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Characterisation of Antifungal Prophylaxis and Therapy Among Inpatients With Haematological Malignancies in Non-Research Clinical Setting: A Multicentre Italian Experience

Criscuolo Marianna[1] | Bonanni Matteo[2,3] | Martino Giordana[4] | Farina Francesca[5] | Verga Luisa[6] | Marchesi Francesco[7] | Basilico Claudia[8] | Del Principe Maria Ilaria[9] | Tisi Maria Chiara[10] | Cattaneo Chiara[11] | Picardi Marco[12] | Bonuomo Valentina[13,14] | Fracchiolla Nicola[15] | Candoni Anna[16] | Perruccio Katia[17] | Stanzani Marta[18] | Cesaro Simone[19] | Fanci Rosa[20] | Dargenio Michela[21] | Forghieri Fabio[16] | Ballanti Stelvio[22] | Cudillo Laura[23] | Cuccaro Annarosa[2] | Carraro Francesca[24] | Zama Daniele[25,26] | Armiento Daniele[27] | Garzia Maria Grazia[28] | Spolzino Angelica[29,30] | Busca Alessandro[31] | Pagano Livio[32,33]

Correspondence: Criscuolo Marianna (marianna.criscuolo@policlinicogemelli.it)

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ABSTRACT

Background: Invasive fungal infections (IFI) are a prominent cause of morbidity and mortality among patients with haematological malignancies (HMs). Diagnostic work-up excluding IFI is mandatory in case of persistent fever while antifungal treatment (AFT) is started.

Objectives: We aimed to describe antifungal prophylaxis (AFP) and AFT among haematological patients with IFI managed in clinical practice, focusing on microbiological and radiological characteristics, 30-day outcome and therapeutic options after AFT failure.

Patients and Methods: We enrolled 461 consecutive adult and paediatric patients with HMs, in which an intravenous AFT was started from September 2019 to December 2021. After serum galactomannan (GM) and chest CT scan, they were stratified as presenting with proven, probable, and possible IFI according to 2008 EORTC-MSG criteria. Fungal isolates were detected from culture tests in 17.5% and from biopsy in 1.5% of patients. Mould active and non-active AFP was used in 42.3% and 16.5% of cases, respectively.

Results: Use of AFP significantly impact on serum GM negativity ($p < 0.001$ for mould active and $p = 0.04$ for mould non active, respectively). Use of mould non-active prophylaxis significantly correlates with radiological imaging (typical $p = 0.0037$, IC (0.370–0.825) and negative -$p = 0.0031$, IC (0.241–0.750)). Toxicity, progression, and drug interaction were responsible for therapy change in 58 (12%) patients: 18 patients with proven/probable IFI needed multiple courses of AFT. At 30 days from starting AFT, overall mortality with IFI was 23/461 (5%).

Conclusions: In this observational study, we recorded an impact of AFP on serum GM results and radiological imaging. Need of AFT should be carefully evaluated, as diagnostic work-up might be affected not only by specific disease risk but also by previous AFP.

SEIFEM (Sorveglianza Epidemiologica Infezioni nelle Emopatie Maligne) group.

For affiliations refer to page 7.

1 | Introduction

Invasive fungal infection (IFI) is still a potential life-threatening event complicating the treatment of patients with haematological malignancies (HMs) [1–3]. As indications for antifungal prophylaxis (AFP) are precisely described [4], classic risk factors for IFI may be modified according to extended indications to cellular therapy and exposition to multiple lines of therapy. Persistent fever despite antibiotic therapy and identification of risk factors prompt comprehensive diagnostic work-up for suspected IFI and guide the need for antifungal therapy (AFT). Efficacy of AFT is crucial, as it impacts on concomitant and subsequent treatments. While intolerance to AFT and drug interaction (DI) with chemotherapy or other treatment may cause suboptimal drug exposure and unsatisfactory clinical response, resistance to single agent and/or combination AFT may negatively impact on the outcome of patients.

