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ARTICLE

Invasive aspergillosis: an important risk factor on the short- and long-term survival of acute myeloid leukemia (AML) patients

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Abstract Invasive aspergillosis (IA) during induction chemotherapy of acute myeloid leukemia (AML) could worsen the prognosis. Our objective was to study how the development of IA during AML interferes with the therapeutic strategy and to evaluate its impact on the short- and long-term survival. Newly diagnosed AML patients between the years 2004 and 2007 were retrospectively analyzed. The outcome was death of the patient. A Cox proportional hazards model with the diagnosis of IA and post-induction response evaluation as the main exposure was fitted. Overall, 262 patients were analyzed and 58 IA were observed. The 2-year survival of patients having had remission of AML was 54% and, for patients with failure of chemotherapy, it was 5% ($p<0.001$). The 2-year survival of patients having had IA was 14%, and without IA, it was 32% ($p=0.01$). Multivariate analysis showed that IA was associated with a higher risk of death in case of remission compared to no IA (hazard ratio [HR]=1.66 [1.05–2.65], $p=0.031$) and also in case of failure (HR=6.43, $p<0.001$). IA was associated with an increased risk of death for patients if they were either in remission or in failure after induction chemotherapy.

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Introduction

Invasive aspergillosis (IA) remains a major clinical complication in immunocompromised patients and especially in those receiving chemotherapy for hematological malignancies [1]. The mortality rate can reach 50% in patients with chemotherapy-induced neutropenia and can exceed 90% in patients receiving hematopoietic stem cell transplantation (HSCT) [2, 3]. Patients with acute myeloid leukemia (AML) are the most frequently affected, with a 10% infection rate during post-induction or consolidation therapy [4, 5]. Patient outcome improvement due to the empiric use of various antifungal (AF) drugs has not been further demonstrated [1, 6]. Prophylaxis is a commonly used treatment strategy because the diagnosis of fungal infection is often delayed or difficult to establish with certainty, and a delay in AF treatment increases mortality. Recently, a preemptive diagnostic approach using high-resolution computed tomography (CT) and serological tests has been introduced and had an impact on IA-related mortality rates [7]. Hence, systematic prophylaxis has become a challenging alternative, with newly available AF drugs. Different risk-stratification strategies have been evaluated in order to identify patients who may benefit from prophylactic and

diagnostic measures [8, 9]. Two large studies have shown significant reductions in the invasive fungal infection (IFI) incidence and IFI-related mortality by using posaconazole as the prophylactic treatment compared to other azole drugs in patients undergoing HSCT or with AML and myelodysplastic syndrome (MDS) [10, 11], but its clinical effectiveness can vary depending on the local epidemiology [12]. Some factors commonly assigned to AML prognosis have been shown to have a role in infection incidence and, thus, may impact the patient outcome [13]. We showed, in a recent study on AML patients undergoing induction chemotherapy, that the incidence of IA infection is independently associated with the patient's age and failure to induction therapy; this has been evaluated in a multivariable model [14]. We also pointed out the AF prophylaxis effect on IA incidence.

The principal aim of our study was to see how the development of an IA during the AML story interferes with the therapeutic strategy and to evaluate its impact on the short- and long-term survival outside of any AF prophylaxis.

Design and methods

Studied population

This retrospective analysis concerned AML patients hospitalized at our hospital between January 2004 and November 2007 to receive first induction chemotherapy, for whom we have evaluated the incidence of IA and its impact according to the objective of this study. Data were extracted from the patient medical chart and IA information was available from the prospective IA surveillance registry within the epidemiology department that has been implemented since January 2004. Before November 2007, no AF prophylaxis recommendations were available for AML patients receiving chemotherapy and patients did not receive any prophylaxis before that time. By the end of the year 2007, AF prophylaxis recommendations appeared and were applied in our hospital [10, 15]. As our aim was to study the effect of IA outside of any AF prophylaxis, the data collection included patients without prophylaxis.

This observational study was carried out according to the institutional guidelines and was approved by the local institutional review board.

