 days demonstrated that among the patients treated empirically, ~30% were not affected by IFIs but rather only by fever of unidentified origin. A comparison between the empirical and the pre-emptive groups showed no significant differences regarding the attributable and overall mortalities.

Conclusions: This study confirms that posaconazole prophylaxis reduces the incidence of breakthrough IFIs and does not modify the efficacy of subsequent systemic antifungal treatment, regardless of the approach (empirical or pre-emptive) or the antifungal drug used.

Keywords: antifungal prophylaxis, acute myeloid leukaemia, empirical therapy

Introduction

Prophylaxis with posaconazole is currently a well-defined form of therapeutic strategy, characterized by a reduction in overall invasive fungal infections (IFIs) and specifically of infections due to *Aspergillus* spp. This reduction has been demonstrated both by clinical trials[1,2] and by many actual clinical experiences.[3–6] However, although there was a significant reduction in the proportion of proven/probable IFIs in all of these studies, a consistent proportion of patients (~30%) still needed subsequent systemic antifungal treatment. This need may be due to breakthrough IFIs or to a delay in the positivity of microbiological diagnostic tests. Furthermore, the most correct therapeutic approach (empirical or pre-emptive) and the most effective antifungal

drugs are not yet established in the setting of posaconazole prophylaxis failure.

In this prospective, multicentre, non-randomized, observational study, we analysed the behaviour of Italian haematologists in cases of suspected failure of posaconazole prophylaxis and the outcome of patients with breakthrough IFIs.

Patients and methods

This prospective study was conducted in 33 haematology wards in tertiary care centres or university hospitals located throughout Italy from 1 January 2010 to 30 April 2012. All consecutive, newly diagnosed adult patients with acute myeloid leukaemia (AML) undergoing first remission induction by chemotherapy who received posaconazole prophylaxis were included in the registry and followed up. Data were prospectively entered into case report forms. ClinicalTrials.gov code: NCT01315925.

Posaconazole was administered at a dose of 200 mg thrice daily. The treatment was started at 1–2 days prior to cytoreductive chemotherapy and continued until neutrophil recovery to $>0.5\times10^9$/L, the occurrence of a confirmed or suspected IFI or drug-related toxicity/intolerance.

The SEIFEM registry was approved by the Ethics Committees of the participating sites. Written informed consent was obtained from all participants.

Given the non-interventional nature of the study, enrolling a patient in the registry had no impact on the standard clinical practice of each haematology unit.

The follow-up of the last patient was completed on 31 August 2012. A minimum follow-up of 12 weeks after the completion of chemotherapy was requested.

For each patient, baseline data were recorded at the time of admission (age, gender, AML subtype and AML treatments). The registry also included data regarding the antifungal therapy, as follows: employed drugs, dosage, type of approach (e.g. empirical, pre-emptive or targeted treatment) and duration of antifungal treatment.

The diagnostic work-up included the following: nasal, pharyngeal and rectal swabs at the time of admission; blood cultures and chest X-rays at the onset of fever; galactomannan assays once or twice per week; and chest computed tomography (CT) scan on days 4–7 of fever. Additional examinations (e.g. an abdominal ultrasound scan, a sinus or brain CT, a skin biopsy, bronchoalveolar lavage and fundus examination) were performed as required.

The IFI incidence within the first 30 days from the end of chemotherapy was assessed. IFIs were classified in accordance with the new 2008 European Organisation for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria.[7] Proven IFIs were considered when fungal elements in diseased tissue were demonstrated. Probable IFIs were defined when host factors (in our series all patients were AML in induction phase), clinical signs, radiological pictures and a positive microbiological test (i.e. galactomannan test) were present.

Mortality due to IFIs (IFI-attributable mortality) was considered when patients died within 12 weeks after the onset of fever and had microbiological, histological or clinical evidence of an active IFI if other potential causes of death could be excluded by the physician responsible.[8]

All causes of death within 12 weeks were recorded (overall mortality).

Statistical analysis

Continuous variables were compared using Student's *t*-test (normally distributed variables) or the Mann–Whitney *U*-test (non-normally distributed variables). Categorical variables were evaluated using the χ^2 or two-tailed Fisher's exact test. Values are expressed as the mean ± standard deviation or the median (range) (continuous variables) or as a percentage of the group from which they were derived (categorical variables).