In this study, we aimed to describe antifungal prophylaxis and treatment in a population of haematological patients with IFI managed in clinical practice, focusing on differences in microbiological and radiological characteristics according to antifungal prophylaxis, 30-day outcome, and therapeutic options after failing first line AFT.

2 | Patients and Methods

This multicentre, non-interventional, observational, prospective study involved 26 Italian centres during an observational period of 28 months. All consecutive inpatients with HMs in which an intravenous AFT was started for suspected IFI were recruited. Antifungal therapy was administered in case of persistent fever, positivity of microbiological assays, suggestive radiological features, or a combination of them. Antifungal prophylaxis was administered as per international guidelines in patients with predictable long-lasting neutropenia [4, 5]. Previous or ongoing transplant procedure, outpatient status and oral AFT were all exclusion criteria. We consider that transplant recipients presented a unique clinical profile and risk factors for IFI. Although suffering from the same pathologies as those treated with conventional chemotherapy, these patients receive highly myeloablative chemotherapy and prolonged immunosuppressive therapy which makes them more susceptible to developing IFIs. Patients treated front-line with oral antifungal therapy in clinical practice are usually outpatients in whom the antifungal treatment is initiated, in most cases, empirically and in which the diagnostic work-up is not as timely and accurate as the one in place for patients hospitalised in treatment departments. In both cases we considered that these patients were subject to an evaluation bias and were therefore excluded from this evaluation. Patients starting IV antifungal therapy and then switched to oral antifungal therapy were allowed in the study if they completed at least 48 h of IV treatment.

Demographics, disease characteristics and treatment schedule, laboratory and radiology evidence, information about AFP and AFT and outcome were gathered on a password-protected database. Both fixed and open answers were allowed in order to ensure accuracy in reporting data. A homogeneous diagnostic work-up for IFI was established among all 26 participating centres. Blood cultures for fungal pathogens and serum galactomannan (GM) were performed before starting AFT, when persistent fever and clinical suspicion of IFI were emerging. Chest high resolution computed tomography (HRCT) scan and bronchoalveolar lavage (BAL) were performed at the beginning of AFT, according to local availability. Sinus and/or central nervous system CT scan were performed if clinically indicated. Serum GM cut-off used was 0.5 at all participating centres. Patients were followed up to 30 days after starting of AFT, to evaluate possible toxicity leading to withdrawal of AFT and outcome. Complete response was defined as resolution of clinical signs and symptoms and normalisation of previous radiological and microbiological findings. Partial response was defined as clinically significant improvement in signs and symptoms, reduction of size and/or number of lesions on radiological imaging and normalisation of microbiological findings. Clinical stability was defined as clinical improvement in signs and symptoms and stability of radiological imaging studies, irrespective of microbiological findings. Local investigators provided information about withdrawal of AFT and cause of death, due to progression of HMs, IFI or a combination of both, according to clinical judgement and known DI. Microbiological and radiological characteristics were defined according to EORTC/MSG 2008 criteria [6]. The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to and the appropriate ethical review committee approval has been received.

2.1 | Statistical Analysis

The data were processed through various statistical analyses. For univariate analysis, a Chi-squared test was chosen for categorical outcomes. ANOVA was chosen to see the effects of prophylaxis on radiological methodology, microbiological methodology and outcome: this preliminary analysis was then corroborated by logistic regression.

A logistic regression was then performed with the outcome as the dependent variable, associated with prophylaxis, radiological methodology, and GM.

Multinomial regression was used to compare the radiological outcome with the various types of prophylaxis. This type of analysis was also chosen to analyse the mortality variable associated with the types of prophylaxis, diagnosis, and radiological variable.

Additionally, a logistic regression was also performed to see the association between GM and the various types of prophylaxis.

All statistical analyses were performed with the RStudio program, version 4.4.2.

