Annals of Hematology (2019) 98:2081–2088
https://doi.org/10.1007/s00277-019-03744-5

ORIGINAL ARTICLE

Incidence and outcome of invasive fungal disease after front-line intensive chemotherapy in patients with acute myeloid leukemia: impact of antifungal prophylaxis

Rebeca Rodríguez-Veiga[1] · Pau Montesinos[1,2] · Blanca Boluda[1] · Ignacio Lorenzo[1] · David Martínez-Cuadrón[1,2] · Miguel Salavert[3] · Javier Pemán[4] · Pilar Calvillo[5] · Isabel Cano[1] · Evelyn Acuña[1] · Ana Villalba[1] · José Luis Piñana[1] · Jaime Sanz[1,2] · Pilar Solves[1,2] · Leonor Senent[1] · Ana Vicente[1] · Amparo Sempere[1] · José Cervera[1,2] · Eva Barragán[1] · Isidro Jarque[1,2] · Antonio Torres[1,6] · Miguel A. Sanz[1,2,7] · Guillermo F. Sanz[1,2,7]

Received: 16 April 2019 / Accepted: 15 June 2019 / Published online: 25 June 2019

Abstract

Few reports analyze the incidence and clinical outcome of invasive fungal disease (IFD) in patients with newly diagnosed acute myeloid leukemia (AML) undergoing intensive chemotherapy, and thus the impact of different antifungal prophylactic regimens remains unclear. We analyze the incidence and clinical outcome of IFD in a large series of adult AML patients undergoing front-line intensive induction and consolidation chemotherapy between 2004 and 2015 in a single institution. Three antifungal prophylaxis regimens were given (2004–2005 oral fluconazole, 2006–2012 intravenous itraconazole, and 2013–2015 voriconazole). Overall, 285 patients and 589 intensive chemotherapy episodes were assessed (47%) (induction courses 47% and consolidation 53%). The median age was 51 years (range, 17–65). We observed 56 (10%) episodes of IFD. According to the EORTC 2008 criteria, IFD was classified as possible (29, 52%), probable (17, 30%), and proven (10, 18%). Possible/probable/proven IFD rate was significantly lower during HiDAC consolidation as compared to any anthracycline-containing chemotherapy courses (2% vs. 11%, $P = 0.001$), and under voriconazole prophylaxis as compared to itraconazole and fluconazole (6% vs. 11% vs. 15%, $P = 0.007$), and the multivariate analysis showed that they were independent risk factors. Patients under voriconazole prophylaxis had shorter hospitalization duration and less frequent use of empirical or directed antifungal therapy. In conclusion, IFD was a frequent complication during upfront intensive chemotherapy courses for adult AML patients. This retrospective study shows that voriconazole prophylaxis was feasible and associated with a lower risk of IFD compared with intravenous itraconazole or oral fluconazole schedules.

Keywords Invasive fungal disease · Intensive chemotherapy · Acute myeloid leukemia · Antifungal prophylaxis · Voriconazole

Rebeca Rodríguez-Veiga and Pau Montesinos contributed equally to this work.

✉ Pau Montesinos
montesinos_pau@gva.es

[1] Department of Hematology, Hospital Universitari i Politècnic La Fe, Avda. Fernando Abril Martorell 106, CP: 46026 Valencia, Spain

[2] CIBERONC, Instituto Carlos III, Madrid, Spain

[3] Department of Infectious Diseases, Hospital Universitari i Politècnic La Fe, València, Spain

[4] Department of Microbiology, Hospital Universitari i Politècnic La Fe, València, Spain

[5] Department of Radiology, Hospital Universitari i Politècnic La Fe, València, Spain

[6] Asociación Medicina e Investigación (A.M.I.), Córdoba, Spain

[7] Department of Medicine, Universitat de València, València, Spain

Introduction

Invasive fungal disease (IFD) is a life-threatening infectious complication frequently occurring in patients with acute myeloid leukemia (AML) experiencing prolonged and severe neutropenia after intensive chemotherapy phase (induction and consolidation) [1–3]. The occurrence of IFD leads to a significant increase in morbidity and mortality in these patients [2, 4]. For these reasons, it is generally accepted that this population might be considered at high risk for development of IFD and could benefit from prophylactic strategies using efficacious and well-tolerated antifungal agents [5, 6]. However, there are few reports analyzing specifically the incidence and clinical outcome of IFD in patients with newly diagnosed AML undergoing intensive chemotherapy [7, 8]. Therefore, there is little evidence about the efficacy of

different prophylactic regimens, being fluconazole and posaconazole [9, 10] the only approved agents for this indication to date. In addition, few real-life clinical practice–derived studies analyzing the usefulness of antifungal prophylaxis in AML patients are available [11–15].

