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Author contributions

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Risk of invasive fungal infection in patients affected by acute promyelocytic leukaemia. A report by the SEIFEM-D registry

Patients with acute promyelocytic leukaemia (APL) are usually considered at lower risk for developing an infectious complication (Girmenia *et al*, 2003), principally because current treatments are mainly based on the induction of myeloid differentiation rather than the highly myeloablative properties of standard chemotherapy used in patients with acute myeloid leukaemia (AML).

This prospective study, conducted in 33 locations throughout Italy, evaluated the incidence of invasive fungal infection (IFI) and the clinical characteristics in patients with APL compared to patients affected by other AML subtypes treated with intensive chemotherapy. Consecutive adult patients with newly diagnosed AML (n = 1192) were enrolled in the study between 1 January, 2010 and 30 April, 2012: 1086 had non promyelocytic-AML (npAML) and 106 had APL.

Only 881 of the 1086 npAML patients received intensive chemotherapy and were considered evaluable. Two-hundred and fourteen cases of IFIs were recorded (24%) after the induction phase, with 23 yeast infections (3%) and 191 moulds (22%). The majority of moulds were possible (136, 71%), while the remaining 55 cases were probable (n = 48) or proven (n = 7) IFIs (Table I). Three of the 106 APL patients were excluded from the analysis (one early haemorrhagic death and two poor performance status). Among the remaining 103 patients, 90 were treated with all trans retinoic

acid (ATRA) plus chemotherapy including idarubicin and 13 received ATRA plus arsenic trioxide (ATO).

Overall, 10 APL patients (9·7%) had an IFI: eight in induction phase, one in consolidation and one at time of relapse. All eight patients (7·7%) who developed an IFI after induction treatment (one proven, three probable and four possible) had a mould infection. All IFIs were observed in patients treated with ATRA plus chemotherapy. Overall, eight APL patients died during the induction phase (one IFI, four cerebral haemorrhage and three bacterial sepsis). A total of 95 patients (92%) achieved a complete remission (CR). All APL patients were further followed for a median duration of 36 months (range 3–54) and only two more cases of IFI have been observed: one possible mould infection during consolidation (mitoxantrone, etoposide and ATRA) at 16 weeks from APL diagnosis, and one probable case in a patient with relapsed APL at 132 weeks. Notably, six of the 95 patients (6%) who achieved CR subsequently relapsed. Among these patients, only four received a second induction treatment, two with ATO + ATRA and two with standard AML-like chemotherapy. One probable pulmonary aspergillosis was reported in a patient who had received a fludarabine-based chemotherapy (Table II). Only one patient died of cerebral aspergillosis during first induction, while the remaining seven patients were successfully treated with antifungal therapy. The patient who developed IFI during consolidation recovered from infection.

During the follow-up, five additional patients died of septicaemia ($n = 1$), cardiac failure ($n = 1$) and haemorrhage ($n = 3$).

Although not completely comparable, the npAML and APL cohorts were evaluated in order to analyse the main differences between the two groups within 90 d of starting their

Table I. Main characteristics of APL and AML patients treated with curative chemotherapy and comparison of these two groups of patients for IFI risk during first induction chemotherapy.