3 | Results

We gathered data on 429 adult and 32 paediatric patients treated with AFT from September 2019 to December 2021 in 26 Italian hematologic centres. Characteristics of patients were reported in Table 1.

TABLE 1 | Characteristics of patients.

Diagnosis	*N*	Age > 60 yo	Phase of disease				ANC < 500/mmc	Antifungal prophylaxis			Serum GM		Radiological imaging			Antifungal therapy			
			Induction	Consolidation/ Manteinance	Refractory/ relapse	Not known		Moulds active	Moulds non active	No prophylaxis	Positive	Negative	Typical	Non typical	Negative	L-Amb	Moulds active azoles	Echinocandins	Combination	Other azoles
AML	267	130	170	35	57	5	155	179	27	58	57	193	101	119	21	180	32	46	8	1
ALL	75	19	37	14	22	2	41	8	18	49	18	53	31	26	8	44	11	16	2	2
NHL/HCL	76	34	44	7	23	2	20	2	21	53	20	54	24	33	12	28	15	25	6	2
MDS	13	4	10	0	2	1	3	7	1	5	1	12	6	5	0	9	0	1	2	1
MDS/MPN	8	7	3	0	1	3	3	1	2	5	3	5	2	6	0	2	4	1	0	1
MM	12	7	5	1	6	0	2	0	5	7	6	6	4	6	2	2	3	5	1	1
CLL	3	2	2	0	1	0	1	0	0	3	1	2	1	0	2	2	0	1	0	0
HD	7	1	3	0	4	0	3	0	2	5	3	0	4	0	3	3	3	1	0	0

Abbreviations: ALL, acute lymphoblastic laeukemia; AML, acute myeloid laeukemia; ANC, absolute neutrophil count; CLL, chronic lymphocytic leukaemia; GM, galattomannan; HCL, hairy cell laeukemia; HD, Hodgkin disease; L-Amb, liposomal amphotericin B; MDS, myelodysplastic syndromes; MM, multiple myeloma; MPN, myeloproliferative neoplasms; NHL, non Hodgkin lymphoma.

Most patients were diagnosed with acute leukaemia, with AML predominance (60.4%) in adult and ALL predominance (62.5%) in paediatric patients. Disease phase was induction in most adult patients (61.1%), while refractory disease was prevalent (46.9%) among paediatric patients.

Almost one third of paediatric patients did not receive AFP, while 14 patients (43.7%) received mould active prophylaxis. Among the whole population, antifungal prophylaxis was prescribed in 271 patients (58.8%) while no prophylaxis was prescribed in 190 patients (41.2%). Among 195 patients with mould active prophylaxis, 173 patients (88.7%) were diagnosed with acute myeloid leukaemia (AML). The other patients were diagnosed with acute lymphoblastic leukaemia (ALL; 8, 4.2%), myelodysplastic syndromes (MDS; 7, 3.5%), acute promyelocytic leukaemia (APL; 4, 2.2%), lymphoproliferative disorders (2, 1.1%) and myeloproliferative neoplasms (MPN; 1, 0.5%). Patients with moulds non-active prophylaxis and without prophylaxis were more heterogeneous. Among 76 patients with moulds non-active prophylaxis, 27 (35.5%) had AML, 23 (30.3%) lymphoproliferative disorders, 18 (23.7%) ALL, 5 (6.5%) multiple myeloma (MM), 2 (2.5%) MPN and 1 (1.5%) MDS. Among 190 patients without prophylaxis, 61 (32.1%) had lymphoproliferative disorders, 58 (30.5%) AML, 49 (25.8%) ALL, 7 (3.7%) MM, 5 (2.7%) MDS and MPN each and 4 (2.1%) APL.

Serum GM was performed in all patients: it was negative in 162 patients (83%) with mould active prophylaxis, in 45 patients (59%) with mould non-active prophylaxis and in 144 patients (76%) without prophylaxis.

