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'Real-life' analysis of the role of antifungal prophylaxis in preventing invasive aspergillosis in AML patients undergoing consolidation therapy: Sorveglianza Epidemiologica Infezioni nelle Emopatie (SEIFEM) 2016 study

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Background: We evaluated the incidence of proven/probable invasive aspergillosis (IA) and the role of antifungal prophylaxis (AP) in a 'real-life' setting of patients with AML receiving intensive consolidation therapy.

Methods: Cases of IA, observed during consolidation in adult/paediatric patients with AML between 2011 and 2015, were retrospectively collected in a multicentre Italian study.

Results: Of 2588 patients, 56 (2.2%) developed IA [43 probable (1.7%) and 13 proven (0.5%)]. IA was diagnosed in 34 of 1137 (2.9%) patients receiving no AP and in 22 of 1451 (1.5%) who were given AP (P=0.01). Number-needed-to-treat calculation indicates that, on average, 71 patients should have received AP (instead of no AP) for one additional patient to not have IA. Initial antifungal therapy was 'pre-emptive' in 36 (64%) patients and 'targeted' in 20 (36%) patients. A good response to first-line therapy was observed in 26 (46%) patients, mainly those who received AP [16 of 22 (73%) versus 10 of 34 (29%); P=0.001]. The overall mortality rate and the mortality rate attributable to IA by day 120 were 16% and 9%, respectively. In multivariate analysis, age ≥60 years (OR=12.46, 95% CI=1.13–136.73; P=0.03) and high-dose cytarabine treatment (OR=10.56, 95% CI=1.95–116.74; P=0.04) independently affected outcome.

Conclusions: In our experience, AP appears to prevent IA from occurring during consolidation. However, although the incidence of IA was low, mortality was not negligible among older patients. Further prospective studies should be carried out particularly in elderly patients treated with high-dose cytarabine to confirm our data and to identify subsets of individuals who may require AP.

Introduction

Over recent years, considerable progress has been made in understanding AML pathogenesis and in the development of diagnostic assays and novel therapies.[1] Despite these advances[2] the outcome of AML remains poor due to features intrinsic to the disease or due to complications, such as infections, occurring as a side effect of the intensive regimens that are adopted. Among infections, invasive aspergillosis (IA) is one of the most frequent conditions in AML. IA can be life-threatening and very difficult to eradicate, so that the normal chemotherapeutic course can be substantially altered, compromising the attempt of a successful cure of underlying AML.

Accordingly, efforts have been made to implement strategies of antifungal prophylaxis (AP) to prevent IA. Cornely *et al.*[3] demonstrated that a prophylaxis with posaconazole, given during neutropenia following AML induction therapy, was superior to a prophylaxis with itraconazole or fluconazole in preventing proven/probable invasive fungal infection and was associated with relative reduction of mortality. Several retrospective studies confirmed these results[4–6] and current international guidelines recommend prophylaxis with posaconazole during the induction phase, based on the high level of evidence.[7–10]

However, investigators focused on the role of AP given during the induction chemotherapy of AML, with few studies exploring whether there was a role for AP also in patients receiving consolidation chemotherapy. The reason for this lack of interest is that the incidence of IA during consolidation therapy is considered a rare event,[11–16] although such a perception does not rely on robust evidence. As a matter of fact, the epidemiology of IA in the induction phase has been extensively investigated, whereas only limited data are available with regards to the incidence and characteristics of IA occurring during consolidation. Actually, considering the bone marrow suppression following consolidation chemotherapy, patients are at risk of developing IA even in this phase of the therapeutic programme. Similarly to induction, a diagnosis of IA during consolidation does have a potential impact on prognosis, since it may cause a delay in the subsequent therapeutic programme and prolong hospitalization, eventually increasing the overall costs of disease. Furthermore, while, among the different haematological centres, there is a consensus about the adopted strategies of AP during induction, the prophylaxis during consolidation varies consistently.

Based on these observations, we analysed, retrospectively, a large 'real-life' series of patients with AML with the aim to: (i) evaluate the current rate of proven and probable IA in patients with AML submitted to intensive consolidation therapy; (ii) identify risk factors that, following consolidation, are associated with IA; and (iii) assess the role of AP as delivered either in induction or consolidation in preventing IA from occurring after consolidation therapy.

