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

Caroline Even,[1] Sylvie Bastuji-Garin,[2,3] Yosr Hicheri,[1,4] Cécile Pautas,[1] Francoise Botterel,[4,5,6] Sébastien Maury,[1,4] Ludovic Cabanne,[1] Stéphane Bretagne,[4,5,6] and Catherine Cordonnier[1,4,5]

[1]Assistance Publique-Hôpitaux de Paris (AP-HP), Groupe Hospitalier Henri Mondor-Albert Chenevier, Hematology Department, Créteil, France; [2]AP-HP, Groupe Hospitalier Henri Mondor-Albert Chenevier, Department of Clinical Research and Public Health; [3]Université Paris Est, Créteil, France; [4]Université Paris Est, Faculté de Médecine, Créteil, France; [5]Université Paris-Est, UMR BIPAR 956, France; and [6]AP-HP, Groupe Hospitalier Henri Mondor-Albert Chenevier, Parasitology-Mycology Laboratory

ABSTRACT

Patients with acute leukemia who initially survive invasive fungal disease must receive chemotherapy or go on to transplant. Many centers change subsequent chemotherapy to decrease the risk of fungal reactivation. This case-control study compared acute leukemia patients (n=28) who developed a proven or probable fungal disease and survived four weeks later, to patients who did not (n=78), and assessed the impact of fungal disease on the chemotherapy regimens, and overall and event-free survival.

Chemotherapy changes (i.e. delays, dose-reduction) were more frequent in the fungal (68%) than in the control group (24%) (P<0.001). Although there was no difference in overall and event-free survival between groups, they were both lower for proven fungal disease cases when compared to controls (HR 2.4, 95% CI 1.1-1.5, and HR 2.9, 95% CI 1.4-5.6, respectively). Patients with invasive fungal disease, even though they initially survive, undergo significant changes to their chemotherapy therapy. This impacts on the survival of patients with proven fungal disease.

Key words: invasive fungal disease, leukemia, survival, infection, chemotherapy.

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Introduction

Invasive fungal diseases (IFD) are a major cause of mortality in acute leukemia (AL), affecting approximately 5-15% of acute myeloid leukemia (AML) patients.[1,2] The mortality of patients with invasive fungal diseases at three months after diagnosis is reported to be between 28-42% in invasive *aspergillosis* and 23-40% in invasive candidiasis.[3-8] Patients surviving invasive fungal diseases may have problems completing the full chemotherapy schedule because the risk of fungal relapse is estimated to be around 30%.[9] Most hematologists give a secondary prophylaxis,[9,10] as supported by international guidelines.[11-12] Additionally, they often delay or reduce the doses of chemotherapy, at least until the invasive fungal disease is stabilized.

Any change in a chemotherapy protocol (delaying courses, dose reduction, or changing the drugs) may impact on the prognosis of acute leukemia patients.[13,14] Despite many data on the mortality rates of invasive fungal diseases in hematology patients, there has been no study which looks at their impact in survivors of the event on the application of the acute leukemia chemotherapy regimen which had been initially planned.

The objectives of this study were to assess the impact of invasive fungal diseases on the application of chemotherapy regimens in patients with acute leukemia surviving invasive fungal diseases, and the possible impact of these changes on the event-free (EFS) and overall survival (OS).

Desgin and Methods

This is a single-center, hospital-based case-control study on patients consecutively treated in our department for acute leukemia between 2000 and 2008. The study was approved by the Comité de Protection des Personnes, Ile de France IX.

All acute leukemia patients aged 60 years or under were housed in laminar-air flow (LAF) rooms during the chemotherapy courses with an expected neutropenia of over ten days. The older patients (> 60 y) were hospitalized in regular single rooms unless a laminar-air flow room was available. All acute leukemia patients received oral non-absorbable polyens, without other antifungal prophylaxis, and were screened twice weekly by galactomannan antigenemia in the blood. Invasive fungal diseases were classified according to the EORTC-MSG criteria.[15] All chemotherapy regimens, and any change in the schedule, were individually discussed among the staff. The department is involved in the Acute Promyelocytic Group (APL),[16] in the Acute Leukemia French Association (ALFA) for other acute myeloid leukemias,[17,18] and in the national acute lymphoblastic leukemia

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Correspondence: Catherine Cordonnier, MD, Hematology Department, CHU Henri Mondor 94000 Créteil, France. Phone: international +33.1.49812059. Fax: international +33.1.49812067. E-mail: carlcord@club-internet.fr and Sylvie Bastuji-Garin, MD, Département de Santé Publique, Henri Mondor Teaching Hospital, 94000 Créteil, France. E-mail: Sylvie.bastuji-garin@hmn.aphp.fr

(ALL) group.[19,20] All patients were treated with regimens defined in a written procedure, whether the patient was or was not included in a prospective study.