CT scan result was available in all cases: it was negative in 15 (8%) and 3 patients (4%) with mould active and mould non-active prophylaxis, respectively, and in 25 patients (13%) without prophylaxis. A typical imaging was found in 69 (35%) and 37 patients (49%) with mould active and mould non-active prophylaxis, respectively, and in 67 patients (35%) without prophylaxis.

Use of AFP significantly impacts serum GM negativity ($p = 0.002$, specifically $p < 0.001$ (CI −1.541 −0.865) and $p = 0.04$ (CI −0.956 −0.026) for mould active and mould non-active drugs, respectively). According to radiological imaging, the use of mould non-active prophylaxis significantly correlates with typical imaging ($p = 0.0037$, CI (0.370–0.825)) and negative imaging ($p = 0.0031$, CI (0.241–0.750)). No significant correlation with the use of mould active drugs was reported. Additional analyses were performed to evaluate the influence of age as a continuous variable, phase and type of disease, intensity of chemotherapy regimens, comorbidities and prophylaxis on radiological imaging. The analysis showed that induction therapy and relapse disease were significantly associated with typical imaging ($p < 0.001$ CI 1.227–2.600 and CI 0.823–2.438, respectively), with a trend for lymphoma type therapy reducing the probability of typical imaging ($p = 0.054$, CI −3.029–0.040). No significant impact was demonstrated for other variables.

After extensive diagnostic work-up, fungal isolates were detected from culture tests in 81 patients (17.5%), while in 7 patients a biopsy was performed (1.5%); no strains were isolated in 374/461 patients (81%) (Table 3). Isolation distribution adjusted for AFP is shown in Table 2.

TABLE 2 | Isolation distribution adjusted for antifungal prophylaxis.

	IFI possible			IFI probable			IFI proven		
	Moulds active	Moulds non active	None	Moulds active	Moulds non active	None	Moulds active	Moulds non active	None
Candida spp			4	2		5	3	5	11
Aspergillus spp	4	2	1	10	6	10	1	5	4
P.jirovecii	1					3	2		1
Rare yeasts				1			1		1
Rare moulds			1			1			2
Criptococcus									1

In 248 adult (57.8%) and 19 paediatric (59.3%) patients liposomal amphotericin B (L-AmB) was the treatment of choice; echinocandins were used in 91 adult (21.2%) and 5 paediatric (15.6%) patients, azoles in 72 adult (16.7%) and 5 paediatric (15.6%) patients, and a drug combination in 16 adult (3.7%) and 3 paediatric (9.3%) patients.

Switch to oral formulation was the cause of antifungal change in 45 adult and 6 paediatric patients (11%), while availability of microbiological isolate requiring a different targeted therapy was reported in 14 adult and 1 paediatric patient (3%). Toxicity, progression and DI were responsible for therapy change in 22 (21 adult and 1 paediatric) (5%), 31 (30 adult and 1 paediatric) (6%) and 5 (1%) patients, respectively. Particularly, 18 patients had a proven/probable IFI for which multiple courses of AFT were prescribed (Table 4). Seven patients changed AFT for toxicity or DI. Five patients switched from VCZ to L-AmB or to ICZ: 2 of them needed a third line of AFT but all died. Two patients switched from amphotericin B lipid complex to VCZ and were cured from infection. Eleven patients changed AFT for progression of IFI: 6 patients switched from L-AmB to ICZ or VCZ (3 cases each) and 5 patients died overall. Three patients switched from caspofungin to L-AmB and responded to AFT, even if in 1 case a further switch to ICZ was needed. One patient successfully switched from ICZ to VCZ, and another one rapidly deteriorated before any change in AFT was possible.

At 30 days, overall mortality with IFI was reported in 20 adult and 3 paediatric on 461 patients (4.6% and 9.3%, overall 4.9%). Among patients with yeasts, 12/20 patients with candidemia and 1/4 patients with rarer yeasts died with IFI. Among patients with moulds, 8/43 patients with *Aspergillus* and 2/4 patients with rarer moulds died with IFI. No deaths were recorded among patients with *Pneumocystis jirovecii* infection.