AML diagnosis, treatment, and evaluation

All patients were diagnosed and treated in the hematology department according to the hospital care standards. Cytogenetic analyses were performed in order to classify the patients into favorable, intermediate, or high-risk diagnosis according to international classifications [16, 17]. After that, patients were allocated to intensive (regimen containing>1 g/m^2/day of cytarabine) or standard (regimen containing<200 mg/m^2/day of cytarabine) chemotherapy regimens, taking into account different risk factors, including age and comorbidities. Patients less than 65 years old with high risk of disease were scheduled to receive an allogeneic HSCT and, thus, a donor selection was set since the diagnosis. Response to induction chemotherapy was evaluated around the 5th week after the beginning of chemotherapy. A complete response (CR) was defined as the presence of morphologically normal bone marrow and at least 1.5×10^9/L granulocytes and 100×10^9/L platelets in the blood. Relapse was defined as at least 5% leukemic blasts in a bone marrow aspirate or new extramedullary leukemia in patients with a previously documented CR, as defined previously [18]. Failure to attain CR was divided into categories of early death (death within 30 days, more likely to be representative of regimen-related toxicity) and late death (more than 30 days, more likely to be associated with resistant disease).

Patient monitoring for IA

Each patient had a daily clinical examination. The presence of *Aspergillus* galactomannan antigen was tested on sera sampled twice a week by using the double-sandwich ELISA Platelia Aspergillus® (Bio-Rad, Marnes-La-Coquette, France); an optical density index ≥0.5 was considered to be positive [19, 20]. CT scanning was repeated in case of positive antigenemia result and persistence of fever on anti-bacterial antibiotherapy. Proven, probable, and possible IA was defined according to the 2008 revised European Organization for Research and Treatment of Cancer (EORTC) criteria [21].

End-points

The primary end-point was to evaluate the overall survival of patients with or without IA; either they were in CR or not after induction chemotherapy. Secondary end-points included the incidence of IA and a study of factors that may impact on the overall survival.

Statistical analysis

Firstly, a descriptive analysis was done. Chi-square or Fisher's exact test were used to compare discrete variables. The Mann–Whitney test was used to compare continuous variables. Secondarily, a survival analysis was done. Four categories we distinguished: no IA and CR after induction chemotherapy; IA and CR; no IA and failure of chemotherapy; and the last category was IA and failure of chemotherapy. Kaplan–Meyer curves with the log-rank test were used to compare survival distributions. A Cox proportional hazards model for the overall survival was

fitted. For multivariate analysis, covariates with a $p<0.15$ after univariate analysis were eligible for entering in the first model. The models were then compared using a backward selection with the likelihood ratio test. HSCT was a time-dependant covariate. All statistical tests were two-tailed and $p<0.05$ was considered to be significant. Stata 8.0 (StataCorp, 2003) was used for the statistical analysis.

Results

Descriptive data

A total of 261 patients, accounting for 148,969 patient-days (407.9 patient-years), were analyzed. There were 140 (54%) males and 121 (46%) females, with a median age at diagnosis of 56.5 years (range 48–65 years). For the World Health Organization (WHO) status, 191 (73%) had a score <2 and 70 (27%) had a score ≥2. Eighty-five (33%) patients received intensive induction chemotherapy, while the other 176 (67%) patients received a standard regimen, either for age or for having comorbidities. The demographic and clinical characteristics of the whole population are summarized in Table 1.

Incidence of IA

Fifty-eight IA were observed: 5 (9%) proven, 24 (41%) probable, and 29 (50%) possible according to the EORTC criteria. IA appeared after a median time of 20 days (range 16–27 days) from the beginning of induction chemotherapy.

Table 1 Comparison of the characteristics of the patients with acute myeloid leukemia (AML), with and without invasive aspergillosis (IA) during disease course, at Edouard Herriot Hospital, Lyon, France, 2004–2009

Characteristics	Invasive aspergillosis (n=58)	No invasive aspergillosis (n=203)	P-value
Gender, male, n (%)	37 (64)	103 (51)	0.079
Age at diagnosis, years, median (IQR)	57.4 (49.9–64.3)	56.3 (46.1–65.5)	0.6
Age at diagnosis, n (%)			0.5
<45 years	9 (16)	46 (23)	
45–54 years	15 (26)	44 (22)	
55–64 years	21 (36)	61 (30)	
>65 years	13 (22)	52 (26)	
Year of diagnosis, n (%)			0.096
2004	18 (31)	53 (26)	
2005	19 (33)	47 (23)	
2006	14 (24)	48 (24)	
2007	7 (12)	55 (27)	
WHO status, median (IQR)	1 (0–2)	1 (0–1)	0.053
WHO status, n (%)			0.067
<2	37 (64)	154 (76)	
≥2	21 (36)	49 (24)	
Cytogenetic group, n (%)			0.2
Favorable	3 (5)	23 (11)	
Intermediate	18 (31)	77 (38)	
Unfavorable	27 (47)	82 (41)	
Not possible to classify or not done	10 (17)	21 (10)	
Induction chemotherapy, n (%)			0.7
Intensive	20 (34)	65 (32)	
Standard	38 (66)	138 (68)	
LAF or PPI room at induction, n (%)	48 (83)	169 (83)	0.9
Post-induction evaluation, n (%)			0.14
Complete remission	39 (67)	156 (77)	
Failure	19 (33)	47 (23)	
Post-induction treatment: protocol, n (%)	20 (34)	130 (64)	<0.001
HSCT, n (%)	14 (24)	53 (26)	0.8
Relapse of AML, n (%)	23 (40)	90 (44)	0.5
Deaths, n (%)	43 (74)	121 (60)	0.043