In this study, we analyze the incidence and clinical outcome of IFD in a large series of AML patients undergoing front-line intensive induction and consolidation chemotherapy between January 2004 and December 2015 in a single institution. Three antifungal prophylactic schedules (fluconazole, itraconazole, and voriconazole) were administered according to institutional guidelines in three subsequent periods, allowing us to perform a retrospective comparison of the incidence and outcome of IFD under different prophylactic strategies.

Material and methods

Study design and patient selection

From January 2004 to December 2015, consecutive unselected adult patients with newly diagnosed AML were diagnosed at the Hospital Universitario y Politécnico La Fe. The clinical records of all patients were reviewed to assess their eligibility for this retrospective study. Patients were eligible if they fulfilled all the following criteria: (1) newly diagnosed AML excluding acute promyelocytic leukemia; (2) age less or equal than 65 years old; and (3) administration of intensive induction chemotherapy. Induction chemotherapy consisted of 3 + 7 combination (idarubicin 12 mg/m^2 × 3 days + Ara-C 200 mg/m^2 in continuous perfusion × 7 days) or mitoxantrone plus cytarabine (MTZ + Ara-C). The first consolidation consisted of 3 + 7 or MTZ+Ara-C (as first induction) (149, 25%) or high-dose cytarabine (3 g/m^2/12 h days 1, 3, 5; 1.5 g/m^2 for patients older than 60 years old) (HiDAC). Second or beyond consolidation courses consisted of HiDAC. All patients provided informed consent according to institutional guidelines. This retrospective study was approved by the Research Ethics Board of the institution according to the Declaration of Helsinki (study number 2013/0036).

Risk stratification, monitoring, and diagnosis of IFD

All the patients were considered at high risk for development of IFD, as the induction and consolidation regimens could potentially lead to long-lasting severe granulocytopenia. Patients were hospitalized during the post-chemotherapy aplastic phase. During the study period, monitoring tests using serial Aspergillus galactomannan antigen (AGA) were performed twice a week during the post-chemotherapy neutropenia. Computed tomography (CT) scan was available all over the study period and performed as per clinical judgment (i.e., in the presence of febrile neutropenia lasting > 5–7 days, or under suspicion of lung infection). Diagnosis and classification of IFD was performed according to the European Organization for Research and Treatment of Cancer and Mycoses Study Group (EORTC/MSG) revised definitions of 2008 [16].

Prophylactic management and treatment of IFD

According to the institutional risk-adapted strategy of IFD prophylaxis, all patients received antifungal prophylaxis from the first day of chemotherapy administration until myeloid recovery (granulocyte count in peripheral blood > 0.5 × 10^9/L). From January 2004 to December 2005, prophylaxis consisted of low-dose oral fluconazole (100 mg/daily), from January 2006 to December 2012 intravenous itraconazole (200 mg/daily), and from January 2013 to December 2015 oral voriconazole (200 mg/twice a day) (the later switch of prophylactic agent was due to repeated shortages of intravenous itraconazole). No pharmacokinetic studies for dose adjustment were performed across all the study period. Oral prophylaxis was withdrawn when limiting toxicity at the physician's discretion appeared or when antifungal treatment was indicated due to suspicion of or documented IFD. Patients with previous documented IFD during the neutropenia were discharged with secondary prophylaxis or long-term antifungal therapy and therefore were not analyzed for subsequent chemotherapy episodes.

Once IFD was suspected, antifungal therapy was started using monotherapy or combination, usually including caspofungin (50 mg once a day) or liposomal amphotericin (3 mg/kg once a day). The clinical course of IFD was monitored using the standard clinical, radiological, and microbiological tests, when available. Granulocyte colony–stimulating factors (G-CSF) were given in older patients and in those with serious infectious complications to accelerate the neutrophil count recovery.

Data collection and prognostic factors

Data were prospectively and retrospectively collected and registered in a specific form. Fourteen patient and treatment characteristics were examined to establish their relationship with the occurrence of IFD. Demographic data, disease, and treatment characteristics included age, sex, ECOG (performance status) at diagnosis, white blood cell (WBC) count, platelet count, hemoglobin level, serum levels of glucose, creatinine, urea nitrogen, uric acid, albumin, AST, ALT, bilirubin, and alkaline phosphatase, presence of extramedullary disease, FAB subtype, secondary or de novo AML, cytogenetic risk according to MRC classification [17], chemotherapy regimen (agents and doses), treatment phase (induction or consolidation), type of antifungal primary prophylaxis, and neutropenia duration.

Clinical records were also reviewed to assess serial serum AGA, computerized tomography scans and other imaging tests, antifungal therapies, length of hospitalization duration, response to chemotherapy, use of therapeutic antifungal agents (empirical or directed therapy), microbiological isolates, and cause of death.