Two-tailed tests were used to determine statistical significance. A P value of <0.05 was considered significant. All statistical analyses were performed with the Intercooled Stata program, version 11, for Windows® (Stata Corporation, College Station, TX, USA).

Results

Over a 28 month period, 1192 adult patients with newly diagnosed AML were enrolled in the study at 33 participating centres. In total, 211 patients received only low-dose therapies or palliative treatments and were excluded from the present analysis.

The present analysis focused on the remaining 981 AML patients who received conventional intensive chemotherapy. Of these patients, 545 were male and 436 were female and the mean age was 55 years (range 18–84). In 746 cases, induction treatment was anthracycline based and in 173 patients the treatment was fludarabine based. Additionally, 43 patients were treated with high doses of cytosine arabinoside and in the remaining 19 cases miscellaneous aggressive treatments were administered (Figure 1).

A total of 510 patients received posaconazole prophylaxis during post-chemotherapy aplasia. Among these patients, nine who received <5 days of posaconazole (early death for AML) were not considered as eligible for the study. No clinical adverse event or laboratory abnormality (WHO >3) attributed to posaconazole and causing a discontinuation of prophylaxis was observed in the remaining patients.

In total, 140 of 510 evaluable patients (27%) needed systemic antifungal therapy. Among these patients, 13 were excluded from analysis because they received treatment for <7 days: 6 due to early death from AML and 1 due to early death from IFIs (1 *Pneumocystis jirovecii* pneumonia). Additionally, six of the patients were evaluated as having no fungal infection and consequently received <7 days of antifungal therapy.

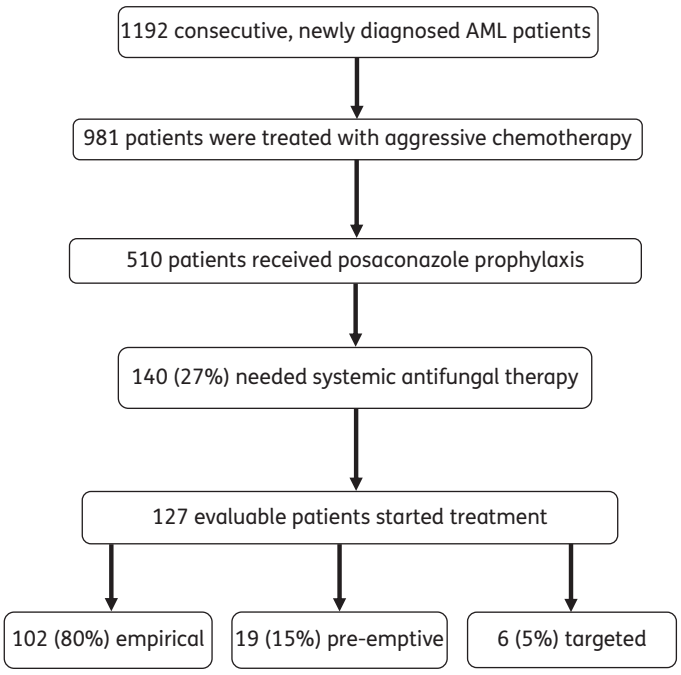

Figure 1. Flow chart of the study.

Among the remaining 127 patients, 102 (80%) started antifungal treatment as an empirical approach and 19 patients (15%) started treatment as a pre-emptive approach. Only six patients (5%) received a targeted treatment. The main characteristics of the three groups are reported in Table 1.

Antifungal treatment was started based on well-established criteria,[9] as follows: empirical approach (based only on host factors plus fever unresponsive to extensive antibiotic treatment); pre-emptive approach (IFI diagnosis suspected due to microbiological factors or clinical factors); and targeted treatment (proven diagnosis according to the EORTC-MSG criteria).

Thirty days from the start of antifungal treatment, a critical review of IFI diagnosis was performed to verify the propriety of the diagnosis.

A total of 90 IFIs were diagnosed. According to the EORTC criteria, these infections consisted of 62 possible, 18 probable and 10 proven IFIs. Among these infections, only four cases (all proven) were due to yeasts (three *Candida* strains and one *Trichosporon* strain). All of the other 86 IFIs were considered to be due to invasive aspergillosis (IA). No cases of rare moulds (i.e. mucormycosis or fusariosis) were diagnosed or suspected. Of note, at the time of the critical review of the diagnosis at 30 days, 37 cases (29%) remained classified as fever of unidentified origin (FUO) without evidence of an IFI.