Overall, prophylaxis use is significantly associated with survival. Particularly, both mould active and mould non-active drugs are associated with better outcome ($p < 0.001$, (CI mould active −1.445 −0.784; CI mould non active −1.727 −0.663)) compared with no prophylaxis. According to radiological imaging, no significant association emerged, although there is a trend for worse outcome among patients with non-typical imaging ($p = 0.0891$, CI (0.916–3.420)). Considering haematological diagnosis, patients with ALL had a reduced risk of mortality compared to AML ($p = 0.033$, CI (0.165–0.927)), with a protective effect for prophylaxis both mould active and mould non-active for patients with ALL ($p < 0.001$ CI (0.055–0.217) and $p = 0.004$ CI (0.132–0.687), respectively). When age as a continuous variable, phase and type of disease, intensity of chemotherapy regimens, comorbidities, prophylaxis and radiological imaging were included, relapse ($p = 0.018$ CI 0.128–1.438) was significantly associated with increased mortality, while mould active prophylaxis ($p = 0.002$ CI −2.123 −0.477) was a protective factor for mortality. No significant impact was demonstrated for other variables, particularly for different radiological presentation of suspected IFI.

4 | Discussion

Our study was designed to define the actual management of IFI among patients with HMs. We reported on the clinical use of AFP and AFT in patients at variable risk of IFI and highlighted how microbiological and radiological findings need to be evaluated in the context of the patient's overall condition.

Recently, a retrospective analysis of 80 patients re-evaluated the role of GM screening for early detection of IFI in high-risk HMs patients (mostly AML) 7 [7]. The authors reported only 7% of early diagnosis of IFI supported by GM positivity, remarking a more important role of GM positivity as a confirmation test. In our study, serum GM resulted positive in 23% of available cases. It is possible that the value in our population is higher because patients with diagnoses other than AML were included, who are not prescribed with AFP. Moreover, we noticed that the percentage of GM positivity was considerably higher among patients with mould non-active prophylaxis, compared to patients without prophylaxis and with mould active prophylaxis. This can be explained by a discrete number of patients with AML being prescribed with the mould non-active prophylaxis, less influencing the blood release of GM from fungi.

According to radiological data, a negative CT scan is recorded in only 9% of cases, mostly among patients without prophylaxis. Moreover, both GM and TC scan were negative in 14% of cases: it is possible that these patients were included in the study for

TABLE 3 | Fungal isolates were detected from culture tests and biopsy.

	Moulds				Yeasts					
	Aspergillus spp., *N* 43	**Mucorales, *N* 1**	**Penicillum spp., *N* 1**	**Scedosporium apiospermum, *N* 2**	**Candida spp., *N* 30**	**Pneumocystis jirovecii, *N* 7**	**Trichosporon asahii, *N* 1**	**Saprochaete capitata, *N* 1**	**Magnusiomyces clavata, *N* 1**	**Cryptococcus, *N* 1**
Blood			1		15		1	1	1	
BAL	36			2		7				
Urine					14					
Sinus	1	1								
Biopsy	6				1					
Liquor										1

Abbreviation: BAL, bronchoalveolar lavage.

persistent fever and overtreated, despite a lower risk of infection. A non-typical CT scan imaging can be found in almost half of cases, more frequently among patients with mould active compared with mould non-active and no prophylaxis, although no statistical difference was highlighted. On the other hand, the use of mould non-active AFP significantly correlates with typical imaging and negative CT scan. PCZ is the most used mould active agent and is known to protect from IFI but also for reducing the elimination of GM by fungal organisms [8, 9]. Moreover, in 2010 a retrospective study recruiting patients with HMs and proven/probable IFI did not find any difference between patients fulfilling all 2008 EORTC-MSG criteria and matched patients without typical radiological features, according to clinical manifestations and outcome [10], as up to 40% of patients with non-typical radiological features developed specific imaging in the next subsequent re-evaluation. In the same line, Girmenia et al. reported no statistically significant differences in terms of response to AFT and outcome comparing patients with HMs and probable IFI presenting with typical vs. non-typical radiological features [11]. A more recent study evaluating CT scan before chemotherapy in higher risk patients with AML revealed no difference in IFI incidence among patients with typical or non-typical radiological findings [12].