Study definitions and end-points

The primary end-point of the study was to assess the crude incidence of IFD (possible, probable, and proven) in all episodes of intensive chemotherapy. For patients who had refractory/resistant AML or developed an IFD episode (possible/probable/proven) during a certain intensive chemotherapy cycle, subsequent chemotherapy courses were not analyzed. Secondary end-points were the type of IFD (according to microbiological isolates, site of infection, and EORTC criteria) and dose-limiting toxicities (DLT) of voriconazole, itraconazole, or fluconazole prophylaxis (defined as dose adjustment or withdrawal of the antifungal agent due to related toxicity). In addition, the main clinical outcomes were assessed as follows: (1) mortality during each chemotherapy phase, (2) mortality due to IFD, (3) induction complete remission rate (CR) with or without full hematologic recovery (CRi) according to the revised Cheson criteria, [18], 4) use of empirical or adapted antifungal therapy, and (5) length of hospitalization duration. The incidences of IFD, as well as the clinical outcomes, were analyzed according to the prophylactic regimen and the type of chemotherapy episode. All patients were followed until discharge of each chemotherapy episode or death during hospitalization.

In addition, the response of IFD therapy was evaluated at the end of antifungal treatment. Resolved IFD was defined as clinical improvement and radiological recovery along with the absence of positive microbiologic results or progressive decline in mycological surrogate biomarkers. Treatment failure was defined as death due to direct consequences of the IFD. Patients still presenting signs or symptoms of IFD when dying by another cause were considered not evaluable.

Statistical methods

The analysis was made on an intent-to-treat principle. The chi-square, ANOVA, Kruskal–Wallis, and Mann–Whitney's U test were used to analyze the differences in the distribution of variables between patient subsets. We measured the crude incidence of IFD (i.e., the number of events/number of observed episodes) overall and per type of chemotherapy and prophylactic schedule. Differences in the crude incidence of IFD were considered statistically significant if the type I error alpha was < 5% ($P < 0.05$). The characteristics selected for inclusion in the multivariate analysis were those for which there was some indication of a significant association in the univariate analysis ($P < 0.1$). Multivariate analysis was performed using the odds ratio by Cox [19]. The patient follow-up information was updated in June 2016. All P values reported are 2-sided. Computations were performed using the R 2.12.2 software package.

Results

Patient and treatment characteristics

Over the period of the study, a total of 285 consecutive adult patients fulfilling the inclusion criteria underwent intensive induction chemotherapy at our institution. Overall, 589 episodes of intensive chemotherapy were assessed: 285 first induction courses (47%) (3 + 7 [278, 47%] and MTZ+Ara-C [7, 1%]) and 304 consolidation courses (53%) (3 + 7 [149, 25%], HiDAC [127, 22%], MTZ+Ara-C [28, 5%]) (Fig. 1). Antifungal prophylaxis consisted of oral fluconazole in 72 (12%) chemotherapy episodes, intravenous itraconazole in 233 (40%), oral voriconazole in 264 (45%), and an echinocandin or low-dose liposomal amphotericin B in 20 episodes (3%).

Table 1 shows the main patient and disease characteristics at diagnosis according to the antifungal prophylaxis schedule for induction (fluconazole [35, 12%] vs. itraconazole [114, 40%] vs. voriconazole [127, 45%] vs. other prophylaxes [9, 3%]). Briefly, 158 patients (55%) were male, median age at AML diagnosis was 51 years (range, 17–65 years), and 51 (18%) were secondary AML arising after other neoplastic condition. A CR/CRi was achieved after one induction cycle in 185 patients (65%), with a 10% of induction death rate. Median duration of grade 4 neutropenia during induction was 20 days (from the end of 3 + 7), ranging from 11 to 63 days. Ten percent (29 out of 228) evaluable patients had a grade 4 neutropenia shorter than 15 days.

Overall incidence and type of IFD

We observed 56 episodes of IFD during the 589 episodes of intensive chemotherapy (10% crude incidence). Of them, 29 were possible (52%), 17 probable (30%), and 10 proven (18%). Table 2 shows the isolates in cases of proven (4 candidemia, 2 mucormycosis, 1 aspergillosis, and 3 others) and probable IFD (17positive AGA). For 29 episodes of possible IFD, the lung (97%) was the most frequent site. Of 56 episodes of IFD, 45 (81%) were resolved after therapy, 5 (8%) resulted in death by IFD, and 6 (11%) were not evaluable for response.