	APL (cases)	AML (cases)	*P*-value*
Patients (*n*)	103	881	
Age, years, median (IQR)	50 (40–64)	58 (47–66)	**0·01**
Male/Female	50/53	448/433	0·5
Performance status (WHO)			
0–1	76	284	**<0·0001**
>1	27	597	
Mucosal barrier disruption	56 (54%)	512 (58%)	0·4
Central venous catheter	52 (50%)	687 (78%)	**<0·0001**
Neutropenia (<1 neutrophils × 10^9/l)	103 (100%)	874 (99%)	0·3
Duration of neutropenia <1 neutrophils × 10^9/l, days, median (IQR)	23·5 (15–30)	23 (18–29)	0·45
Duration of severe neutropenia <0·5 neutrophils × 10^9/l, days, median (IQR)	18 (6–25)	20 (15–26)	**0·003**
Antifungal prophylaxis	94 (91%)	837 (95%)	0·1
Topical antifungal prophylaxis only	17 (17%)	60 (7%)	**0·0005**
Prophylactic used			
Fluconazole	33 (32%)	168 (19%)	**0·002**
Itraconazole	13 (12%)	117 (13%)	0·8
Posaconazole	38 (37%)	513 (58%)	**<0·0001**
Other	1 (1%)	23 (3%)	
IFI			
All cases	8 (7%)	214 (24%)	**0·0001**
Proven/probable	4 (4%)	77 (9%)	0·08
Moulds			
All cases	8 (7%)	191 (22%)	**0·0006**
Proven/probable	4 (4%)	55 (6%)	0·4
Yeasts			
All cases	0	23 (3%)	**<0·0001**
Antifungal treatment	11 (11%)	275 (31%)	**<0·0001**
Duration of treatment, days, median (IQR)	14 (7–30)	12 (8–16)	0·6
Overall mortality at 30 d	8 (8%)	110 (12%)	0·1
Mortality due to IFI at 30 d	1 (1%)	25 (3%)	0·5

APL, acute promyelocytic leukaemia; AML, acute myeloid leukaemia; IQR, interquartile range; WHO, World Health Organization; IFI, invasive fungal infection.

*The Wilcoxon rank sum test was used to compare continuous variables. Categorical variables were evaluated with the χ^2 or two-tailed Fisher's exact test.

Table II. Clinical characteristics of patients who developed IFI.

Patient	Age (years) Sex	Treatment	Prophylaxis	Duration (d)	IFI	Level of certainty	Time of diagnosis (weeks)	Location	Signs and symptoms	Antifungal treatment	IFI Duration (d)	Outcome
1	65/M	Induction (AIDA)	None		Not identified	Probable	3	Lung	Fever, dyspnea	L-AmB	14	Complete response
2	31/M	Induction (AIDA)	Itraconazole	20	Not identified	Possible	3	Lung	Fever, dyspnea	L-AmB followed by voriconazole	35	Complete response
3	63/F	Induction (AIDA)	Fluconazole Itraconazole Aerosol L-AmB	6 25 15	*Aspergillus* spp	Proven	4	CNS	Sensory alterations, coma	Caspofungin	2	Death
4	48/M	Induction (AIDA)	Posaconazole	20	*Aspergillus* spp	Probable	3	Lung	Fever, dyspnea, thoracic pain	L-AmB	15	Complete response
5	42/F	Induction (AIDA)	Posaconazole	14	*Aspergillus* spp	Probable	2	Lung	Acute respiratory distress syndrome	L-AmB followed by voriconazole	90	Complete response
6	44/M	Induction (AIDA)	None		Not identified	Possible	2	Lung	Fever, acute respiratory failure	1st line: posaconazole 2nd line: L-AmB	36	Complete response
7	49/M	Induction (AIDA)	Posaconazole	18	Not identified	Possible	2	Lung	Rash, fever, dyspnea	L-AmB	7	Complete response
8	55/M	Induction (AIDA)	Posaconazole	15	Not identified	Possible	2	Lung	Fever, pain, septic shock	L-AmB	15	Death due to bacterial infection
9	25/F	Consolidation (AIDA 2nd course) (MTZ/ETO + ATRA)	None		Not identified	Possible	16	Lung	Fever, thoracic pain	L-AmB followed by voriconazole	>60	Complete response
10	44/F	Salvage (FLAI)	Posaconazole	23	*Aspergillus* spp	Probable	132	Lung	Fever	1st line: L-AmB followed by voriconazole1 2nd line: L-AmB + caspofungin	33 23	Progression progression

