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Impact of invasive aspergillosis occurring during first induction therapy on outcome of acute myeloid leukaemia (SEIFEM-12B study)

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Abstract

Background: Acute myeloid leukaemia (AML) patients are at high risk of invasive aspergillosis (IA) after first induction chemotherapy (CHT). Although IA risk factors have been identified, few data are available on impact of IA, occurring during induction phase, on overall AML outcome.

Patients and results: The end point of this multicentre, case-control, study was to evaluate whether IA, occurring after first induction CHT, can affect treatment schedule and patient's outcome. We identified 40 AML patients (cases) who developed IA during first induction phase, 31 probable (77.5%) and 9 proven (22.5%). These cases were matched with a control group (80 AML) without IA, balanced according to age, type of CHT, AML characteristics and cytogenetic-molecular risk factors. The overall response rate to induction CHT was the same in the 2 groups. In the 40 cases with IA, the overall response rate to antifungal treatment was favourable (80%) but it was significantly affected by the achievement of leukaemia complete remission (CR) with induction CHT. In fact, in cases with AML responsive to induction CHT, responses of IA to antifungal therapy were 96% compared to 21% in cases of AML not responsive to induction treatment ($P < .0001$). The adherence to the schedule and full doses of CHT were reported in 35% of cases (14/40) and in 76% of controls (61/80) ($P = .0001$; OR 6.7; 95% CI 2.7-16.6). After first induction CHT, a significant higher number of cases (15/40; 37.5%) compared to controls (9/80; 11%) could not receive additional cycles of CHT ($P = .0011$, OR 4.8; 95% CI 1.9-12.3). The IA-related mortality was 22.5%. The median OS of cases was significantly worse than OS of controls with a difference of 12.3 months (12.1 vs 24.4 months, $P = .04$). However, the occurrence of IA during first induction phase did not have a significant impact on the OS of cases who achieved a CR of AML with induction CHT which are able to proceed, despite

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the IA, with their therapeutic program, achieving the same OS as the control group with AML in CR (P = ns).

Conclusions: These data show that IA during first induction CHT can delay the subsequent therapeutic program and has a significant impact on OS, specifically in AML patients who did not achieved a CR of AML with the first course of CHT.

KEYWORDS
AML, induction chemotherapy, invasive aspergillosis, SEIFEM

1 | INTRODUCTION

Patients with acute myeloid leukaemia (AML) undergoing remission-induction chemotherapy (CHT) are at high risk of developing mould invasive fungal infections (IFIs), and *Aspergillus spp* represent the pathogen most frequently identified.[1-4] Despite improvements in diagnosis and treatment, Invasive Aspergillosis (IA) remains a common life-threatening complication, particularly after the first induction CHT treatment.[5-8] The SEIFEM (Sorveglianza Epidemiologica Infezioni Fungine nelle EMopatie) 2010 study showed that advanced age, use of steroids and an absolute neutrophil count of less than $1x10^9$/L at the time of IFI onset were the factors that negatively influenced the outcome of AML patients with IA.[9] However, the observation period of SEIFEM 2010 study was limited to the first 30 days from AML diagnosis, thereby limiting the analysis of long-term outcome.[9] This SEIFEM-12B study was designed to evaluate the impact, of a probable/proven IA occurring after the first cycle of intensive induction CHT on the planned therapeutic program and patient's outcome.

2 | PATIENTS AND METHODS

The SEIFEM-12B was a multicentre, case-control (1:2) study, including 120 AML adult patients: 40 patients who developed a proven or probable IA (according to EORTC/MSG criteria) after first induction intensive CHT (cases, IA+) were compared to a matched control group of 80 AML patients with no evidence of IA (IA-). Patients with possible IA were not included in the study. The 120 patients were followed up to 36 months after the start of induction CHT. Control patients were selected according to the demographic and disease characteristics of cases: IA + and IA- were well matched with respect to age, sex, disease risk factors, intensive first induction CHT regimen and cytogenetic or molecular risk factors of AML, as reported on Table 1. All 120 patients received mould active prophylaxis. The study was carried out after approval by the local ethic committees.