Incidence of IFD and clinical outcomes according to type of chemotherapy

Table 3 shows the crude incidence of IFD according to the type of intensive chemotherapy regimen. IFD (possible/probable/proven) was significantly lower during HiDAC consolidation as compared to any anthracycline-containing chemotherapy courses (2% vs. 11%, $P = 0.001$). The incidence of

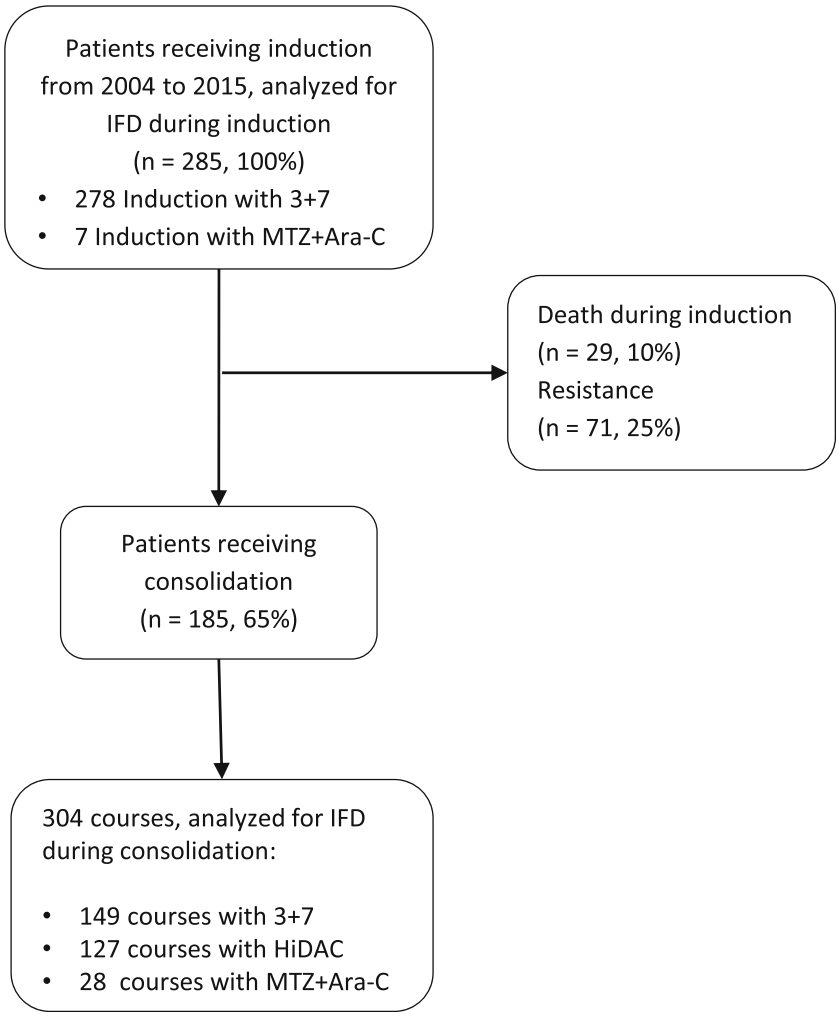

Fig. 1 Consolidated Standards of Reporting Trials (CONSORT) diagram showing the included in the study

probable/proven IFD was also significantly lower in HiDAC episodes (0% vs. 5%, $P = 0.002$). As well, outcomes were favorable in the HiDAC episodes: death during chemotherapy episode (2% vs. 10%, $P = 0.001$), hospitalization duration among survivors (24 vs. 35.3 days, $P < 0.001$), and use of empirical or directed antifungal therapy (18% vs. 64%, $P < 0.001$). The rate of use of empirical or directed antifungal therapy was especially high among 3 + 7 induction episodes (75%, significantly higher than in anthracycline-based consolidation episodes, $P < 0.001$).

Incidence of IFD and clinical outcomes according to antifungal prophylaxis

Table 4 shows the crude incidence of IFD according to the type of antifungal prophylaxis. IFD (possible/probable/proven) was significantly lower under voriconazole prophylaxis as compared to itraconazole and fluconazole (6% vs. 11% vs. 15%, $P = 0.007$). As well, IFD was less frequent in the voriconazole vs. itraconazole cohort ($P = 0.03$). The frequency of probable/proven IFD was not significantly lower among the voriconazole prophylaxis cohort. Hospitalization duration was shorter and the use of empirical or directed antifungal therapy less frequent in the voriconazole prophylaxis cohort ($P < 0.001$ and $P = 0.008$, respectively).

Dose-limiting toxicity of antifungal prophylaxis

No DLT was observed among fluconazole courses, but 1 (0.5%) hepatotoxicity and 1 (0.5%) cardiotoxicity among itraconazole courses. DLT was observed in 2.2% of voriconazole courses (4 hepatotoxicity, 1 neurotoxicity, and 1 cardiotoxicity).