In our study, almost all patients treated with mould active AFP were diagnosed with AML, while patients treated with mould non-active AFP were more heterogeneous, including patients with both lymphoproliferative neoplasms and AML, which have a different risk of IFI. While the widespread negativity of GM during prolonged AFP use may confirm the reduced predictive power reported by other authors, the role of AFP in the CT scan imaging may be more challenging. Mould non-active AFP is associated with both typical CT scan and negative imaging. These results may reflect the heterogeneous population of AFP recipients, as lymphoproliferative neoplasms often carry a lower risk of IFI and possibly have negative imaging. On the other hand, in a higher risk population as AML patients, mould non-active prophylaxis may not interfere with the typical biology of IFI resulting in CT scan typical imaging. According to these data, the risk of IFI may be misjudged and antifungal therapy misused, at least in some cases, even because diagnostic tools may be less effective. Considering disease characteristics, it is not surprising that abnormal imaging was mostly detected during induction therapy and relapse disease, irrespective of HMs and chemotherapy intensity regimens.

In the setting of AFT, the most used drugs were L-AmB and echinocandins, while PCZ and VCZ were less used. This is not surprising, as international guidelines recommend the use of these two drugs as antifungal therapy for suspected infections from moulds and yeasts, respectively [13].

In our population, 18 patients with proven/probable IFI needed to modify AFT. Among them, 5 patients had no response to first line AFT and eventually died, in 3 cases after 3 lines of treatment. In another 2 cases, patients experienced liver toxicity and needed to change AFT, but had no response to second and third line treatment and died. Although reasons for changing therapy may be different, these patients cannot be cured from IFI with direct impact on outcome. Antifungal class switching (triazoles to polyene) and combination therapy (triazoles and echinocandins)

TABLE 4 | Patients with proven/probable IFI and multiple courses of antifungal therapy.