The primary end points of this case-control study were a) to evaluate whether IA, occurring after first induction therapy, can affect CHT program and b) to compare the overall survival (OS) of cases (IA+) and controls (IA-).

TABLE 1 Patients' characteristics

Characteristics	Cases (IA+) 40	Controls (IA-) 80	*P* value
Age			
Mean, DS	59 ± 11.2	59 ± 10.8	ns
Median-Range	61.5(25-81)	62.5(24-77)	
Age >65 y	10/40 (25%)	26/80 (33%)	ns
Sex (F/M)	16/24	39/41	ns
Secondary AML	10/40 (25%)	16/80 (20%)	ns
Hyperleucocytosis	16/40 (40%)	26/65 (40%)	ns
Cytogenetic-Molecular Risk			
Unfavourable	15/40 (37%)	23/80 (29%)	ns
Favourable	8/40 (20%)	17/80 (21%)	ns
Intermediate	16/40 (40%)	29/80 (36%)	ns
Not available	1/40 (3%)	11/80 (14%)	ns
AML response to induction CHT			
CR	23/40 (57.5%)	51/80 (64%)	ns
PR	7/40 (17.5%)	5/80 (6%)	ns
RES	7/40 (17.5%)	20/80 (25%)	ns
DDI-NV	3/40 (7.5%)	4/80 (5%)	ns
Intensive Induction CHT	40/40 (100%)	80/80 (100%)	ns

Abbreviations: AML, acute myeloid leukaemia; CHT, chemotherapy; CR, complete remission; DDI-NV, death during induction-not evaluable; PR, partial remission; RES, resistance.

Response to induction CHT was evaluated around the 4th week after first cycle of CHT according to the Cheson criteria, and a complete response (CR) to CHT was defined as the presence of morphologically normal bone marrow with less than 5% leukaemic blasts.[10] Risk assessment for AML was defined according to ELN 2010 guidelines.

Complete or partial response to antimycotic therapy was based on clinical, radiologic and/or mycological data as defined by the EORTC/MSG consensus group.[11,12] Overall response rate (ORR) was defined as complete responses + partial responses.

Statistical analysis. Descriptive statistics (including mean, standard deviation, median, range and percentages) were calculated

to analyse and compare the two study cohorts (IA + and IA-). Overall survival (OS), defined as the interval between the date of AML diagnosis and death or last follow-up, was estimated by Kaplan-Meier survival analysis, censoring survival assessment at 36 months after inclusion. OS curves were compared using the log-rank test. Hazard ratio (HR) and 95% CI were estimated using Cox's proportional hazard model. The odds ratio (OR) was calculated, and Fisher's exact test was used to compare group differences in categorical variables. All p-values are two-sided, with statistical significance evaluated at the 0.05 alpha level. Data were analysed with MedCalc software (version 12.5.0.0; MedCalc Software bvba, Ostend, Belgium).

3 | RESULTS

Patients' characteristics are reported on Table 1. Median follow-up was 13 months (range 0.6-32 months) in cases group and 24.4 months (range 0.5-36 months) in controls.

3.1 | Cases (IA+)

Overall, 31 (77.5%) probable and 9 (22.5%) proven fungal infections caused by Aspergillus species (100%) were observed among the 40 cases; in 36/40 cases the IA involved only the lung, in 3/40 lung + paranasal sinuses and in 1 case only the central nervous system. Twenty-three cases (57.5%) achieved a CR after first induction CHT; 14/40 (35%) achieved a partial remission (PR) or had refractory disease (REF); in 3 cases (7.5%), response to induction CHT was not evaluable for early death (DDI). The median time to IA onset after first induction CHT was 21 days (range 5-36 days). All 40 cases received antifungal treatment with voriconazole or liposomal amphotericin B. The overall response rate (ORR) of IA to antifungal treatment was 80% (32/40), without significant differences between the two antifungal treatments. In detail, 25/40 (62.5%) cases achieved a complete resolution of IA and 7/40 (17.5%) a partial response. Response to antifungal therapy was significantly better in cases who reached haematological CR after induction CHT (22/23, 96%) as compared to cases with refractory AML (3/14, 21%) ($P < .0001$). Seventeen (53%) cases who continued the AML therapeutic program received a secondary antifungal prophylaxis with azoles (12/17) or liposomal amphotericin B (5/17): only 4/32 of IA + patients (12.5%) experienced a relapse of fungal infection in the subsequent cycles (2 out of 4 cases were receiving antifungal prophylaxis with itraconazole and voriconazole, respectively). Overall mortality was 62.5% (25/40), while IA-related mortality was 22.5% (9/40) (Table 2).