Multivariate analyses for IFD

The multivariate analysis, including age, gender, treatment phase, type of chemotherapy, antifungal therapy, and neutropenia duration showed that voriconazole prophylaxis (odds ratio 0.54, 95% confidence interval 0.29–0.99, $P = 0.049$) and HiDAC (odds ratio 0.13, 95% confidence interval 0.03–0.56, $P = 0.006$) were independently associated with lower risk of IFD (possible/probable/proven).

Table 1 Patient and disease characteristics according to antifungal prophylaxis during induction

Characteristic	Overall *n* (%)	Fluconazol *n* (%)	Itraconazole *n* (%)	Voriconazole *n* (%)	Other prophylaxes *n* (%)	*P* value*
Total	285 (100)	35 (12)	114 (40)	127 (45)	9 (3)	
Age, years, mean (range)	51 (17–65)	50 (17–65)	47 (21–65)	50 (19–65)	42 (17–65)	0.26
Male gender	158 (55)	21 (60)	64 (56)	69 (54)	4 (44)	0.84
ECOG 0–1 (*N* = 281)	229 (82)	30 (86)	86 (76)	108 (82)	5 (86)	0.29
Secondary AML	51 (18)	5 (14)	21 (18)	24 (19)	1 (11)	0.21
FAB subtype (*N* = 279)						
M0	16 (6)	3 (9)	4 (4)	8 (6)	1 (12)	0.69
M1	54 (19)	9 (26)	20 (18)	24 (19)	1 (12)	
M2	62 (22)	6 (17)	34 (30)	26 (21)	0 (0)	
M4	52 (19)	8 (23)	24 (21)	19 (15)	1 (12)	
M5	38 (14)	5 (15)	13 (12)	18 (15)	2 (25)	
M6	15 (5)	2 (6)	6 (5)	7 (6)	0 (0)	
M7	4 (1)	0 (0)	2 (2)	2 (2)	0 (0)	
Other	30 (10)	2 (6)	9 (8)	20 (15)	3 (38)	
WBC × 10^9/L, mean (range)	10.5 (0.3–434)	21.2 (0.8–324)	9.1 (0.8–182)	9.2 (0.3–434)	16.4 (3.3–180)	0.22
Hemoglobin g/dL, mean (range)	8.9 (3.8–15.5)	9.3 (5–14.2)	9 (5–13.5)	8.4 (3.8–15.5)	8.7 (6–10.5)	0.29
Extramedullary disease, (*N* = 271)	62 (23)	8 (24)	27 (25)	26 (21)	1 (14)	0.83
Cytogenetics						
Core-binding factor	34 (12)	6 (17)	17 (15)	11 (9)	0 (0)	0.42
Normal karyotype	121 (43)	16 (46)	48 (42)	53 (42)	4 (44)	
Intermediate	39 (14)	1 (3)	13 (11)	24 (19)	1 (11)	
Unfavorable	70 (25)	11 (31)	28 (25)	28 (22)	3 (33)	
No metaphases/unknown	21 (7)	1 (3)	8 (7)	11 (9)	1 (11)	
Response to induction						
CR/CRi	185 (65)	23 (69)	79 (69)	79 (62)	4 (44)	0.39
Resistance/PR	71 (25)	8 (19)	22 (19)	38 (30)	3 (33)	
Induction death	29 (10)	4 (11)	13 (11)	20 (8)	2 (22)	

*Comparison between itraconazole plus fluconazole cohorts vs. voriconazole cohort

AML, acute myeloid leukemia; *CR*, complete remission; *CRi*, complete remission with incomplete blood counts; *PR*, partial remission

Discussion

Despite using universal antifungal prophylaxis during intensive chemotherapy phase for AML patients, IFD was a frequent complication. In our historical cohort comparison, oral voriconazole prophylaxis was well tolerated and could lead to a significant reduction of the risk of development of IFD compared with itraconazole or fluconazole. Patients treated during voriconazole prophylaxis period had shorter hospitalization duration and less frequent use of empirical or directed antifungal therapy. We also demonstrate that anthracycline-containing chemotherapy courses were associated with higher IFD rate compared with the HiDAC monotherapy.