IQR, interquartile range; LAF: laminar airflow; PPI: positive pressure isolation; AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplantation

Table 2 Causes of death in patients with AML, with and without IA during disease course according to the post-induction evaluation (complete remission or failure), at Edouard Herriot Hospital, Lyon, France, 2004–2007

Cause of death, *n* (%)	Complete remission		Failure	
	IA (*n*=25)	No IA (*n*=75)	IA (*n*=18)	No IA (*n*=46)
Failure, leukemia progression	11 (44)	45 (60)	6 (33)	36 (78)
HSCT toxicity	0 (0)	1 (1)	0 (0)	0 (0)
Multiorgan failure/shock	6 (24)	8 (11)	1 (6)	3 (7)
Hemorrhage	2 (8)	3 (4)	0 (0)	2 (4)
Graft-versus-host disease	1 (4)	1 (1)	0 (0)	0 (0)
Invasive aspergillosis	5 (20)	–	8 (44)	–
Other infection	0 (0)	15 (20)	3 (17)	5 (11)
Other cause	0 (0)	2 (3)	0 (0)	0 (0)

IA, invasive aspergillosis; HSCT, hematopoietic stem cell transplantation

Among the IA cases, 57 (98%) had fever (persistent fever for >96 h refractory to appropriate antibiotic treatment) and 45 (79%) had pulmonary signs. The CT scan was abnormal for 57 (98%) patients; a halo was found in 52 (90%) patients and excavated nodules were found in 1 (2%) patient. The *Aspergillus* antigen was positive in 24 (41%) patients, negative in 33 (57%) patients, and not done in 1 (2%) patient. Four (7%) patients received glucocorticosteroid treatment.

Chemotherapy response evaluation

Response to induction chemotherapy was evaluated after a median time of 37 days (range 31–48 days). A total of 185