3.2 | Controls (IA-)

Overall 51 of the 80 controls (64%) obtained a CR after induction CHT while 25/80 (31%) achieved a PR or had a REF AML; in 4 controls (5%), response to induction therapy was not evaluable for early death (DDI)-(Table 1). The overall mortality during the fixed

TABLE 2 Outcome. Comparison between cases (IA+) and controls (IA-)

	Cases (IA+) 40	Controls (IA-) 80	*P* value
Adherence in CHT schedule			
YES	14/40 (35%)	61/80 (76%)	*P < .0001;*
NO	20/40 (50%)	13/80 (16%)	*OR 6.7;*
Not Evaluable	6/40 (15%)	6/80 (8%)	*95% CI 2.7-16.6*
N°/Patient CHT cycles ≤ 2	20/40 (50%)	21/80 (26%)	*P = .01*
N°/Patient CHT cycles > 2	20/40 (50%)	59/80 (64%)	
Only 1 cycle CHT/patient	15/40 (37.5%)	9/80 (11%)	*P = .001;* *OR 4.8;* *95% CI 1.9-12.3*
Allo SCT	8/40 (20%)	23/80 (29%)	*P = ns*
Median OS (months)	*12.1*	*24.4*	*Δ 12.3*
Causes of death			
Active AML	11/25	27/41	
DDI	3/25	4/41	
AML + IA	5/25	//	
IA only	4/25	//	
TRM	//	3/41	
Other	2/25	7/41	

Note: Not Evaluable: IA+[3 DDI, 3 lost at follow-up], IA-[4 DDI, 2 lost at follow-up].
Abbreviations: DDI: death during induction; TRM, transplant related mortality.

observation period of the study (36 months) was 51% (41/80), and the main cause of death was AML in 66% of the cases (27/41) (Table 2).

The adherence to schedule and/or to full doses of CHT was observed in 35% of cases (IA+) (14/40) and in 76% of controls (IA-) (61/80) ($P < .0001$; OR 6.7; 95% CI 2.7-16.6). After first induction CHT, a significant higher number of cases (15/40; 37.5%) could not receive additional cycles of CHT as compared to controls (9/80; 11%) ($P = .0011$; OR 4.8; 95% CI 1.9-12.3) (Table 2). The OS of cases and controls is shown in Figure 1. The median OS of 40 cases was significantly worse as compared to the 80 controls with a difference of 12.3 months (12.1 vs. 24.4 months, $P = .04$-Figure 1). However, the occurrence of IA during induction phase did not have a significant impact on OS of cases who achieved a CR that were able to proceed, despite the IA, with the intensive therapeutic program (P = ns-Figure 2A). Conversely, the median OS of cases (IA+) who did not reached a CR was significantly worse compared to controls (IA-) with active AML after induction CHT (median OS IA + 4.75 months vs. OS IA- 14.7 months; $P = .001$-Figure 2B). In a multivariate analysis considering as variables the patient's age (≤ or > of 65 years), response of AML to induction CHT, response of IA to antimycotic therapy and changes of CHT program, only the response of induction CHT retained a significant favourable effect on OS (HR 6.2; 95%CI 1.24-31.14; $P = .02$).

Basically, these data show that an IA occurring during induction CHT can delay the subsequent therapeutic program but, specifically, it has a significant impact on OS only in AML patients who did not achieved a CR of AML with the first course of CHT (Figure 2B). These patients, due to the concomitant IA, are not able to achieve a leukaemia response with subsequent cycles of therapy, and therefore, they die either for IA or for their active haematological disease.