IFI, invasive fungal infection; M, male; F, female; ATRA, all trans retinoic acid; AIDA, ATRA, idarubicin; FLAI, fludarabine, cytarabine, idarubicin; MTZ, mitoxatrone; ETO, etoposide; FUO, fever of unidentified origin; L-AmB, lipid formulation of amphotericin B; CNS, central nervous system.

first treatment for leukaemia (Table I). Significant differences were observed regarding the prophylactic drug used: posaconazole was more frequently applied in npAML. Although the prophylaxis was less mould-oriented in APL, the overall incidence of IFI and the incidence of mould infections were both markedly higher in npAML. A significant difference was observed between APL and npAML with regard to systemic antifungal treatment, as it was more frequently utilized in npAML. Interestingly, while the number of patients who developed neutropenia was similar in the two groups, the median duration of severe neutropenia (<0·5 neutrophils $\times$ 10^9/l) was significantly shorter in the APL arm. No significant difference regarding overall mortality and attributable mortality among the two patient cohorts was recorded. No significant factors associated with the onset of an IFI among APL were identified.

Before the advent of ATRA, patients were treated with chemotherapy alone, which yielded CR rates of 50–80%. However, deaths were often caused by infections owing to the use of chemotherapy regimens similar to those administered to npAML patients, leading to prolonged severe neutropenia (Cordonnier *et al*, 1985; Tallman *et al*, 1997). The inclusion of ATRA in combination with chemotherapy and subsequently that of ATO definitely improved patient outcomes thus turning APL into a highly curable disease. Meanwhile, the use of these agents enabled a decrease/de-escalation of the chemotherapeutic agents used. The reduction of the chemotherapeutic 'burden' also reduced chemotherapy-related toxicity; in particular, the reduced duration of severe neutropenia observed may, in turn, affect morbidity and mortality from infectious complications. However the risk of infection is not completely absent, especially if high dose cytarabine is included in the consolidation regimen (Lo-Coco *et al*, 2010; Sanz *et al*, 2010; Iland *et al*, 2012).

Few IFIs in APL have been reported in clinical trials (de la Serna *et al*, 2008; Iland *et al*, 2012), and only four cases (4·5%) of non-fatal IFI were reported (one pulmonary mycetoma, two hepatosplenic candidiasis and one candidaemia) in a series of 89 APL patients treated with the AIDA protocol (ATRA + idarubicin) (Girmenia *et al*, 2003), while in a paediatric series of 33 APL, only two patients (6·1%) experienced fungal infection (Cellot *et al*, 2013).

Similar to the results reported in npAML patients (Pagano *et al*, 2006), the majority of APL cases in the present study developed IFI after first induction treatment. All IFIs occurred in patients treated with ATRA plus chemotherapy. Only a few patients relapsed and it is noteworthy that one of the two patients treated with an aggressive second line induction therapy developed an IFI. This suggests that if the patients had received an aggressive chemotherapy, characterized by a prolonged neutropenia, the risk of IFI would probably have been similar to that of npAML.

Overall, the rate of IFI was significantly lower among patients with APL compared to those with npAML. Unlike the npAML cohort, posaconazole was significantly less utilized in APL patients. Another interesting observation is the total absence of yeast infections in the APL group in our series.

On the basis of this study, APL patients must be considered at lower risk of IFI if treated with differentiation-inducing agents. Taking the substantial cost of prophylactic antifungal treatment and the possible side effects, interaction between azoles and drugs active for the treatment of APL (Naito *et al*, 2006) into account, a mould active antifungal prophylaxis could be omitted in APL patients at the first induction phase of their treatment.

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Author contributions

LP and FA designed the study and wrote the paper. MT, MC and MS analysed the data and wrote the paper. AB, AN, CC and AC participated in the data collection and revision of the paper. All the other authors collected the data. All the authors approved the submitted final version.

Disclosures

L.P. 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.T. has received honoraria from Gilead Sciences and Merck. A.N. has received honoraria from Gilead Sciences and Merck. A.B. has received honoraria from Gilead Sciences and Merck.

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