HM diagnosis	State of disease	ANC < 500/mmc	Prophylaxis	Duration	Isolates	IFI category	First line therapy	Duration	Reason for change	Second line therapy	Third line therapy	Response to therapy	Outcome at 40 days from last switch	Outcome at 90 days from last switch	Outcome at 180 days from IFI diagosis	Final outcome
AML	Induction	Yes	Posaconazole	39 days	*Aspergillus flavus*	Probable IA	L-amphotericin B	26 days	Progression	Isavuconazole	Voriconazole and L-amphotericin B	PR	Remission	Remission	Remission	Dead (18 months after IFI)
AML	Induction	Yes	Posaconazole	7 days		Probable IA	Caspofungin	8 days	Progression	L-amphotericin B	Isavuconazole	PR	SD	PR	PR	Alive
MM	Induction	No	None		*Aspergillus spp*	Probable IA	Voriconazole	11 days	Liver toxicity	Isavuconazole		CR	CR	Dead	Dead	Dead from HM
MDS	Relaspse	Yes	None		*Aspergillus spp*	Probable IA	L-amphotericin B	18 days	Progression	Isavuconazole	L-amphotericin B and caspofungin	Progression	Progression	Dead	Dead	Dead
MDS	Onset	Yes	None		*Aspergillus flavus*	Proven IA	L-amphotericin B	14 days	Progression	voriconazole	voriconazole and anidulafungin	Progression	Dead	Dead	Dead	Dead
AML	Induction	Yes	Posaconazole	28 days		Probable IA	L-amphotericin B	5 days	Progression	No		Progression	Dead	Dead	Dead	Dead
AML	Induction	Yes	Posaconazole	21 days		Probable IA	Caspofungin	8 days	Progression	L-amphotericin B		Remission	Remission	Remission	Remission	Alive
ALL	Induction	Yes	None			Probable IA	Caspofuingin	2 days	Progression	L-amphotericin B		Remission	Remission	Remission	Remission	Alive
NHL	Induction	Yes	Fluconazole	15 days		Probable IA	Voriconazole	3 days	Liver toxicity	L-amphotericin B	isavuconazole	SD	Non rivalutato	Dead	Dead	Dead
AML	Induction	Yes	Posaconazole	8 days		Probable IA	Voriconazole	3 days	Visual hallucination	Isavuconazole		SD	Not evaluable	Not evaluable	Remission	Dead (7 months after IFI)
AML	Induction	Yes	None			Probable IA	Voriconazole	13 days	Liver toxicity	L-amphotericin B		Not evaluable	Dead	Dead	Dead	Dead
ALL	Induction	No	None			Probable IA	L-amphotericin B	13 days	Progression	isavuconazole		Progression	Dead	Dead	Dead	Dead
ALL	Induction	Yes	None		*Aspergillus spp*	Probable IA	Voriconazole	6 days	DDI with imatinib	L-amphotericin B	isavuconazole	PR	Remission	Remission	Remission	Dead (11 months after IFI)
NHL	Induction	Yes	Fluconazole	27 days		Probable IA	L-amphotericin B	6 days	Progression	Voriconazole		CR	PR	CR	CR	Dead from HM
AML	Induction	Yes	Fluconazole	16 days		Probable IA	L-amphotericin B	5 days	Progression	Voriconazole	isavuconazole and anidulafungin	Progression	Dead	Dead	Dead	Dead
AML	Relaspse	Yes	Fluconazole	15 days		Probable IA	Isavuconazole	15 days	Progression	Voriconazole		Not evaluable	Not evaluable	Not evaluable	Not evaluable	Alive
AML	Induction	Yes	Fluconazole	10 days		Probable IA	Amphotericin B lipid complex	7 days	Severe hypokalemia	Voriconazole		CR	CR	CR	CR	Alive
ALL	Induction	Yes	None			Probable IA	Amphotericin B lipid complex	2 days	Systemic reaction	Voriconazole		CR	PR	CR	CR	Alive

Abbreviations: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; ANC, absolute neutrophil count; CR, complete response; MDS, myelodysplastic syndromes; MM, multiple myeloma; NHL, non Hodgkin lymphoma; PR, partial response; SD, stable disease.

are valid approaches, with different strengths of recommendation and level of evidence [14]. In case of multiple lines failure, the prognosis is dismal as only 6/18 patients survived in our population. The use of novel agents is desirable, and patients should be enrolled in clinical trials, if available. According to outcome, we confirm the role of mould active prophylaxis in reducing mortality, with a protective effect even for patients with ALL, and the absence of differences in terms of outcome for different radiological presentations of suspected IFI.

This study has some limitations. First, we are not able to analyse the incidence of IFI among patients with and without AFP, as we have no information about contemporary patients with HMs who did not start AFT. Second, according to the design of the study, we cannot compare the overall response to AFT among patients with and without AFP. Third, we cannot further investigate the role of mould active prophylaxis in the survival of patients with ALL due to the small sample size.

In conclusion, although the role of serum GM assay and radiological imaging in the diagnosis of suspected IFI can be affected by mould active prophylaxis, AFT start should be carefully evaluated. The use of newer antifungal therapy in clinical practice is warranted to reduce mortality among patients not responsive to or complicating after first line antifungal drugs.