4 | DISCUSSION

Invasive fungal infections (IFIs) are one of limiting factors for the successful outcome of AML patients with a fatality rate ranging from 30% to 60%.[1-4,8] However, few published studies described the impact of IFIs, occurring during the first induction phase, on the survival (OS) of AML patients.[13-17] Furthermore, it should be emphasised that these studies were retrospective with heterogeneous data on IFI aetiology (including possible cases) or including both acute myeloid and lymphoid leukaemias (ALL) in different phases of their therapeutic program.[14-17] As reported in Table 3, the only case-control (1:3) study was published by Even et al in 2011; this monocentric study included patients with both AML and ALL who developed mould (IA and Zygomycosis) and yeast (Candidiasis) IFI during either the induction and the consolidation phase. This study showed a significant impact of IFI, occurring in the induction phase, on the CHT program while the impact on OS of AML patients was significant only for the proven IFIs.[14] The other few available retrospective studies, summarised in Table 3, are monocentric and also included a substantial percentage of possible cases.[15-17] Furthermore, three less recent trials included patients who did not receive anti-mould prophylaxis.[14-16] Keeping in mind these differences and limitations, all these studies showed a negative impact of IFI on OS of AML and, in the 2 studies with a specific subanalysis, a negative impact on CHT program.[14-17]

The primary objective of our study is to evaluate the impact of IA occurring during the first induction phase, on the therapeutic planned program and on OS in patients with AML. Of note, this is a prospective and multicentre study, including a more homogeneous population than the previous studies.[14-17] In fact, only AML patients receiving first induction intensive CHT with proven or probable IA were eligible for our study. We found that patients who experienced an IA after the first cycle of CHT had less chance to respect the therapeutic program

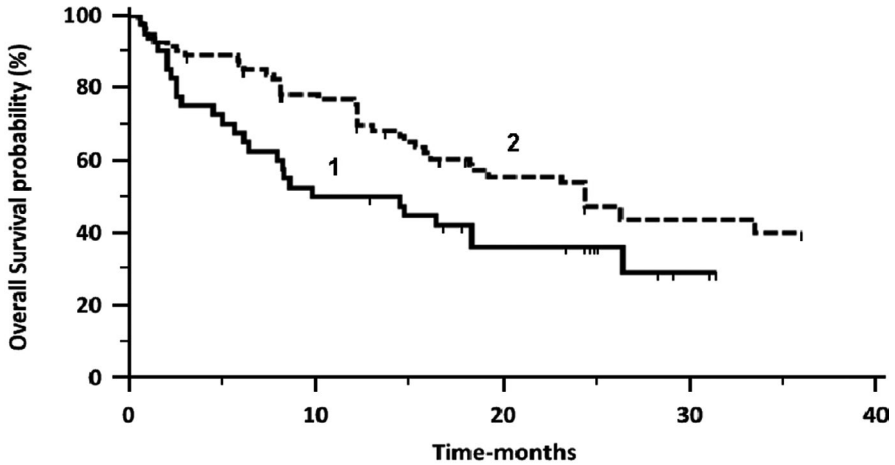

FIGURE 1 Overall Survival (OS) curves. Group 1 cases (40)-Median OS = 12.1 months; Group 2 controls (80)-Median OS = 24.4 months (Log-rank $P = .04$). OS Probability at 1 year: 50% AI + and 77% AI-. OS Probability at 3 years: 29% AI + and 40% AI-