Male and female acute leukemia patients aged over 15 years were included in the study. All patients had a probable or proven invasive fungal disease, were treated within or according to a given protocol of chemotherapy, survived at least four weeks after the invasive fungal disease diagnosis, and were not transplanted, either because they had no indication of hematopoietic cell transplantation (HCT) or they had no donor. Patients who were to receive an allogeneic hematopoietic cell transplantation and had a donor benefited from a reduced-intensity conditioning regimen with a secondary antifungal prophylaxis and were excluded from this analysis. Possible invasive fungal diseases were not considered. Patients who had only experienced an invasive fungal disease during their last planned course were excluded since assessing any change in the subsequent course would not have been relevant. The patients were only included at their first episode of invasive fungal disease. To create the control group, for each case patient, we selected 3 individually matched control subjects. The control subjects were aged over 15 years and did not present invasive fungal diseases. Matching criteria were sex, age (± 5 years), leukemia type, chemotherapy protocol, treatment phase (first induction, consolidation or relapse treatment), leukemia status (remission or failure), and year of treatment. The target sample was 30 cases and 90 controls to detect an odds ratio (OR) of 4 to 5 for a prevalence of 10% to 20% of changes in the chemotherapy among controls, with an 80% power and for a two-sided type I error of 5%.

A delay in the chemotherapy regimen was defined by a chemotherapy course starting after the maximal period allowed in the protocol. A change of chemotherapy regimen was defined by any dose reduction, cytotoxic switch, change of timing, or switch to a palliative treatment justified in the chart by the severity of the invasive fungal disease.

Acute leukemias were classified according to the FAB classification. Karyotypes in acute myeloid leukemia were considered to be indicative of good (translocations t(8,21), inv16 or t(16,16); t(15,17)), poor (monosomy 5, monosomy 7, complex karyotype, chromosome 3-long arm abnormalities, t(6,9), t(9,22) or Philadelphia chromosome) or intermediate (all others, including normal karyotypes) prognosis. Karyotypes in acute lymphoblastic leukemia were considered to be indicative of good (hyperdiploidy and tetraploidy), poor (t(9, 22), t(4, 11) or t(1, 19) for B-lineage, any complex karyotype) or intermediate (other) prognosis.

Our hypothesis was that even though the patients initially survived invasive fungal disease, its occurrence may modify the application of the chemotherapy regimens, and consecutively may impact on the overall survival or event-free survival. The changes of chemotherapy were compared between cases (patients with IFD) and controls (patients without IFD) using Fisher's exact test or the non-parametric Mann-Whitney test as appropriate. Quantitative variables are expressed as median (range) and qualitative variables as number (%). Odds ratios (OR) with their 95% confidence intervals (CI) were estimated separately for each parameter using unconditional logistic regression. Survival assessment was censored at 30 months after inclusion.

Event-free survival was defined as survival without leukemia relapse or fungal death.

To analyze the impact of invasive fungal disease on event-free survival and overall survival, time from beginning of the last course of chemotherapy to the event of patients with no, probable or proven invasive fungal disease was estimated using the Kaplan-Meier method and compared using log rank analysis. Hazard ratios and their 95% CI were estimated using Cox's proportional hazard models. Other variables that could potentially influence event-free survival (age at diagnosis, hyperleukocytosis, karyotype, type of leukemia, and changes in protocol) were also analyzed. Proportional hazards assumption was graphically assessed, and the Schoenfeld residuals were used in case of uncertainty. Invasive fungal disease was then entered into a multivariate Cox's proportional hazard analysis of event-free survival and of overall survival, along with potential confounders (other variables with a P value ≤ 0.15 in univariate analysis). P 0.05 or under was considered statistically significant. All significance tests were two-tailed. Data were analyzed using the Stata Statistical Software (StataCorp 2003, Release 8.0, College Station, Texas).