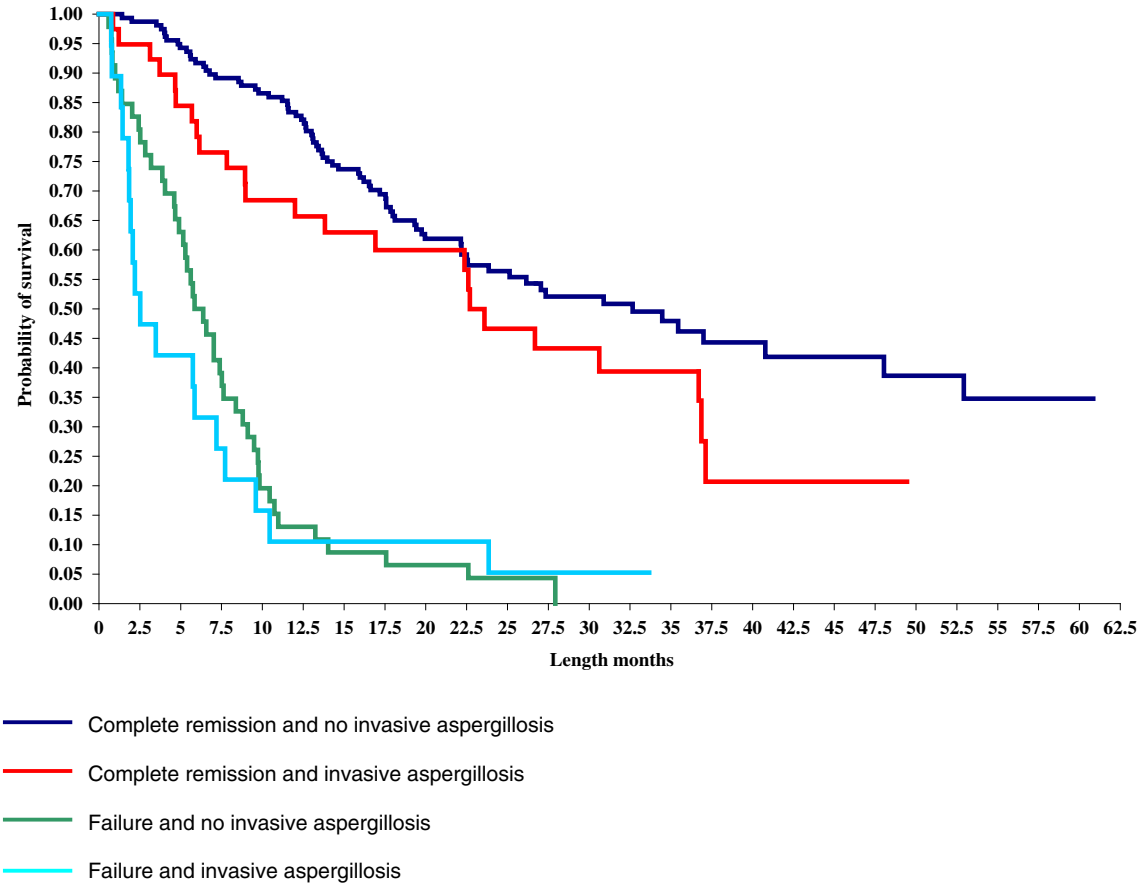

Fig. 1 Survival of patients with acute myeloid leukemia (AML), by invasive aspergillosis (IA) diagnosis and post-induction evaluation, at Edouard Herriot Hospital, Lyon, France, 2004–2007, Kaplan-Meier curves. Note that survival is defined as complete remission and no IA vs. complete remission and IA: log-rank test, $p=0.085$. Failure and no IA vs. failure and IA: log-rank test, $p=0.5$

Table 3 Probabilities of survival after the diagnosis of AML according to the diagnosis of IA and to the post-induction evaluation

Characteristics	Delay after diagnosis					P*		Median survival, months (95% CI)
	30 days	100 days	1 year	2 years	4 years			
Patients at risk, N°	254	235	163	77	15			
Probabilities of survival, %								
Overall	97	90	63	42	28			18 (15-23)
Invasive aspergillosis								
Invasive aspergillosis	95	78	47	33	15	0.016		10 (6-23)
No invasive aspergillosis	98	93	67	44	32			20 (17-26)
Post-induction evaluation								
Remission	99	97	80	54	37	$<10^{-3}$		31 (23-37)
Failure	89	66	12	5	NE			6 (4-7)
Remission of AML								
Invasive aspergillosis	97	92	66	47	21	0.085	$<10^{-3}$	23 (12-39)
No invasive aspergillosis	100	99	83	56	42			33 (23-48)
Failure of induction chemotherapy								
Invasive aspergillosis	0.89	47	11	5	NE	0.5		3 (2-7)
No invasive aspergillosis	0.89	74	13	4	NE			6 (5-8)

CI, confidence interval; AML, acute myeloid leukemia; NE, nonestimable

*Log-rank test

(75%) patients were in CR, while 66 (25%) were in less than CR and, thus, considered to be in failure to chemotherapy.

Survival analysis

The median overall survival for the whole population was 18 months (range 15–23 months). Overall, 164 (63%) deaths were observed during the study period. The death rate was higher in patients with IA than in patients without IA (respectively, 74% vs. 60%, $p=0.043$). The different causes of death in patients with and without IA according to their post-induction evaluation (CR or failure) are shown in Table 2. The 2-year survival of patients with IA was 15% versus 32% for those without IA (log-rank test, $p=0.016$). The 2-year survival of patients achieving a CR after induction chemotherapy was 54% vs. 5% for those with failure of chemotherapy (log-rank test, $p<0.001$); accordingly, the survival rate depending on the presence or absence of IA was different in the two response groups (log-rank test, $p<0.001$) (Fig. 1). Survival rates according to the presence or absence of IA and to the post-induction evaluation are shown in Table 3

Univariate and multivariate analyses

After Cox univariate analysis, compared with CR without IA, IA with CR was associated with lower survival rates (hazard ratio [HR]=1.50, 95% confidence interval [CI] 0.95–2.38, $p=0.084$), without reaching the statistical threshold. Failure of

Table 4 Factors associated with the survival in AML patients undergoing induction chemotherapy; multivariate Cox proportional hazards model