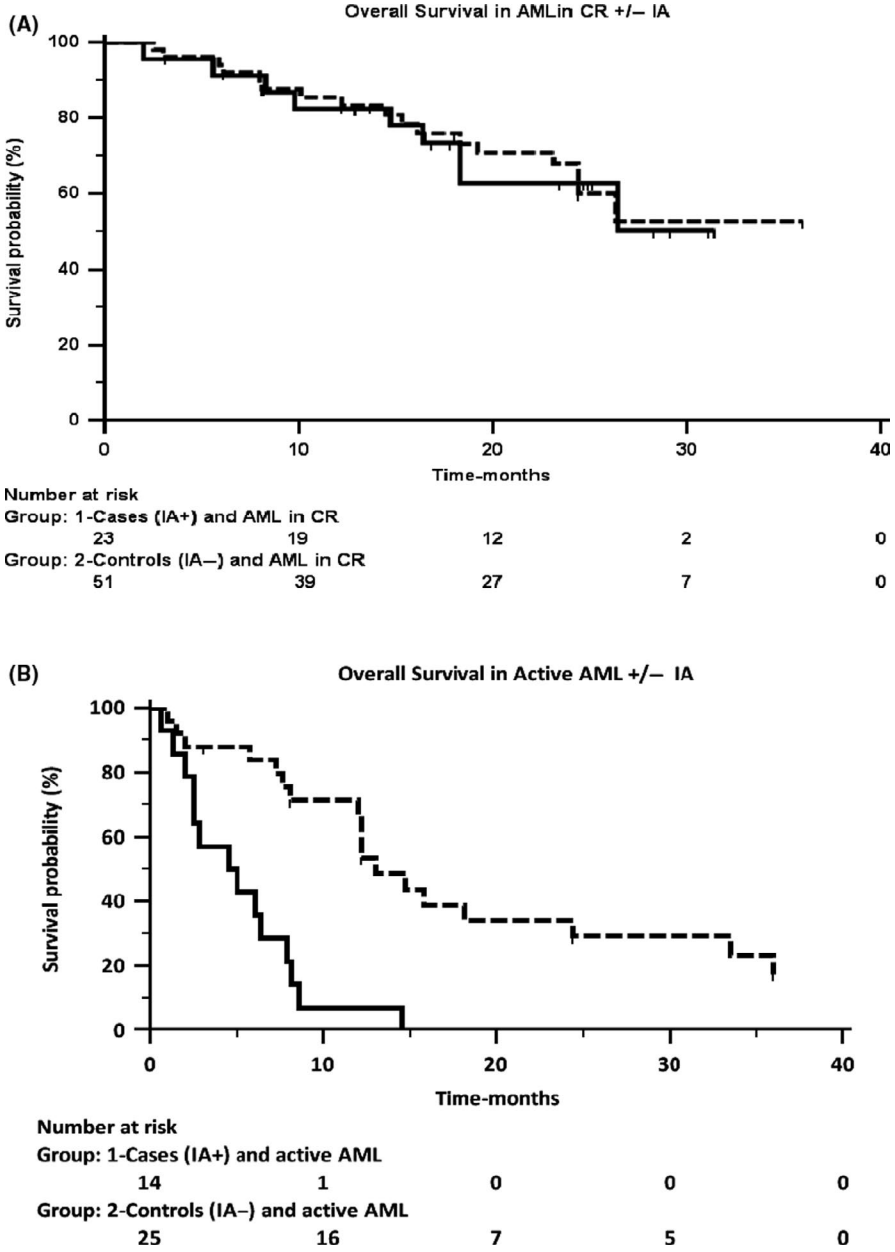

FIGURE 2 Overall survival (OS) of cases (IA+) and controls (IA-) according to AML response to Induction CHT. A, OS of patients with AML in CR after induction CHT: median OS of 23 evaluable cases and 51 evaluable controls = not reached (log-rank-*P* = .96). B, OS of patients with active AML (REF/PR) after induction CHT: median OS of 14 cases = 4.75 months, median OS of 25 controls = 14.7 months (log-rank *P* = .0001)

(35% vs 76% in patients IA + vs. IA-; *P* = .0001) and had a significantly poorer outcome (median OS 12.1 in patients IA + vs. 24.4 months in IA-; *P* = .04). However, the multivariate analysis showed that the unfavourable impact of IA on survival appears to be closely associated with failure to achieve the leukaemia CR after the first induction CHT (HR 6.2; 95%CI: 1.24-31.1; *P* = .02). Furthermore, it should be underscored that complete responses to antifungal therapy were significantly higher in cases (IA+) who obtained the haematological CR after induction CHT (22/23, 96%) compared to cases with refractory AML (3/14, 21%) (*P* < .0001). As reported in Figure 2, the occurrence of IA during the induction phase had a significant impact on the OS only in patients who did not achieve a leukaemia CR and were not able to proceed with their intensive program of CHT. These cases (IA+) had a worse OS compared to the control group of patients without IA (IA-) and with resistant AML at the end of first induction CHT (*P* = .0001-Figure 2B). It should be emphasised that none of the previous studies showed this close relationship between the response of leukaemia to induction CHT and response of IA to antifungal therapy, eventually resulting in a better AML outcome.