Table 2 Site, isolates, and classification of IFD episodes

Type of IFD	*N* (%)
Overall	56 (10)
Proven	10 (18)
Candidemia	4 (40)
Rhinosinusal aspergillosis	1 (10)
Disseminated mucormycosis	2 (20)
Other	3 (30)
Probable	17 (30)
Pulmonary aspergillosis	16 (94)
Disseminated aspergillosis	1 (6)
Possible	29 (52)
Lung	28 (97)
Rhinosinusal	1 (3)

As far as we know, this is the larger series analyzing the risk of IFD in AML patients receiving induction chemotherapy and the impact of different antifungal prophylaxis schedules. We must acknowledge several limitations of our study: (1) the non-randomized design should prevent us from drawing any strong conclusion, especially when comparing antifungal prophylactic regimens; (2) a potential historical bias could be favorable to newer patients (i.e., those receiving voriconazole or itraconazole) because of improvements in general management. However, in our opinion, management in our institution was homogeneous across the study period, including the same diagnostic tools and criteria for IFD. In addition, the three historical cohorts were comparable in the main baseline patients and disease characteristics; and (3) this was an intent-to-treat analysis in real-life population; we can argue that protocol and guidelines on management are less strict than in clinical trials. However, our study could provide more practical and reliable results in comparison with some trials. As an example, the randomized study by Marks et al. [20] compared

Table 3 Incidence of IFD and clinical outcomes according to the chemotherapy schedule

Type of chemotherapy	*N* (%)	Deaths during chemotherapy episode, *N* (%)	*P* value	Total IFD episodes, *N* (%)	*P* value	Proven and probable IFD episodes, *N* (%)	*P* value	Inpatient stay by chemotherapy cycle, survivors, days mean (range)	*P* value	Use of intravenous antifungal therapy, *N* (%)	*P* value
IDA + ARA-C, 3 + 7 (induction)	278 (47)	31 (11)		34 (12)		17 (6)		34.1 (16–94)		207 (75)	
MTZ + ARA-C (induction)	7 (1)	1 (14)		1 (14)		1 (14)		30.9 (24–36)		3 (43)	
IDA + ARA-C, 3 + 7 (consolidation)	149 (25)	11 (7)		15 (10)		8 (5)		35.2 (18–117)		73 (49)	
MTZ + ARA-C (consolidation)	28 (5)	3 (11)		3 (11)		1 (4)		32.1 (9–53)		12 (43)	
HD-ARA-C (consolidation)	127 (22)	2 (2)		2 (2)		0 (0)		24.0 (16–54)		22 (18)	
Anthracycline-containing (induction and consolidation)	462 (78)	46 (10)	0.001*	53 (11)	< 0.001*	27 (5)	.002*	34.3 (9–117)	< 0.001*	295 (64)	< 0.001*

*Comparison between anthracycline containing schedules vesus non-anthracycline containing schedules

Table 4 Incidence of IFD and main clinical outcomes according to antifungal prophylaxis

Antifungal prophylaxis	*N* (%)	Deaths during chemotherapy episode, *N* (%)	*P* value	Total IFD episodes, *N* (%)	*P* value	Proven and probable IFD episodes, *N* (%)	*P* value	Inpatient stay by chemotherapy cycle, days mean (range)	*P* value	Use of intravenous antifungal therapy, *N* (%)	*P* value
Fluconazole	72 (13)	7 (10)	0.28	11 (15)	0.007*	7 (10)	0.19*	34.5 (20–88)	< 0.001*	41 (57)	0.008*
Itraconazole	233 (40)	22 (9)		26 (11)	0.03**	11 (5)	0.26**	35.0 (9–117)		143 (61)	
Voriconazole	264 (45)	17 (6)		15 (6)		8 (3)		31.6 (17–102)		126 (48)	
Other prophylaxes	20 (3)	2 (11)		2 (11)		1 (5)		36.4 (24–91)		7 (37)	

*Comparison between itraconazole plus fluconazole cohorts vs. voriconazole cohort

**Comparison between itraconazole vs. voriconazole cohort

voriconazole vs. itraconazole prophylaxis following allogeneic stem cell transplantation, using strict assessment and inclusion criteria, thus showing very low rates of IFD (< 2%).

Although it is generally accepted that AML patients receiving intensive chemotherapy are at high risk for development of IFD [21, 22], there are few studies critically analyzing the incidence and risk factors for this complication in this setting. To our knowledge, only two retrospective studies were exclusively focused on AML patients receiving intensive schedules: Egerer et al. [14] reported 1.3% of proven IFD among 40 patients (76 chemotherapy courses) receiving posaconazole prophylaxis, and Vehreschild JJ et al. [15] found, in another retrospective study, a probable/proven IFD incidence of 3.9% under posaconazole vs. 19.5% under topic polyenes prophylaxis in 159 subjects. Larger studies were performed in heterogeneous cohorts including not only AML patients: (1) a large ($n = 602$) randomized clinical trial compared posaconazole vs. fluconazole or itraconazole prophylaxis in AML/MDS patients with neutropenia after chemotherapy, showing 2% vs. 8% of probable/proven IFD [9]; (2) Hachem R et al. [13] retrospectively compared voriconazole vs. posaconazole prophylaxis in 200 patients with hematological malignancies (67% were AML), showing 3% vs. 0% of probable/proven IFD; (3) Tormo M et al. [11] analyzed posaconazole vs. itraconazole in 174 AML/MDS patients undergoing intensive chemotherapy (293 cycles), resulting in 1.7% vs. 5.3% rates of probable/proven IFD; and (4) a retrospective study by Ananda-Rajah MR et al. [12] analyzed 216 AML/MDS patients and 576 cycles of intensive chemotherapy or allograft conditioning, showing possible/probable/proven IFD rates of 13% under fluconazole, 20% with itraconazole, and 8% with voriconazole and posaconazole. Our results are in line with previous reports, with an overall crude incidence of 10% of possible/probable/proven IFD per chemotherapy courses (6% in the voriconazole cohort), and 5% when considering only probable/proven IFD (3% in the voriconazole cohort). A higher incidence of IFD was seen in patients receiving fluconazole (15%), possibly due to the lack of activity of fluconazole against filamentous fungi [9]. As expected, *Aspergillus* was the most frequent isolate, and the lung was the preferred site of infection [4, 7].