Results and Discussion

During the study period, 362 new cases of acute leukemia and 151 relapses were cared for in our department. Sixty-nine patients (13.4%) developed a first proven or probable invasive fungal disease. Among the 64 patients who survived four weeks later, 24 received an allogeneic hematopoietic cell transplantation within three months, 5 experienced invasive fungal disease during the last planned course of chemotherapy, 6 were not treated in a specific protocol which precludes the matching, and one patient was lost to follow up. Therefore, 28 patients were analyzed (1st induction n=21; consolidation n=4; relapse induction n=3). Our aim was to include 90 control subjects; however, only 78 appropriate controls could be enrolled.

Patients' characteristics are summarized in Table 1. The two cohorts were comparable with respect to age, sex,

Table 1. Demographic and hematologic characteristics of cases and control patients.

Characteristic: n (%)	Cases (n=28)	Control Subjects (n=78)	P value*
Matching variables			
Sex: Male	15 (53.6)	42 (53.9)	1
Age at diagnostic, years	56 [16- 76]	54 [20-75]	0.89
Leukemia Type (FAB classification):			
AML† 0,1,2,4,5,	20 (71.4)	62 (79, 5)	
AML 6, secondary, or not specified.	6 (21, 4)	10 (12, 8)	
AML 3	1 (3.6)	3 (3.9)	
ALL ‡	1 (3.6)	3 (3.9)	0.72
Chemotherapy protocol:			
ALFA 98-01	13 (46.4)	37 (47.4)	
ALFA 98-02	7 (25.0)	20 (25.6)	
ALFA 98-03	6 (21.4)	15 (19.2)	
APL 2000	1 (3.6)	3 (3.9)	
LALA 94	1 (3.6)	3 (3.9)	1
Karyotype:			
Good prognosis	3 (10.7)	7 (9.0)	
Intermediary prognosis	15 (53.6)	47 (60.3)	
Poor prognosis	9 (32.1)	20 (25.6)	
Not done	1 (3.6)	4 (5.1)	0.90
Hyperleukocytosis (WBC§ > 100×10⁹/L) at diagnosis	3 (10.7%)	5 (6.4%)	0.43
Follow-up, months [extrems]	24 [5-104]	23 [5-112]	-

*Qualitative variables are expressed as number (%), quantitative as median [range]. *P value of Fisher's exact test or of the non-parametric Mann-Whitney test as appropriate. †AML: acute myeloid leukemia; ‡ALL: acute lymphoblastic leukemia; §WBC: white blood cell count.*

leukemia type and status, cytogenetic risk, chemotherapy protocol, treatment phase, and follow up.

Among the 28 invasive fungal disease patients, 21 events (75%) occurred during induction therapy. There were 20 *aspergillosis*, 7 candidiasis (6 candidemia and one hepatosplenic candidiasis), and one zygomycosis. Eleven (39%) cases were proven (5 *aspergillosis* and 6 candidemia), 17 (61%) were probable (one candidiasis, 15 *aspergillosis*, and one zygomycosis). Three patients with *aspergillosis* benefited from surgery and 20 of 28 invasive fungal disease patients received a secondary antifungal prophylaxis during subsequent chemotherapy. Four patients subsequently developed a new episode of invasive fungal disease: 3 patients *aspergillosis* relapse, and one patient candidemia relapse at induction developed an IA during a consolidation course. None of these new fungal episodes was a cause of death.

The administration of the next chemotherapy course was delayed in 16 cases (57.1%) and in 16 control subjects (20.5%) (P=0.001). In patients whose treatment was delayed, this delay was of a median of 11 days (1-38 days) in the case group, and of 4.5 days (1-45 days) in the control group (P=0.0058). The chemotherapy protocol was changed in 8 cases (28.6%) and 6 control subjects (7.7%) (P=0.009). The protocol changes were: 1) an early switch to a maintenance treatment for 4 cases (14.3%) and no control subject; 2) a switch to a palliative treatment for 2 cases (7.1%) and 2 control subjects (2.6%); 3) a dose-reduction of chemotherapy in one case (3.6%) and 2 control subjects (2.56%); 4) a switch to outpatient management for one control subject (1.3%); and 5) a change for a less myeloablative drug for one control subject (1.3%). Finally, 19 (68%) of the cases and 19 (24.4%) of the controls had some change to the chemotherapy schedule (P<0.001). Furthermore, this proportion significantly increased from controls (24.4%) to probable (64.7%) and proven (71.1%) invasive fungal disease (P value of the χ^2 for trend <0.001).