Characteristics	Hazard ratio*	95% CI	*P*-value
Invasive aspergillosis and post-induction evaluation			
No invasive aspergillosis and complete remission	1.00 (reference)	–	–
Invasive aspergillosis and complete remission	1.63	(1.02–2.61)	0.043
No invasive aspergillosis and failure	6.30	(4.18–9.49)	<0.001
Invasive aspergillosis and failure	6.49	(3.76–11.23)	<0.001
WHO status			
<2	1.00 (reference)	–	–
≥2	1.86	(1.32-2.64)	<0.001
Cytogenetic group			
Favorable	1.00 (reference)	–	–
Intermediate	4.52	(1.62–12.62)	0.004
Unfavorable	5.32	(1.93–14.72)	0.001
Not possible to classify or not done	8.11	(2.81–23.42)	<0.001
Induction chemotherapy			
Intensive	1.00 (reference)	–	–
Standard	2.07	(1.41–3.04)	<0.001

CI, confidence interval

*Adjusted on the other covariates reported in the table

chemotherapy without IA was associated with higher death rate (HR=6.67, 95% CI 4.49–9.90, $p<0.001$), as well as failure of chemotherapy with IA (HR=7.52, 95% CI 4.44–12.75, $p<0.001$). At the time of diagnosis, older patients, those with worse WHO status, unfavorable cytogenetic group (vs. favorable), and standard type of induction chemotherapy (vs. intensive) were associated with lower survival rates. The gender, year of diagnosis, and receipt of HSCT had not impact on the survival. After Cox multivariate analysis (Table 4), IA in the presence of CR was found to be an independent factor for higher death rate (HR=1.63, 95% CI 1.02–2.61, $p=0.043$). Failure of chemotherapy was strongly associated with higher death rates, with or without IA. Higher WHO status, unfavorable cytogenetics, and standard chemotherapy intensity remained independently associated with lower survival.

Discussion

We conducted this retrospective study in order to evaluate the impact of IA on the long-term overall survival of AML patients undergoing induction chemotherapy outside of any AF prophylaxis. Since a few years ago, different scientific societies have published several clinical guidelines to assist physicians in choosing the appropriate treatment strategy for fungal infections [15, 22, 23]. However, adherence to these recommendations is not always feasible due to the patients' clinical conditions and comorbidities that make the recommended AF drug a non-applicable strategy [24].

We have shown, in a recent study, that factors commonly assigned to AML as potentially impacting the incidence of fungal infection independently of any prophylaxis [14]. Here, we aimed to go further and study the impact of IA on the survival of AML patients cared in the same department of the same hospital settings outside any AF prophylaxis. IA occurred in 58 (22%) patients, of which the majority were associated to fever and pulmonary signs. Concerning the response to induction chemotherapy, 75% were evaluated to be in CR, while the rest of the population was considered to be in failure. Survival analysis, especially in the long term (after 2 years), showed a clearly worse survival in patients having had IA versus those who did not ($p=0.016$). When adjusting according to response to induction chemotherapy, patients with IA and in CR were found to, potentially, have a worse survival than those in CR without IA ($p=0.08$). Interestingly, the multivariate analysis showed, in addition to the impact of cytogenetics, WHO status, and chemotherapy intensity, that IA has a significant impact on the overall survival of AML patients, whether they are in CR ($p=0.04$) or not ($p<0.001$).

In our study, no change in the environmental settings has been made during the study period, and a careful classification of the chemotherapy type and intensity has been made. Many other clinicians are concerned that randomized clinical trials and related guidelines do not reflect the complexity of the real world [25–27]. In the recent years, two large studies have shown the efficacy of posaconazole to significantly reduce the incidence and IFI-related mortality in patients with AML, MDS, or undergoing HSCT [10, 11]. In addition, AML-related variables with prognostic value and heterogeneity in chemotherapy regimens have not been taken into account in previous studies, which can have an important impact on the overall and disease-free survival. In this context, our study indicated the negative role of IA on the survival of AML patients independently of any other factors; this supports the application of prophylaxis in this immunocompromised population and incites physicians to devote all of their efforts in order to avoid its occurrence.

In conclusion, IA remains an important cause of morbidity and mortality in patients with hematological diseases. Physicians should be aware of different risk factors not necessary related to the environmental settings, but related to the disease itself, patient characteristics, and treatment settings; this is in order to overcome the infection effects and address the optimal chance to cure the hematological disease.

Conflict of interest No conflict of interest to declare.

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