Methods

This retrospective multicentre study was conducted between January 2011 and December 2015, in 38 Italian haematology units affiliated with the Sorveglianza Epidemiologica Infezioni nelle Emopatie (SEIFEM) consortium. The incidence of probable and proven IA was assessed according to the revised European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria.[17]

Cases were documented using a case report form. Variables included the following data: age, gender, AML onset, genetic/cytogenetic risk factors,[1] duration of neutropenia ($<$10 versus $\geq$10 days), comorbidity conditions (diabetes, COPD, renal/hepatic failure), mucosal damage, diarrhoea, steroid administration and details of chemotherapeutic regimens. The clinical characteristics of patients with IA were compared with those of a control group, including 102 individuals matched for age and treatment, selected in the same period and in the same centres. Additional data collected were: AP, infections, site of infection, diagnostic microbiology, (direct microscopy, cultures, and galactomannan assay in serum or in bronchoalveolar lavage), imaging and histology, date of antifungal therapy initiation and whether this was 'pre-emptive' or 'targeted', and date of death. 'Pre-emptive' treatment was initiated in patients with persistent fever and imaging suspected of having IA. In patients with compatible radiological signs and microbiological tests allowing identification of the pathogen and in those with histopathological evidence of an aspergillosis, 'targeted' therapy was initiated. The assessment of response to therapy relied on clinical evaluation, quantitative laboratory tests and to a lesser extent imaging studies.[18,19] Death was defined as early ($<$30 days) or late ($>$30 days) after the diagnosis of IA. Mortality was regarded as attributable to IA if the patient died within 120 days since consolidation initiation and had microbiological, histological or clinical evidence of IA and when any alternative cause had been excluded.

Statistical analysis

Continuous variables were compared with Student's *t*-test (for normally distributed variables) or the Mann–Whitney *U*-test (for non-normally distributed variables). Categorical variables were evaluated with the χ^2 or two-tailed Fisher's exact test. ORs and 95% CIs were calculated for all associations that emerged. Results are expressed as mean $\pm$ SD or median (range) (continuous variables) or as percentages of the group from which they were derived (categorical variables). Two-tailed tests were used to determine statistical significance; $P < 0.05$ was considered significant. Multivariate analysis was used to identify independent risk factors for mortality. For this analysis, we used logistic regression, and variables found to be significant in univariate testing were incorporated with a stepwise approach. The number needed to treat to achieve one additional patient free from IA was calculated as the reciprocal of the rate difference between AP and no prophylaxis.

Ethical considerations

Approval of the local institutional review board and ethics committee was obtained at all participating sites.

Results

Of 2588 patients in complete remission after induction therapy and therefore submitted to consolidation, 56 (2.2%) developed IA. Cases of IA probable predominated over histologically proven cases [43 (1.7%) versus 13 (0.5%)]. Characteristics of the 56

Table 1. Clinical characteristics of patients who developed a proven/probable IA after consolidation treatment

Patient characteristic	Total	Proven IA	Probable IA	*P*
Total number of patients	56	13	43	
Gender, *n* (%)				0.21
male	38 (68)	7 (54)	31 (72)	
female	18 (32)	6 (46)	12 (28)	
Age (years)				0.95
median	59	60	58	
range	5–79	5–71	15–79	
≥50, *n* (%)	37 (66)	9 (69)	28 (65)	
<50, *n* (%)	19 (34)	4 (31)	15 (35)	
Comorbidity, *n* (%)				0.93
yes	35 (63)	8 (62)	27 (63)	
no	21 (37)	5 (38)	16 (37)	
Inpatient stay (days)				0.80
median	31	39	31	
range	3–114	3–114	8–79	
Cytogenetic/genetic risk group, *n* (%)				0.72
favourable	22 (40)	5 (38)	17 (39)	
intermediate	17 (30)	5 (38)	12 (28)	
adverse	12 (21)	2 (16)	10 (23)	
unknown	5 (9)	1 (8)	4 (10)	
Year of observation, *n* (%)				0.15
2011	5 (9)	0	5 (12)	
2012	5 (9)	3 (23)	2 (5)	
2013	13 (23)	3 (31)	10 (23)	
2014	17 (30)	4 (23)	13 (30)	
2015	16 (29)	3 (23)	13 (30)	
Central venous catheter, *n* (%)				0.35
yes	51 (91)	11 (85)	40 (93)	
no	5 (9)	2 (25)	3 (7)	
Cytarabine dose, *n* (%)				0.86
standard	14 (25)	5 (38)	16 (37)	
intermediate/high	42 (75)	8 (62)	27 (63)	
Mucositis (Grade >2), *n* (%)				0.28
yes	15 (27)	2 (15)	13 (30)	
no	41 (73)	11 (85)	30 (70)	
Steroid therapy, *n* (%)				0.87
yes	16 (28)	4 (31)	12 (28)	
no	40 (72)	9 (69)	31 (72)	