The IFI-attributable mortality rate at 12 weeks was 4% (5/127 cases: 2 possible IA, 1 probable IA and 2 candidaemia) and overall mortality was 27% (34/127 cases). These percentages were 5.5% (5/90) and 38% (34/90), respectively, excluding the 37 cases reclassified as FUO at 30 days revision.

Empirical treatment

The majority of patients started an empirical antifungal approach (102/127, 80%). The most utilized antifungal drug was liposomal amphotericin B (L-AmB), administered to 69 patients (68% of cases). At 30 days of follow-up, a review of L-AmB-treated patients indicated 37 cases of possible IA, 4 cases of probable IA and 2 cases of proven IA, whereas in 26 cases the diagnosis remained FUO.

The second most frequently utilized antifungal drug was caspofungin, administered to 26 patients. The same review performed at 30 days showed possible IA in 12 patients and probable IA in 5 patients. Nine patients had FUO.

Four of the remaining seven patients received amphotericin B lipid complex (ABLC) and three received voriconazole. At 30 days, five cases were defined as possible IA (two treated with ABLC and three with voriconazole) and two, treated with ABLC, were considered as only FUO.

Three patients (3%), all in the L-AmB group, died from IFIs (two cases treated for possible IA and one treated for probable IA). Of note, the two patients with proven IA recovered from infection. The overall mortality at 12 weeks among these patients was 25% (26/102).

Pre-emptive treatment

Nineteen patients were treated based on a positive diagnostic work-up. All patients presented a positive galactomannan test with clinical and radiological signs compatible with IA. L-AmB was administered to 12 patients: for possible IA in 5 cases and probable IA in 7 cases. Voriconazole was administered to four patients for possible IA and to two patients for probable IA. One patient with possible IA was treated with a therapeutic dose of posaconazole (400 mg ×2). Thirty days from the start of treatment, a critical review of the diagnosis was performed and two probable cases treated with voriconazole were observed to have become proven IA. No death due to an IFI was observed. The overall mortality at 12 weeks among these patients was 21% (4/19).

The distribution of patients subject to the different systemic antifungal empirical or pre-emptive approaches or to targeted treatments is reported in Table 2.

Targeted treatment

In all cases, treatment was started when a proven diagnosis was made in three candidaemia, one *Trichosporon* fungaemia and two IA cases. The three patients with candidaemia (one *Candida*

Table 1. Main characteristics of patients who received systemic antifungal therapy after posaconazole prophylaxis, evaluation of the distribution of certain levels of invasive fungal disease 30 days from the start of treatment and comparison between the empirical and the pre-emptive approaches

	Empirical ($n=102$)	Pre-emptive ($n=19$)	Comparison of empirical versus pre-emptive (P)	Targeted ($n=6$)
Age (years), mean (range)	55 (18–79)	58 (44–72)	0.2	57 (47–74)
Male/female, *n*/*n*	55/48	12/7	0.45	3/3
Duration of previous prophylaxis (days), mean (range)	22 (6–150)	24 (6–120)	0.8	18 (8–27)
Duration of neutrophils $<500/mm^3$ (days), mean (range)	21 (6–48)	17 (8–38)	0.06	21 (15–30)
Treatment duration (days), mean (range)	13 (12–14)	18 (13–23)	0.04	22 (15-35)
Follow-up of invasive fungal disease at 30 days				
FUO	37	—		—
possible	54	10		—
probable	9	7		—
proven	2	2		6[a]
IFI-attributable mortality, *n* (%)	3 (3)	0	0.5	2 (33)
Overall mortality at 12 weeks, *n* (%)	26 (25)	4 (21)	0.2	4 (66)

[a]Three candidaemia, one *Trichosporon* fungaemia and two invasive aspergillosis.