There was no significant difference in the probability of overall survival and event-free survival between invasive fungal disease cases and controls (HR 1.28, 95% CI 0.74-2.22 and HR 1.30, 95% CI 0.71-2.39, respectively). However, when proven and probable invasive fungal disease were separated, proven invasive fungal disease was significantly associated with lower overall survival and event-free survival in the univariate analysis (HR 2.9, 95% CI 1.4-5.6 and HR 2.4, 95% CI 1.1-5.1, respectively). The probability of event-free survival was also significantly worse in the older patients, in patients with hyperleukocytosis, poor prognosis cytogenetics, and in patients with AML6 or secondary leukemia (Figure 1 and Table 2).

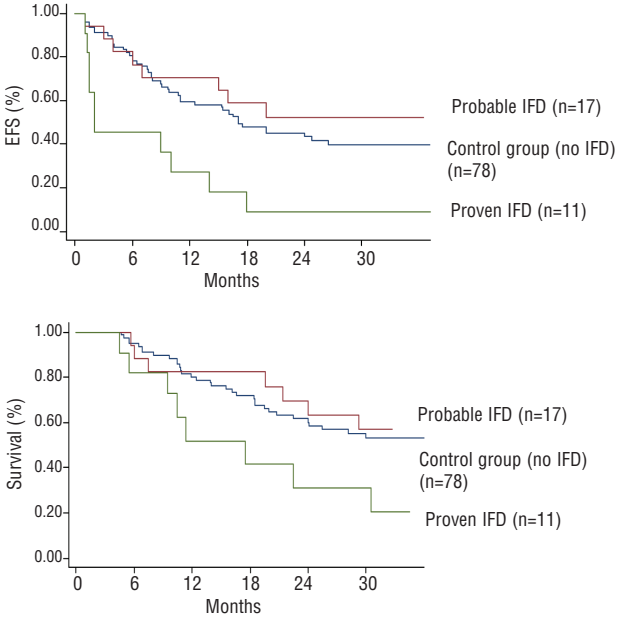

Figure 1. (A) Event-free survival according to IFD. (B) Overall survival according to IFD.

Table 2. Influence of parameters on the event free survival.

	Event (n=62)	No event (n=44)	Univariate analysis *P* value	Univariate analysis HR* [95% CI]	Multivariate analysis *P* value	Multivariate analysis HR [95% CI]
Age at diagnosis, median [range], years	58.5 [15-76]	43.5 [51-68]	<0.0001	1.05 [1.03-1.07]†	0.001	1.04 [1.02-1.06]†
WBC† > 100×10⁹/L at diagnosis, n (%)	6 (9.7)	2 (4.6)	0.17	1.8 [0.8-4.2]	0.005	3.7 [1.5-9.2]
Cytogenetics, n (%)						
Good prognosis	3 (4.8)	7 (15.9)		1		1
Intermediary prognosis	36 (58.1)	31 (70.5)	0.14	2.4 [0.7-7.9]	0.38	1.7 [0.5-6.0]
Poor prognosis or no cytogenetics	23 (37.1)	6 (13.6)	0.001	4.9 [1.5-16.5]	0.04	3.8 [1.1-13.7]
AML 6, secondary, or not specified, n (%)	15 (24.2)	1 (2.3)	<0.0001	3.7 [6.8-18.3]	0.009	2.4 [1.2-4.6]
Chemotherapy delayed, n (%)	16 (25.8)	16 (36.4)	0.23	0.7 [0.4-1.2]	-	
Protocol change, n (%)	9 (14.5)	5 (11.4)	0.36	1.4 [0.7-2.8]	-	
Total delay and/or change in chemotherapy schedule, n (%)	21 (33.9)	17 (38.6) -	0.68	0.9 [0.6-1.6]		
Fungal infection (yes *vs.* no) , n (%)	18 (29.0)	10 (22.7)	0.51	1.3 [0.7-2.2]		
Diagnosis of fungal infection, n (%)						
None	44 (71.0)	34 (77.3)		1		1
Probable	8 (12.9)	9 (20.5)	0.42	0.7 [0.3-1.6]	0.18	0.6 [0.3-1.3]
Proven	10 (16.1)	1 (2.3)	0.003	2.9 [1.4-5.6]	0.001	3.4 [1.6-7.2]

**HR 95% CI: Hazard ratios, 95% confidence intervals and P value were estimated using a univariate Cox's proportional model. † WBC: white blood cell count; AML: acute myeloid leukemia.*

Similar results were observed for overall survival. The changes or delays in chemotherapy had no significant impact on overall survival and event-free survival. In the multivariate analysis, a proven invasive fungal disease remained significantly associated with a poor prognosis after adjusting for the parameters which negatively influenced the survival (older age, white blood cell count at diagnosis, cytogenetics, and type of leukemia).