patients with IA are summarized in Table 1. As consolidation therapy, 14 (25%) patients received standard-dose cytarabine (100 mg/m^2, days 1–5, continuous infusion), 21 (37.5%) patients received intermediate-dose cytarabine (500 mg/m^2 every 12 h, days 1–6) and 21 patients received high-dose cytarabine (≥2 g/m^2/day, days 1–5 or 1, 3, 5 and 7). Thirty-four patients were also given anthracycline together with cytarabine. The lung was the most frequently involved site (50 of 56; 89%); 8 patients (14%) had a disseminated IA with at least three sites involved. Four patients also presented a history of IA during the induction phase. No significant differences were observed between patients who developed proven IA and those with probable IA (see Table 1).

Risk factors

To identify potential risk factors associated with the development of proven/probable IA during/after consolidation therapy, we compared the clinical characteristics of patients diagnosed with IA with those of the control group. In univariate analysis none of the variables analysed were significantly associated with the risk of IA during consolidation (see Table 2).

Prophylaxis during induction and consolidation

Most patients (2199, 85%) received prophylactic posaconazole during the previous induction phase while the remaining 389 (15%) received other antifungal agents. There were no significant differences in the incidence of IA after consolidation based on the type of AP delivered in the induction (posaconazole versus other agents). On the other hand, delivering AP in consolidation was associated with a significant benefit. In fact, the diagnosis of IA was made in 34 of 1137 (2.9%) patients who did not receive AP and in 22 of 1451 who did receive it (1.5%) ($P < 0.01$). The number needed to treat to achieve one additional patient who will benefit from the AP was 71. In other words, on average, 71 patients would have to receive AP (instead of no AP) for one additional patient to not have IA.

Table 3 summarizes the distribution of patients in the different consolidation-course AP groups.

Furthermore, AP was able to reduce the failure of the first antifungal therapy. In fact, the success of antifungal therapy was observed in 16 of 22 (73%) patients who received AP and in 10 of 34 (29%) who did not receive AP (P=0.001).

Treatment and response to antifungal therapy

'Pre-emptive' antifungal therapy was started in 36 patients (64%), mainly with liposomal amphotericin B [22 (61%); $P < 0.0005$], while the remaining 20 (37%) received a 'targeted' approach. Thirteen patients switched from liposomal amphotericin B to voriconazole, so that the most frequently targeted antifungal therapy was voriconazole (28 of 56, 50%). Combined therapy was given as first-line targeted therapy in four patients (7%). The most frequent combination was liposomal amphotericin B plus voriconazole. Efficacy of treatment was assessed by the rate of success of the first-line therapy. Of 56 patients, 26 (46%) had a good response. However, when considering the drugs most frequently used in first-line therapy, no significant differences emerged in univariate analysis with regard to outcome (Table 4).

Outcome

The early mortality rate was 9% (5 of 56) while the late mortality rate was 16% (9 of 56). No significant inter-centre differences were observed. Death due to IA or occurring in the presence of IA (mortality attributable to IA) occurred in 7% of patients (4 of 56) by day 30 and in 9% (5 of 56) by day 120. Other causes of mortality were bacterial infections and AML progression (the latter particularly for late deaths). Univariate analysis showed that the parameters that influenced outcome were the duration of neutropenia ≥10 days, treatment with high-dose cytarabine or age ≥60 years (see Table 4). Multivariate analysis confirmed that age ≥60 years (OR=12.46, 95% CI=1.13–136.73; P=0.03) and high-dose cytarabine (OR=10.56, 95% CI=1.95–116.74; P=0.04) were factors that

Table 2. Univariate analysis of clinical characteristics of controls and IA cases