Regarding the prognostic factors for IFD, we observed that this complication was more frequent during induction chemotherapy compared with consolidation phase. Moreover, we observed that consolidation cycles containing an anthracycline had a similar frequency of IFD (10%) than induction cycles (12%). As far as we know, this is the first study showing that the inclusion of an anthracycline is a risk factor for the development of IFD. We can argue that this was due to less severe neutropenia duration in courses containing an anthracycline plus cytarabine combination compared with HiDAC monotherapy. However, we were not able to show a correlation between neutropenia duration and the development of IFD, probably because the vast majority of patients had a critically prolonged grade 4 neutropenia (> 21 days) irrespectively of the chemotherapy regimen (data not shown). We can speculate that an excess of mucosal barrier damage induced by anthracyclinic agents could lead to an increased rate of IFD [23]. On the other hand, we show that, along with HiDAC monotherapy schedule, voriconazole was an independent protective risk factor for the development of possible/probable/proven IFD. This finding is aligned with other studies showing less IFD among patients receiving a second-generation triazole (i.e., posaconazole or voriconazole). We show here that an appropriate voriconazole dosage of 200 mg/12 h was well tolerated and efficacious. In contrast, we have shown that lower dose voriconazole (100 mg/12 h) was no efficacious and did not spare toxicity in a large series of allografted patients in our institution [24]. Although a 200 mg/12 h voriconazole prophylaxis seems appropriate in the setting of standard upfront chemotherapy AML, we still need to face up the following questions: (1) are posaconazole, isavuconazole, and voriconazole exchangeable options for primary prophylaxis? and (2) whether a triazole antifungal agent will be appropriate in the era of new small molecules which usually are metabolized through the CY3A4 leading to significant drug-drug interactions. After analyzing our experience, we are currently using full-dose voriconazole profilaxis, instead of posaconazole, during upfront intensive chemotherapy cycles. The main reason for keeping this policy is that voriconazole is now a generic drug with a significantly lower price than posaconazole.

In conclusion, IFD was a frequent complication during upfront intensive chemotherapy courses for adult AML patients. This retrospective study shows that voriconazole prophylaxis was feasible and associated with a lower risk of IFD as compared with intravenous itraconazole or oral fluconazole schedules.

Authorship Pau Montesinos, Rebeca Rodríguez-Veiga, and Antonio Torres conceived the study, analyzed, and interpreted the data; Pau Montesinos, Rebeca Rodríguez-Veiga, Blanca Boluda, and Antonio Torres wrote the paper; Pau Montesinos, Ignacio Lorenzo, and Rebeca Rodríguez-Veiga performed the statistical analyses; Ignacio Lorenzo, David Martínez-Cuadrón, Miguel Salavert, Javier Pemán, Pilar Calvillo, Isabel Cano, Evelyn Acuña, Ana Villalba, José Luis Piñana, Jaime Sanz, Pilar Solves, Leonor Senent, Ana Vicente, Amparo Sempere, José Cervera, Eva Barragán, Isidro Jarque, Miguel A. Sanz, and Guillermo F. Sanz reviewed the manuscript and contributed to the final draft.

Funding information This study was in part supported by Asociación Medicina e Investigación (A.M.I.), a grant 2012/023 from the Instituto de Investigación Sanitaria La Fe. This paper was supported by an independent medical grant provided by Pfizer, Inc.

Compliance with ethical standards

This retrospective study was approved by the Research Ethics Board of the institution according to the Declaration of Helsinki (study number 2013/0036).