Author Contributions

P.L. and B.A. have made substantial contributions to conception and design. C.M., B.A., F.F., V.L., M.F., B.C., D.P.M.I., T.M.C., C.C., P.M., B.V., F.N., C.A., P.K., S.M., C.S., F.R., D.M., F.F., B.S., C.L., C.A., C.F., Z.D., A.D., G.M.G., S.A. have made substantial contributions to acquisition of data. M.G. have made substantial contributions to analysis and interpretation of data; C.M. have been involved in drafting the manuscript. All authors have been involved in revising it critically for important intellectual content, have given final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Affiliations

[1]Dipartimento di Laboratorio e Scienze Ematologiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy | [2]National Cancer Institute, Fondazione 'G. Pascale', IRCCS, Hematology-Oncology & Stem Cell Transplantation Unit, Napoli, Italy | [3]Dipartimento di Scienze Radiologiche Ed Ematologiche, Università Cattolica del Sacro Cuore, Roma, Italy | [4]Sapienza University, Roma, Italy | [5]Hematology and Bone Marrow Transplantation, IRCCS San Raffaele Scientific Institute, Milano, Italy | [6]Fondazione IRCCS San Gerardo Dei Tintori, Monza, Italy | [7]Hematology and Stem Cell Transplant Unit, IRCCS Regina Elena National Cancer Institute, Roma, Italy | [8]UO di Ematologia, Ospedale di Circolo - Fondazione Macchi, ASST Settelaghi, Varese, Italy | [9]Department of Biomedicine and Prevention, University of Rome Tor Vergata, Roma, Italy | [10]Hematology Unit, San Bortolo Hospital, AULSS 8 Berica, Vicenza, Italy | [11]Hematology Division, ASST-Spedali Civili di Brescia, Brescia, Italy | [12]Department of Clinical Medicine and Surgery, Federico II University, Napoli, Italy | [13]Department of Clinical and Biological Sciences, University of Turin, Turin, Italy | [14]Department of Medicine, Section of Hematology, University of Verona, Verona, Italy | [15]UOC Ematologia, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milano, Italy | [16]Department of Medical and Surgical Sciences, Section of Hematology, University of Modena and Reggio Emilia, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy | [17]Pediatric Oncology Hematology, Ospedale Santa Maria Della Misericordia, Perugia, Italy | [18]Hematopoietic Stem Cell Transplantation and Cellular Therapy, Hematology Unit, Ca' Foncello Hospital, Treviso, Italy | [19]Pediatric Hematology Oncology, Department of Mother and Child, Azienda Ospedaliera Universitaria Integrata, Verona, Italy | [20]SOD Complessa di Ematologia, Azienda Ospedaliero-Universitaria Careggi e Università di Firenze, Florence, Italy | [21]Hematology and Stem Cell Transplan Unit, Lecce, Italy | [22]Sezione di Ematologia e Immunologia Clinica, Ospedale Santa Maria Della Misericordia, Perugia, Italy | [23]Hematology, San Giovanni Addolorata Hospital, Rome, Italy | [24]Pediatric Oncology-Hematology, Regina Margherita Pediatric Hospital, Torino, Italy | [25]Department of Medical and Surgical Sciences, Alma Mater Studiorum, University of Bologna, Bologna, Italy | [26]Pediatric Emergency Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy | [27]University Campus Bio-Medico and, Fondazione Policlinico Universitario Campus Bio-Medico, Roma, Italy | [28]Department of Hematology, Hematology San Camillo Forlanini Hospital, Roma, Italy | [29]Department of Medicine and Surgery, University of Parma and Hematology, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy | [30]Onco Hematology, Department of Oncology, Veneto Institute of Oncology IOV, IRCCS, Padova, Italy | [31]Department of Hematology and Stem Cell Transplant Unit, Azienda Ospedaliera Universitaria Citta' Della Salute e Della Scienza, Torino, Italy | [32]Sezione di Ematologia, Dipartimento di Scienze Radiologiche Ed Ematologiche, Università Cattolica del Sacro Cuore, Roma, Italy | [33]Dipartimento di Diagnostica Per Immagini, Radioterapia Oncologica Ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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