Variable	Controls	IA cases	*P*
Total number of patients	102	56	
Gender, *n* (%)			0.72
male	66 (65)	38 (68)	
female	36 (35)	18 (32)	
Age (years)			0.17
median	57	59	
range	1–79	5–79	
≥50, *n* (%)	56 (55)	37 (66)	
<50, *n* (%)	46 (45)	19 (34)	
Comorbidity, *n* (%)			0.16
yes	54 (53)	35 (63)	
no	48 (47)	21 (37)	
Cytogenetic/genetic risk group, *n* (%)			0.88
favourable	42 (41)	22 (40)	
intermediate	28 (37)	17 (30)	
adverse	32 (22)	12 (21)	
unknown	0	5 (9)	
Neutropenia >10 days, *n* (%)			0.13
yes	91 (89)	51 (91)	
no	11 (11)	5 (9)	
Cytarabine dose, *n* (%)			0.58
standard	30 (30)	14 (25)	
intermediate/high	72 (70)	42 (75)	
Mucositis (Grade >2), *n* (%)			0.72
yes	30 (29)	15 (27)	
no	72 (71)	41 (73)	
Steroid therapy, *n* (%)			1
yes	25 (25)	16 (28)	
no	77 (75)	40 (72)	

independently affected outcome. Taking into account the overall population receiving the consolidation course, the overall mortality rate and the mortality rate attributable to IA on day 120 were 0.34% and 0.19%, respectively.

Discussion

This retrospective study focuses on the incidence of proven/probable IA and the role of AP in a multicentre large 'real-life' series of consecutive adult and paediatric patients with AML submitted to consolidation chemotherapy. Overall, the incidence of IA was 2.2%: our observation is comparable to that reported in the past decade, in which the frequency of invasive fungal infection ranged from 2%[16,20] to 3%.[13] Thus, although significant progress has been made in the cure of patients with AML, the incidence of IA after consolidation is stable over time.

Owing to the inhalation of dormant spores from the environment, the lung is the most frequent site of IA development.[13] The *Aspergillus* spores break quiescence and grow in the human lung, exploiting the neutropenia and mucosal damage.[18] The pivotal role of neutrophils in the host defence against *Aspergillus* infections is well known,[21,22] particularly when mucosal barriers have been disrupted. As reported in other studies[23–25] the use of high-dose cytarabine-based regimens was not associated with a higher incidence of IA. However, in our experience, treatment with high-dose cytarabine had a significant impact on the mortality rate attributable to IA, due to the profound neutropenia and extensive gastrointestinal mucosal damage associated with the administration of this high-dose regimen. In addition, the profound neutropenia occurring after high-dose cytarabine may represent the reason explaining such a correlation, as previously reported.[13] Finally, in multivariate analysis we found that age is an independent factor affecting the outcome. Indeed, almost all deaths due to IA were observed in patients aged ≥60 years.

We wanted also to explore the role of AP, given in induction and consolidation, in preventing IA from occurring after consolidation. The AP during induction did not show a protective effect on the onset of IA during the consolidation phase of the chemotherapeutic programme. Such a lack of benefit may depend on the fact that the patients, immunosuppressed and frail, acquire the infection in the community, after hospital discharge.[26] Otherwise, posaconazole may control subclinical fungal infection or colonization at the time of prophylaxis,[27] reducing but not abrogating the risk of an overt infection at the time of subsequent episodes of immunosuppression.

The centres involved in this survey had different antifungal policies during the AML consolidation phase. Indeed, about half of them did not deliver AP, while the others used mould-active prophylaxis. Itraconazole was the most frequently dispensed drug, followed by posaconazole. The choice of some centres to use posaconazole was dictated by different reasons such as ongoing construction works nearby the hospital, absence of a laminar air flow room[28] or physicians' simple opinion that the patients were at high risk of developing IA. The results from our study show that in a large real-world setting, mould-active AP with itraconazole or posaconazole decreases the rate of IA after the consolidation course. The rate of our proven/probable breakthrough IA in patients treated with posaconazole was in line with the others' experience.[29]

In our experience, AP appears to reduce the risk of IA after the consolidation course and strengthens the efficacy of antifungal therapy. Most of the patients who received AP responded well when the first-line antifungal therapy was instituted, and therefore we can assume that a broad-spectrum AP may decrease the rate of resistant pathogens, enhancing the action of the subsequent antifungal therapeutic regimen. The beneficial effect of prophylaxis was translated into number needed to treat, a metric of comparative efficacy that can be utilized to inform decision-making in clinical practice.

Our observation is in line with other studies previously reported[30,31] and does not seem to confirm the increase of resistant *Aspergillus* species in breakthrough infections, although it remains difficult to draw any firm conclusion due to the low number of proven cases. Alternatively, AP may reduce the burden of fungal infections resulting in the occurrence of less severe forms of IA, which may better respond to antifungal treatment.