Our study shows that despite an initial favorable outcome, the occurrence of invasive fungal disease during acute leukemia treatment led us to change the chemotherapy program, either by delaying the next course, changing the drug, or reducing dosage. Second, the event-free survival and overall survival of acute leukemia patients was negatively influenced by the occurrence of a proven invasive fungal disease, although this does not seem to be significantly related to the chemotherapy changes, it may be due to the low number of proven invasive fungal disease in our study. Also, the fact that 86% of the invasive fungal disease patients received secondary antifungal prophylaxis may have minimized the risk of fungal reactivation.

Our study has several limits. First, we did not include patients with possible invasive fungal disease. The reason is the uncertainties of fungal diagnosis in this group. The fact that survival in our patients was significantly lower in the proven subgroups when compared to the non-IFD group or to the probable IFD group, suggests that the higher the level of proof of the invasive fungal disease, the greater the impact on survival, as recently shown in hematopoietic cell transplantation patients.[21] Also, the criteria for probable *aspergillosis*, mostly based on galactomannan antigen and imaging, may select some patients who in the end have no invasive fungal disease.[15] Second, we excluded patients who underwent an allogeneic hematopoietic cell transplantation after the invasive fungal disease episode. As our policy was to favor hematopoietic cell transplantation each time indicated by the characteristics of the disease, these patients are not comparable to the chemotherapy patients. Moreover, there are already many data on such patients in the literature.[22] Third, we did not include the rare patients who died early during induction, from or with invasive fungal disease, for whom the impact of the fungal event is obvious. The 3-month mortality rate of invasive fungal disease is widely illustrated in the literature.[1,2,4] On the other hand, there were no data so far on the outcome of patients getting invasive fungal disease, surviving the event, and needing ongoing chemotherapy.

Our study shows that in cases of invasive fungal disease during the course of acute leukemia therapy, despite initial survival, this event impacts on the chemotherapy regimen, and on overall survival and event-free survival, at least for proven invasive fungal disease. In order to decrease this impact of invasive fungal disease in acute leukemia patients, several approaches may be combined: primary prophylaxis, environmental measures,[26-28] empirical or preemptive antifungal treatment,[23,24] and secondary prophylaxis. However, every effort should be made to maintain unchanged the chemotherapy regimen since any change may have a negative impact on the overall prognosis.