In conclusion, these data show that IA during first induction CHT can delay the subsequent therapeutic program and has a significant impact on OS, specifically in AML patients who did not achieve a CR of AML with the first course of CHT. An accurate evaluation of the risk of IA at the time of AML diagnosis would allow a more intensive diagnostic work-up and a more aggressive prophylaxis to prevent or early treat an IA and to proceed with the CHT program.[18-20]

CONFLICT OF INTEREST

Anna Candoni has received honoraria, as Advisory Board Member and Speaker, from Novartis, Janssen, Pfizer, Gilead, Celgene, Incyte, Merck (MSD), outside this submitted paper. Mario Delia has received personal fees from Gilead, outside this submitted

TABLE 3 Comparison of available data on impact of IFI occurring in AML during first induction therapy (Girmenia, Candoni) or during CHT program (Even, Michelet, Cattaneo)

	Even, 2011 [14]	Michelet, 2012 [15]	Girmenia, 2014 [16]	Cattaneo, 2019 [17]	Present Study (Candoni, 2020)
Type of Study	Single centre; retrospective Case-control (1:3) study	Single centre; retrospective	Two centres, retrospective	Single centre; retrospective	Multicentre; prospective Case-control (1:2) study
No of cases and controls and haematological disease	28 cases (27 AML; 1 ALL) 78 controls (75 AML; 3 ALL)	58 cases (58 AML) 203 controls (203 AML)	34 cases (34 AML) 164 controls (164 AML)	28 cases (22 AML; 6 ALL) 175 controls (136 AML; 39 ALL)	40 cases (40 AML) 80 controls (80 AML)
IFIs	Only Proven or Probable 20 IA; 7 Candidiasis; 1 Zygomycosis	Proven/Probable/ Possible 58 IA (50% possible)	Proven/Probable/ Possible 25 IA; 1 Penicillium sp; 7 Candida sp; 2 Geotricum c; 9 Possible IFI	Proven/Probable/ Possible 28 IA (39% possible)	Only Proven/Probable IA occurring during first induction phase
Antifungal Prophylaxis	Oral, non-adsorbable polyenes	No prophylaxis	Centre 1: posaconazole Centre 2: no mould active prophylaxis	Anti-mould prophylaxis	Anti-mould prophylaxis
Primary Objective	To assess the impact of IFI on the application of CHT regimens and the possible impact on OS and EFS	To evaluate the OS of patients with or without IA occurring after induction therapy	To assess the association of IFI occurring during first induction CHT with the achievement of CR, OS and DFS	Prognostic impact of IA in acute leukaemia occurring during CHT (induction consolidation, salvage)	To evaluate if IA occurring after first induction therapy can affect CHT program and impact on OS
IFI and Changes in CHT program	YES (68% CHT changes in cases vs 24% in controls; $P < .001$)	Not evaluated	YES (administration of second course of CHT in 35% of cases and 76% of controls; $P = .002$)	Not evaluated	YES (adherence to CHT schedule in 35% of cases and in 76% of controls; $P = .001$)
IFI and Impact on OS	YES but only for the Proven IFIs	YES (2 years OS 14% IA + and 32% in IA-; $P = .01$)	YES (3 years OS 19.6% cases and 37.3% in controls; $P = .007$)	YES (2 years OS 31.7% IA + and 69.8% in IA-; $P = .002$)	YES (median OS of cases 12.1 months vs controls 24.4 months; $P = .04$)

paper. Roberta Di Blasi has received personal fees from Gilead and Novartis, outside this submitted paper. All other authors have nothing to disclose.

AUTHOR CONTRIBUTIONS

LP, AC and AB: Conception of the study and research coordination. AC, FF and KP: Manuscript preparation. RDB, MC, CC, MD, MEZ, GD, RF, BM, MIDP, LF, NV, AC, MG, GP, GN and LV: Data collection and patient care provision. AC and GP: Performance of statistical analysis and manuscript revision.