Table 2. Distribution of patients in the different groups of systemic antifungal treatments

Type of evidence/ drug (cases)	Diagnosis of invasive fungal disease at 30 days	Duration of treatment (days), mean (range)	Attributable mortality rate, *n* (%)	Overall mortality, *n* (%)
Empirical (102)		14 (6–90)	3 (3)	26 (25)
L-AmB (69)	FUO (26) possible (37) probable (6)	13 (6–40)	3	15
caspofungin (26)	FUO (9) possible (12) probable (5)	11 (14–58)	—	9
other (7) (4 ABLC, 3 voriconazole)	FUO (2) possible (5)	11 (7–19)	—	2
Pre-emptive (19)		18 (8–42)	0	4 (21)
L-AmB (12)	possible (5) probable (7)	15 (8–30)	—	2
voriconazole (6)	possible (4) probable (2)	23 (10–42)	—	1
posaconazole (1)	possible (1)	22	—	1

glabrata, one *Candida krusei* and one *Candida albicans*) received caspofungin in two cases (one recovered and one died of infection) and voriconazole in one case (died of infection). The patient with *Trichosporon* was treated with voriconazole and recovered from infection. The remaining two patients, with IA, were each treated with L-AmB and ABLC and recovered from infection. The attributable mortality rate was 33% (2/6 patients) and overall mortality at 12 weeks among these six patients was 67% (4/6).

Univariate analysis

Patients treated with one of the two different strategies, *empirical* or *pre-emptive*, were compared and the results are reported in Table 1. A significant difference was observed between groups only for the treatment duration, which was longer in the pre-emptive group (18 days versus 13 days, $P<0.04$). A trend was observed for neutropenia duration ($P=0.06$), which was longer in the empirical approach (21 days versus 17 days). No significant differences were observed for the attributable mortality rate or overall mortality between the two groups. Even excluding cases of FUO in the empirical treatment group (37 patients), no significant difference regarding attributable mortality was observed between the two groups (data not shown).

In the empirical group, a comparison between L-AmB and caspofungin, the two most utilized agents, was not statistically significant.

Discussion

The introduction of prophylaxis with posaconazole has changed the epidemiology of IFIs in patients with haematological malignancies. In fact, various actual clinical experiences have confirmed the results of clinical trials documenting an important reduction in the incidence of IFIs in patients with AML and in patients undergoing allogeneic stem cell transplantation.[1–6] However, this type of prophylaxis has also reduced the efficacy of certain microbiological diagnostic tools that previously seemed absolutely predictive (i.e. serum galactomannan).[10,11]

In general, the new scenario that we are facing is a reduction in the IFI burden. However, when a breakthrough IFI is suspected during posaconazole prophylaxis, there is less diagnostic certainty. How to treat this patient? The IDSA guidelines seem to be clear:[12] if the patient receives mould-active prophylaxis, the use of an empirical approach is preferable and the class of antifungal agent for treatment should be switched. Therefore, given that posaconazole is an azole, voriconazole therapy would not be indicated. The second question that arises is whether after prophylaxis with posaconazole, select fungal strains, and especially *Aspergillus* spp., are unresponsive to subsequent systemic antifungal treatment with other non-azole drugs? A number of studies, including one recently published by De la Serna *et al*.[13] in Spain, show that previous mould-active antifungal prophylaxis, including posaconazole, does not change susceptibility to treatment with L-AmB.[14]

Our study, conducted on a large and homogeneous series of patients with AML undergoing first-line chemotherapy treatment for remission induction, confirms that the need for systemic antifungal therapy after oral posaconazole prophylaxis has significantly decreased in patients with AML. This decline has progressed from 50%–60%, as reported several years ago in the pre-posaconazole era, to <30%, reported in the current posaconazole era.[6] Our experience is in line with all the recent real-life experience regarding posaconazole prophylaxis.[15]

In clinical practice today, perhaps more than ever, we observe a greater tendency to use an empirical antifungal strategy. In fact, >80% of our patients have been treated with this approach. However, comparing data regarding IFI-attributable mortality between the empirical and the pre-emptive therapies, we did not confirm the results of the Hema e-Chart study, although only 2 years elapsed between the two studies.[16] In the Hema e-Chart study, it was shown that empirical therapy, regardless of the type of systemic antifungal treatment, resulted in a

significant reduction in IFI-attributable mortality compared with pre-emptive treatment. This discrepancy is likely due to the completely different type of prophylaxis used in the Hema e-Chart study (no prophylaxis or non-mould-active azoles, such as fluconazole or itraconazole), which is less effective than posaconazole prophylaxis, and to the narrow selection criteria for the cohort of patients in the present study (only AML in the induction phase). All of these factors could explain why we could not confirm the previously observed significant difference in mortality between patients treated empirically and patients treated pre-emptively in the present study. On the other hand, it must be taken into account that the small number of patients treated with pre-emptive therapy limits the comparison with the empirical group.