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Pagano L, Caira M, Candoni A et al (2010) Invasive aspergillosis in patients with acute myeloid leukemia: a SEIFEM-2008 registry study. Haematologica 95:644–650
2. Pagano L, Caira M, Nosari A et al (2011) Etiology of febrile episodes in patients with acute myeloid leukemia: results from the Hema e-Chart Registry. Arch Intern Med 171:1502–1503
3. Caira M, Candoni A, Verga L, SEIFEM Group (Sorveglianza Epidemiologica Infezioni Fungine in Emopatie Maligne) et al (2015) 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 100(2):284–292. https://doi.org/10.3324/haematol.2014
4. Neofytos D, Treadway S, Ostrander D et al (2013) Epidemiology, outcomes, and mortality predictors of invasive mold infections among transplant recipients: a 10-year, single-center experience. Transpl Infect Dis. 15:233–242
5. Tacke D, Buchheidt D, Karthaus M et al (2014) 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 93:1449–1456
6. Maertens J, Marchetti O, Herbrecht R et al (2011) European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3–2009 update. Bone Marrow Transplant 46:709–718
7. Lien MY, Chou CH, Lin CC et al (2018) Epidemiology and risk factors for invasive fungal infections during induction chemotherapy for newly diagnosed acute myeloid leukemia: a retrospective cohort study. PLoS One. 13(6):e0197851. https://doi.org/10.1371/journal.pone.0197851
8. Girmenia C, Micozzi A, Piciocchi A et al (2014) Invasive fungal diseases during first induction chemotherapy affect complete remission achievement and long-term survival of patients with acute myeloid leukemia. Leuk Res. 38(4):469–474. https://doi.org/10.1016/j.leukres.2014.01.007
9. Cornely OA, Maertens J, Winston DJ et al (2007) Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 356:348–359
10. Pagano L, Caira M, Candoni A et al (2012) Evaluation of the practice of antifungal prophylaxis use in patients with newly diagnosed acute myeloid leukemia: results from the SEIFEM 2010-B registry. Clin Infect Dis 55:1515–1521
11. Tormo M, Pérez-Martínez A, Calabuig M et al (2018) 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 61:206–212. https://doi.org/10.1111/myc.12728
12. Ananda-Rajah MR, Grigg A, Downey MT et al (2012) Comparative clinical effectiveness of prophylactic voriconazole/posaconazole to fluconazole/itraconazole in patients with acute myeloid leukemia/myelodysplastic syndrome undergoing cytotoxic chemotherapy over a 12-year period. Haematologica 97:459–463
13. Hachem R, Assaf A, Numan Y et al (2017) Comparing the safety and efficacy of voriconazole versus posaconazole in the prevention of invasive fungal infections in high-risk patients with hematological malignancies. Int J Antimicrob Agents. 50(3):384–388. https://doi.org/10.1016/j.ijantimicag.2017.03.021
14. Egerer G, Geist MJP (2011) Posaconazole prophylaxis in patients with acute myelogenous leukaemia–results from an observational study. Mycoses 54(Suppl. 1):7–11
15. Vehreschild JJ, Rüping MJGT, Wisplinghoff H et al (2010) Clinical effectiveness of posaconazole prophylaxis in patients with acute myelogenous leukaemia (AML): a 6 year experience of the Cologne AML cohort. J Antimicrob Chemother 65:1466–1471
16. De Pauw B, Walsh TJ, Donnelly JP et al (2008) 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 46:1813–1821
17. Grimwade D, Hills RK, Moorman AV et al (2010) National Cancer Research Institute Adult Leukaemia Working Group. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. Blood. 116(3):354–365. https://doi.org/10.1182/blood-2009-11-254441
18. Cheson BD, Bennett JM, Kopecky KJ et al (2003) Revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol 21(24):4642–4649
19. Fine J, Gray R (1999) A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 94:496–509
20. Marks DI, Pagliuca A, Kibbler CC, IMPROVIT Study Group et al (2011) Voriconazole versus itraconazole for antifungal prophylaxis following allogeneic haematopoietic stem-cell transplantation. Br J Haematol 155(3):318–327
21. Maertens JA, Girmenia C, Brüggemann RJ et al (2018) European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia. J Antimicrob Chemother 73(12):3221–3230. https://doi.org/10.1093/jac/dky286
22. Tissot F, Agrawal S, Pagano L et al (2017) ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. Haematologica 102(3):433–444
23. Atallah E, Cortes J, O'Brien S et al (2007) Establishment of baseline toxicity expectations with standard frontline chemotherapy in acute myelogenous leukemia. Blood 110:3547
24. Rodríguez-Veiga R, Montesinos P, García E, Boluda B, Rojas R, Serrano J et al (2019) Validation of a multivariable prediction model for post-engraftment invasive fungal disease in 465 adult allogeneic hematopoietic stem cell transplant recipients. Mycoses. https://doi.org/10.1111/myc.12891