With the limitations of its retrospective nature, our study demonstrates that, in patients with AML, IA remains, even in consolidation, a rare but potentially life-threatening complication mainly among older patients treated with high-dose cytarabine.

Table 3. Distribution of patients in the different consolidation-course AP groups

IA	No AP	AP	Itraconazole	Posaconazole	Liposomal amphotericin B	Voriconazole
Yes	34 (2.9%)	22 (1.5%)	8 (1.03%)	8 (1.28%)	4 (12.9%)	2 (15.3%)
No	1103 (97.1%)	1429 (98%)	772 (98.97%)	619 (98.7%)	27 (87.1%)	11 (84.6%)
Total	1137 (44%)	1451 (56%)	780 (21%)	627 (15%)	31 (1%)	13 (1%)

Table 4. Univariate analysis of the mortality attributable to IA in 56 cases of IA

	Number of IA cases (%)	Number of cases with mortality attributable to IA (%)	*P*
Age (years)			**0.02**
≥60	19 (33.9)	4 (21.1)	
<60	37 (66.1)	1 (2.7)	
Site of infection			0.70
lung	48 (86)	4 (8)	
disseminated	8 (14)	1 (12)	
Certainty of diagnosis			0.85
proven	13 (23)	1 (7)	
probable	43 (77)	4 (9)	
Mean duration of neutropenia (days)			**0.03**
<10	36 (64.3)	1 (2.8)	
≥10	20 (35.7)	4 (20)	
Comorbidity			0.28
yes	32 (57)	4 (12)	
no	24 (43)	1 (4)	
Cytarabine dose			**0.04**
standard/intermediate	35 (63)	1 (3)	
high	21 (37)	4 (19)	
Steroid therapy			0.53
yes	16 (28)	2 (12)	
no	40 (72)	3 (7)	
Prophylaxis			0.96
yes	22 (39)	2 (9)	
no	34 (61)	3 (8)	
Pre-emptive versus targeted therapy			0.44
pre-emptive	36 (64)	4 (11)	
targeted	20 (36)	1 (5)	

Furthermore, our data support the protective role of mould-active AP in this category of patients. Balancing the clinical efficacy versus the cost-effectiveness, in our opinion the use of AP during consolidation should be limited to older patients receiving high-dose cytarabine. Prospective randomized studies should be performed to confirm our data and to identify the subset of patients who require anti-mould prophylaxis even during consolidation chemotherapy.

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References

1 Döhner H, Estey E, Grimwade D *et al*. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood* 2017; **129**: 424–7.

2 Burnett A, Wetzler M, Löwenberg B. Therapeutic advances in acute myeloid leukemia. *J Clin Oncol* 2011; **29**: 487–94.

3 Cornely OA, Maertens J, Winston DJ *et al*. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med* 2007; **356**: 348–59.

4 Egerer G, Geist MJ. Posaconazole prophylaxis in patients with acute myelogenous leukaemia—results from an observational study. *Mycoses* 2011; **54**: 7–11.

5 Hahn J, Stifel F, Reichle A *et al*. Clinical experience with posaconazole prophylaxis—a retrospective analysis in a haematological unit. *Mycoses* 2011; **54**: 12–6.

6 Michallet M, Sobh M, Morisset S *et al*. Risk factors for invasive aspergillosis in acute myeloid leukemia patients prophylactically treated with posaconazole. *Med Mycol* 2011; **49**: 681–7.

7 Tacke D, Buchheidt D, Karthaus M *et al*. Primary prophylaxis of invasive fungal infections in patients with haematologic malignancies. 2014 update of the recommendations of the Infectious Diseases Working Party of the German Society for Haematology and Oncology. *Ann Hematol* 2014; **93**: 1449–56.

8 Patterson TF, Thompson GR, Denning DW *et al*. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2016; **63**: e1–60.

9 Tissot F, Agrawal S, Pagano L *et al*. ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. *Haematologica* 2017; **102**: 433–44.

10 Mellinghoff SC, Panse J, Alakel N *et al*. Primary prophylaxis of invasive fungal infections in patients with haematological malignancies: 2017 update of the recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO). *Ann Hematol* 2018; **97**: 197–207.

11 Pagano L, Caira M, Candoni A *et al*. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. *Haematologica* 2006; **91**: 1068–75.

12 Pagano L, Caira M, Valentini CG *et al*. Current therapeutic approaches to fungal infections in immunocompromised hematological patients. *Blood Rev* 2010; **24**: 51–61.