Another important issue is the possible difference in the efficacy between caspofungin and L-AmB in the empirical approach. A study by Walsh *et al.*[17] has already shown that in empirical antifungal therapy, these two drugs were equivalent. However, subsequent studies by Viscoli *et al.*[18] and Herbrecht *et al.*[19] demonstrated the unsatisfactory efficacy of caspofungin in the case of a targeted therapy for IA, requiring reconsideration of the role of caspofungin against IA in patients with haematological malignancies. Our study was not a randomized trial or a large enough series to be able to reach definitive conclusions on this topic. However, our study shows that even in the era of posaconazole prophylaxis, there are no differences in favour of either drug.

When we analysed the different drugs used in the pre-emptive approach, no difference was observed between L-AmB and voriconazole treatments. Of note, no IFI-attributable deaths were observed in the voriconazole arm. This could be due to the small number of patients (only six cases) treated with voriconazole. However, the previous posaconazole prophylaxis does not seem to have changed the response to voriconazole treatment.

Interestingly, among our patients, beyond the case of fungaemia due to *Trichosporon*, there were no cases of other rare fungal agents and no breakthrough mucormycosis was documented. Overall IFI-attributable mortality was only 5.5%, showing that previous prophylaxis with posaconazole did not affect the subsequent course of the fungal infection. Furthermore, our study confirmed the decreasing trend in the attributable mortality rate that was already observed in our previous epidemiological studies.[20,21] Thanks to the available systemic antifungal treatments, at present, mortality due to invasive fungal diseases in patients with haematological malignancies treated with conventional chemotherapy is $<20\%$. In particular, in AML, during the first induction of remission, mortality is lower than in other phases not only due to antifungal prophylaxis and treatments but also due to improvements in recent years in supportive care.

Our study confirmed one last important point. A significant percentage of patients (37/127, 29%) initially with antifungal therapy subsequently had no evidence of an IFI. This finding means that in at least one-third of patients who are receiving empirical antifungal therapy, the antifungal treatment is probably unnecessary and started in an inappropriate manner, based more on an emotional driver than on a scientific process. However, we cannot exclude the possibility that empirical treatment can clear an undetectable fungal infection.

In conclusion, this observational study of a large number of AML patients allows us to understand current practice in antifungal treatment after failure of posaconazole prophylaxis. The introduction of this prophylaxis has led to a marked reduction in the incidence of IFIs. In our study about one-third of patients undergoing antifungal prophylaxis needed treatment with systemic antifungals, however this rate could have been markedly reduced because most of the patients were finally defined as affected by FUO and not by true fungal infections. Posaconazole has not had a negative impact on subsequent treatment in cases of failure of prophylaxis. However, our findings have highlighted the need for more specific diagnostic tools, particularly to reduce the 30% of antifungal treatments that are unnecessary.

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Transparency declarations

L. P. has received honoraria from Gilead Sciences, Schering-Plough, Astellas Pharma, Merck and Pfizer Pharmaceuticals, and has

been a speaker for Gilead Sciences, Schering-Plough, Merck, Pfizer Pharmaceuticals and Astellas Pharma. A. B. has received honoraria from Gilead Sciences, Schering-Plough-Merck and Pfizer Pharmaceuticals, and has been speaker for Gilead Sciences, Schering-Plough-Merck, Pfizer Pharmaceuticals, Astellas Pharma and Novartis. M. E. M. has received honoraria from Gilead Sciences. R. F. has received honoraria from Merck. S. B. has received honoraria from Cephalon, Celgene, Janssen and Novartis. A. N. has received research support and honoraria from Pfizer Pharmaceuticals, Gilead Sciences, Cephalon and Merck. A. C. has received honoraria from Gilead Sciences, Schering-Plough, 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. T. has been a consultant for Gilead Sciences and MSD, and has been a speaker for Gilead Sciences, MSD and Pfizer Pharmaceuticals. All other authors: none to declare.

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