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REFERENCES

1. Pagano L, Caira M, Candoni A, et al. The epidemiology of fungal infections in patients with hematological malignancies: the SEIFEM-2004 study. *Hematologica*. 2006;91:1068-1075.
2. Maschmeyer G, Haas A, Cornely OA. Invasive aspergillosis: epidemiology, diagnosis and management in immunocompromised patients. *Drugs*. 2007;67:1567-1601.
3. Hammond SP, Marty FM, Bryar JM, De Angelo DJ, Baden LR. Invasive fungal disease in patients treated for newly diagnosed acute leukemia. *Am J Hematol*. 2010;85:695-699.
4. Pagano L, Caira M, Candoni A, et al. Invasive aspergillosis in patients with acute myeloid leukemia: a SEIFEM-2008 registry study. *Haematologica*. 2010;95(4):644-650.
5. Neofytos D, Lu K, Hatfield-Seung A, et al. Epidemiology, outcomes and risk factors of invasive fungal infections in adult patients with acute myelogenous leukemia after induction chemotherapy. *Diagn Microbiol Infect Dis*. 2013;75(2):144-149.
6. Tang JL, Kung HC, Lei WC, et al. High incidence of invasive fungal infections in acute myeloid leukemia patients receiving induction chemotherapy without systemic antifungal prophylaxis: a prospective observational study in Taiwan. *PLoS One*. 2015;10(6):e0128410.
7. Sun Y, Huang H, Chen J, et al. Invasive fungal infections in patients receiving chemotherapy for haematological malignancies: a multicenter prospective observational study in China. *Tumour Biol*. 2015;36(2):757-767.

8. Dragonetti G, Criscuolo M, Fianchi L, Pagano L. Invasive aspergillosis in acute myeloid leukemia: Are we making progress in reducing mortality ? *Med Mycol*. 2017;55(1):82-86.
9. Caira M, Candoni A, Verga L, et al. SEIFEM Group (Sorveglianza Epidemiologica Infezioni Fungine in Emopatie Maligne). 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(2):284-292.
10. Cheson BD, Cassileth PA, Head DR, et al. Report of the National Cancer Institute-sponsored workshop on definitions of diagnosis and response in acute myeloid leukemia. *J Clin Oncol*. 1990;8(5):813-819.
11. 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;15(46):1813-1821.
12. Segal BH, Herbrecht R, Stevens DA, et al. Defining responses to therapy and study outcomes in clinical trials of invasive fungal diseases: Mycoses Study Group and European Organization for Research and Treatment of Cancer consensus criteria. *Clin Infect Dis*. 2008;47(5):674-683.
13. Lien MY, Chou CH, Lin CC, et al. Epidemiology and risk factors for invasive fungal infections during induction chemotherapy for newly diagnosed acute myeloid leukemia: A retrospective cohort study. *PLoS One*. 2018;13(6):e01978.
14. 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. *Hematologica*. 2011;96(2):337-341.
15. Michallet M, Bénet T, Sobh M, et al. Invasive aspergillosis: an important risk factor on the short-and long-term survival of acute myeloid leukemia (AML) patients. *Eur J Clin Microbiol Infect Dis*. 2012;31(6):991-997.
16. Girmenia C, Micozzi A, Piciocchi A, et al. Invasive fungal diseases during first induction chemotherapy affect complete remission achievement and long-term survival of patients with acute myeloid leukemia. *Leuk Res*. 2014;38(4):469-474.
17. Cattaneo C, Gramegna D, Malagola M, et al. Invasive pulmonary aspergillosis in acute leukemia: a still frequent condition with a negative impact on the overall treatment outcome. *Leuk Lymphoma*. 2019;60(12):3044-3050.
18. 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;1:e1-e38.
19. Nucci M, Nouer SA, Cappone D, et al. Early diagnosis of invasive pulmunary aspergillosis in hematologic patients: an opportunità to improve the outcome. *Haematologica*. 2013;98:1657-1660.
20. Pagano L, Busca A, Candoni A, et al. Risk stratification for invasive fungal infections in patients with hematological malignancies: SEIFEM recommendations. *Blood Rev*. 2017;31:17-61.

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