13 Pagano L, Caira M, Candoni A *et al*. Invasive aspergillosis in patients with acute myeloid leukemia: a SEIFEM-2008 registry study. *Haematologica* 2010; **95**: 644–50.

14 Pagano L, Stamouli M, Tumbarello M *et al*. Risk of invasive fungal infection in patients affected by acute promyelocytic leukaemia. A report by the SEIFEM D registry. *Br J Haematol* 2015; **170**: 434–9.

15 Even C, Bastuji-Garin S, Hicheri Y *et al*. Impact of invasive fungal disease on the chemotherapy schedule and event-free survival in acute leukemia patients who survived fungal disease: a case-control study. *Haematologica* 2011; **96**: 337–41.

16 Lewis G, Hall P, Eisa N *et al*. Acute myelogenous leukemia patients are at low risk for invasive fungal infections after high-dose cytarabine consolidations and thus do not require prophylaxis. *Acta Haematol* 2010; **124**: 206–13.

17 De Pauw B, Walsh TJ, Donnelly JP *et al*. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 2008; **46**: 1813–21.

18 Nucci M, Anaissie E. How we treat invasive fungal diseases in patients with acute leukemia: the importance of an individualized approach. *Blood* 2014; **124**: 3858–69.

19 Ullmann AJ, Aguado JM, Arikan-Akdagli S *et al*. Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. *Clin Microbiol Infect* 2018; **24** Suppl 1: e1–38.

20 Heng SC, Slavin MA, Al-Badriyeh D *et al*. Pharmacoeconomic evaluation of fluconazole, posaconazole and voriconazole for antifungal prophylaxis in patients with acute myeloid leukaemia undergoing first consolidation chemotherapy. *J Antimicrob Chemother* 2013; **68**: 1669–78.

21 Pagano L, Girmenia C, Mele L *et al*. Infections caused by filamentous fungi in patients with hematologic malignancies. A report of 391 cases by GIMEMA Infection Program. *Haematologica* 2001; **86**: 862–70.

22 Feldmesser M. Role of neutrophils in invasive aspergillosis. *Infect Immun* 2006; **74**: 6514–6.

23 Palmieri S, Sebastio L, Mele G *et al*. High-dose cytarabine as consolidation treatment for patients with acute myeloid leukemia with t(8;21). *Leuk Res* 2002; **26**: 539–43.

24 Böhm A, Piribauer M, Wimazal F *et al*. High dose intermittent ARA-C (HiDAC) for consolidation of patients with de novo AML: a single center experience. *Leuk Res* 2005; **29**: 609–15.

25 Wang L, Hu J, Sun Y *et al*. Does high-dose cytarabine cause more fungal infection in patients with acute myeloid leukemia undergoing consolidation therapy: a multicenter, prospective, observational study in China. *Medicine (Baltimore)* 2016; **95**: e2560.

26 Grow WB, Moreb JS, Roque D *et al*. Late onset of invasive *Aspergillus* infection in bone marrow transplant patients at a university hospital. *Bone Marrow Transplant* 2002; **29**: 15–9.

27 Baistrocchi R, Liu H, Brüggeman RJM *et al*. In vivo pharmacokinetics and pharmacodynamics of posaconazale in a mouse model of invasive aspergillosis. In: *Abstracts of Eighth Trends in Medical Mycology, Belgrade, Serbia,* 2017. Abstract P345.

28 Caira M, Candoni A, Verga L *et al*. Pre-chemotherapy risk factors for invasive fungal diseases: prospective analysis of 1,192 patients with newly diagnosed acute myeloid leukemia (SEIFEM 2010—a multicenter study). *Haematologica* 2015; **100**: 284–92.

29 Tormo M, Pérez-Martínez A, Calabuig M *et al*. Primary prophylaxis of invasive fungal infections with posaconazole or itraconazole in patients with acute myeloid leukaemia or high-risk myelodysplastic syndromes undergoing intensive cytotoxic chemotherapy: a real-world comparison. *Mycoses* 2018; **61**: 206–12.

30 De la Serna J, Jarque I, López-Jiménez J *et al*. Treatment of invasive fungal infections in high risk hematological patients. The outcome with liposomal amphotericin B is not negatively affected by prior administration of mold-active azoles. *Rev Esp Quimioter* 2013; **26**: 64–9.

31 Pagano L, Verga L, Busca A *et al*. Systemic antifungal treatment after posaconazole prophylaxis: results from the SEIFEM 2010-C survey. *J Antimicrob Chemother* 2014; **69**: 3142–7.