Authorship and Disclosures

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References

1. Pagano L, Caira M, Candoni A, Offidani M, Martino B, Specchia G, et al. invasive aspergillosis in patients with acute myeloid leukemia: SEIFEM-2008 registry study. Haematologica. 2010;95(4):644-50.
2. Nivoix Y, Velten M, Letscher-Bru V, Moghaddam A, Natarajan-Ame S, Fohrer C, et al. Factors associated with overall and attributable mortality in invasive aspergillosis. Clin Infect Dis. 2008;47(9):1176-84.
3. Cornely O, Maertens J, Bresnik M, Ebrahimi R, Ullmann AJ, Bouza E, et al. Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). Clin Infect Dis. 2007;44(10):1289-97.
4. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med. 2002;347(6):408-15.
5. Kuse ER, Chetchotisakd P, da Cunha CA, Ruhnke M, Barrios C, Raghunadharao D, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. Lancet. 2007;369(9572):1519-27.
6. Pappas PG, Rotstein CM, Betts RF, Nucci M, Talwar D, De Waele JJ, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. Clin Infect Dis. 2007;45(7):883-93.
7. Reboli AC, Rotstein C, Pappas PG, Chapman SW, Kett DH, Kumar D, et al. Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med. 2007;356 (24):2472-82.
8. Slobbe L, Polinder S, Doorduijn JK, Lugtenburg PJ, el Barzouhi A, Steyerberg EW, et al. Outcome and medical costs of patients with invasive aspergillosis and acute myelogenous leukemia-myelodysplastic syndrome treated with intensive chemotherapy: an observational study. Clin Infect Dis. 2008;47(12):1507-12.
9. Sipsas NV, Kontoyiannis DP. Clinical issues regarding relapsing aspergillosis and the efficacy of secondary antifungal prophylaxis in patients with hematological malignancies. Clin Infect Dis. 2006;42(11):1584-91.
10. Cordonnier C, Rovira M, Maertens J, Olavarria E, Faucher C, Bilger K, et al. Voriconazole for Secondary Prophylaxis of Invasive Fungal Infection in Allogeneic Stem Cell Transplant Recipients: Results of the VOSIFI Study. Haematologica. 2010;95 (10):1762-8.
11. Maertens J, Marchetti O, Herbrecht R, Cornely OA, Flückiger U, Frere P, et al. European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: Summary of the ECIL3 – 2009 Update. Bone Marrow Transplant, 2010.2010 Jul 26. [Epub ahead of print].
12. Walsh TJ, Anaissie EJ, Dennin DW, Herbrecht R, Kontoyaiannis DP, Marr K, et al. Treatment of aspergillosis: Clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis. 2008; 46(3):327-60.
13. Bishop JF, Matthews JP, Young GA, Szer J, Gillett A, Joshua D, et al. A randomized study of high-dose cytarabine in induction in acute myeloid leukemia. Blood. 1996; 87(5):1710-7.
14. Buchner T, Hiddemann W, Berdel W, Wormann B, Loffler H, Schoch C, et al. Remission induction therapy: the more intensive the better? Cancer Chemother Pharmacol. 2001;48 (Suppl 1):S41-4.
15. Ascioglu S, Rex JH, de Pauw B, Bennett JE, Bille J, Crokaert F, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis. 2002;34(1):7-14.
16. Ades L, Sanz MA, Chevret S, Montesinos P, Chevallier P, Raffoux E, et al. Treatment of newly diagnosed acute promyelocytic leukemia (APL): a comparison of French-Belgian-Swiss and PETHEMA results. Blood. 2008;111(3):1078-84.
17. Gardin C, Turlure P, Fagot T, Thomas X, Terre C, Contentin N, et al. Postremission treatment of elderly patients with acute myeloid leukemia in first complete remis-

sion after intensive induction chemotherapy: results of the multicenter randomized Acute Leukemia French Association (ALFA) 9803 trial. Blood. 2007;109(12):5129-35.
18. Thomas X, Raffoux E, Botton S, Pautas C, Arnaud P, de Revel T, et al. Effect of priming with granulocyte-macrophage colony-stimulating factor in younger adults with newly diagnosed acute myeloid leukemia: a trial by the Acute Leukemia French Association (ALFA) Group. Leukemia. 2007;21(3):453-61.
19. Dombret H, Gabert J, Boiron J, Rigal-Huguet F, Blaise D, Thomas X, et al. Outcome of treatment in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia - results of the prospective multicenter LALA-94 trial. Blood. 2002;100(7):2357-66.
20. Thomas X, Boiron J, Hughet F, Dombret H, Bradstock K, Vey N, et al. Outcome of treatment in adults with acute lymphoblastic leukemia: Analysis of the LALA-94 trial. J Clin Oncol. 2004;22(20):4075-86.
21. Baddley JW, Andes DR, Marr KA, Kontoyiannis DP, Alexander BD, Kauffman CA, et al. Factors associated with mortality in transplant patients with invasive aspergillosis. Clin Infect Dis. 2010;50 (1):1559-67.
22. Martino R, Parody R, Fukuda T, Maertens J, Theunissen K, Ho A, et al. Impact of the intensity of the pretransplant conditioning regimen in patients with prior invasive aspergillosis undergoing allogeneic stem cell transplantation: A retrospective survey of the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Blood. 2006;108(9):2928-36.
23. Cordonnier C, Pautas C, Maury S, Vekhoff A, Farhat H, Suarez F, et al. Empirical versus pre-emptive antifungal strategy in high-risk febrile neutropenic patients: A prospective randomized study. Clin Infect Dis. 2009;48 (8):1042-51.
24. Cornely OA, Maertens J, Winston DJ, Perfect JR, Ullmann AJ, Walsh TJ, et al. Posaconazole vs. Fluconazole or Itraconazole prophylaxis in patients with neutropenia. N Engl J Med. 2007;356:348-59.