Mediterranean Journal of Hematology and Infectious Diseases

Original Articles

International Multicenter Experience in the Treatment Outcome of Invasive Aspergillosis in Immunocompromised Cancer Patients

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Competing interests: The authors have declared that no competing interests exist.

Abstract. ***Background:*** **Invasive aspergillosis (IA) is a life-threatening infection in immunocompromised patients. In this study, we compared the efficacy of voriconazole containing regimen vs non-voriconazole containing regimen in patients with IA.**
Methods: **In this retrospective study, we reviewed the medical records of all immunocompromised cancer patients diagnosed with proven or probable IA between February 2012 and March 2018. This trial included 26 patients from the American University of Beirut, Lebanon, 20 patients from Hospital das Clinicas da Faculdade de Medicina, Universidade de São Paulo, Brazil, and 10 patients from St. Luke's International Hospital Tokyo, Japan.**
Results: **A total of 56 patients were analyzed. They were divided into 2 groups voriconazole containing regimen and non-voriconazole containing regimen (90% Amphotericin B based regimen). Both groups had similar characteristic, age, gender, and immunocompromised status. The majority of patients had underlying leukemia (63%), followed by lymphoma (20%), myeloma (16%) and other hematologic malignancy (1%). Antifungal primary therapy with voriconazole-containing regimen was associated with better response to treatment (p = 0.003). Survival analysis showed that primary therapy with a voriconazole containing regimen was significantly associated with improved survival (p =0.006). By multivariate logistic regression analysis, mechanical ventilation was a predictor of worse outcomes (poor response to therapy and increased mortality within 6 months), whereas primary treatment with voriconazole containing regimen was associated with improved outcomes including response to primary therapy (OR=18.1, p=0.002) and 6-month mortality (OR=0.14, p=0.011).**
Conclusions: **Based on international experience in immunocompromised cancer patients with IA, primary therapy with voriconazole-containing regimen is associated with improved response and survival compared with non-voriconazole amphotericin B based regimen**

Keywords: Invasive aspergillosis, Immunocompromised, Voriconazole.

Citation: Hachem R., Batista M.V., Kanj S.S., El Zein S., Haddad S., Jiang Y., Mori N., Vanderson R., Chaftari A.M., Raad I. International multicenter experience in the treatment outcome of invasive aspergillosis in immunocompromised cancer patients. Mediterr J Hematol Infect Dis 2019, 11(1): e2019003, DOI: http://dx.doi.org/10.4084/MJHID.2019.003

Published: January 1, 2019 **Received: September 19, 2018** **Accepted: November 8, 2018**

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Introduction. Invasive aspergillosis (IA) is a life-threatening infection in immunocompromised patients. It is associated with high morbidity and mortality rates, especially in patients with hematologic malignancies (HM) and in patients undergoing hematopoietic stem cell transplantation (HSCT).[1-3] Several studies conducted in the United States and Europe demonstrated the superiority of voriconazole over amphotericin B based regimen in the primary treatment of IA in patient with HM or HSCT.[4-8] Voriconazole is now the preferred first line agent for primary therapy of IA especially in high risk patients with HM according to the practice guideline for the management of IA.[9] Hence, in this current study we wanted to determine if this finding is observed on a worldwide basis. Therefore in this international study, we compared the efficacy of a voriconazole containing regimen vs non-voriconazole containing regimen in immunocompromised HM patients with IA. Outside the US and Europe namely Asia and Latin America.

Methods. This is a retrospective, multicenter study that included all immunocompromised cancer patients diagnosed with proven or probable IA between February, 2012 and March, 2018 from 3 centers. We recruited 26 patients from the American University of Beirut, Lebanon, 20 patients from Hospital das Clinicas da Faculdade de Medicina, Universidade de São Paulo, Brazil, and 10 patients from St. Luke's International Hospital Tokyo, Japan.

The study was approved by the Institutional Review Board of all participating centers under a waiver of informed consent due to the retrospective nature of the study.

Definitions. Proven and probable IA were defined according to the European Organization for Research and Treatment of Cancer and Mycoses Study Group criteria.[10] In brief, proven IA was documented by Histopathologic or cytopathologic examination showing hyphae from needle aspiration or biopsy specimen with evidence of associated tissue damage; or positive culture result for a sample obtained by sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with infection. Probable IA was characterized by the presence of radiologic and microbiologic features supporting an IA diagnosis (the presence of nodules or cavities or a halo or air-crescent sign computerized tomography and documentation of *Aspergillus* spp. infection by direct microscopy or culture or Galactomannan (GM) positive from serum or Bronchoalveolar lavage (BAL)[11,12] in a patient with an absolute neutrophil count of <500 cells/mm^3, who had undergone prolonged steroid therapy, or who had used cytotoxic agents. Aspergillosis-attributable mortality was defined as: Aspergillosis was considered to have contributed to the death of a patient if the patient died with clinical, radiographic or microbiological evidence of aspergillosis and had not had a favorable response to the anti-mold therapy, regardless of the presence of other causes contributing to the death.

Primary antifungal therapy was defined as the first antifungal regimen (single agent or combination) that was administered for at least 7 consecutive days. Salvage therapy was defined as any other regimen administered after primary antifungal therapy.

Successful Response to Primary Therapy: was defined as improvement (partial or complete) resolution of the clinical signs and symptoms assessed by the treating physician and or radiological findings after receiving at least 7 days of same antifungal therapy.

Statistical analysis. Categorical variables were compared using the chi-square or Fisher's exact test, as appropriate. Continuous variables were compared using Wilcoxon rank-sum test. Logistic regression method was used to identify the independent predictors of response to primary therapy and mortality within 6 months of IA diagnosis, respectively. All tests were two-sided with a significance level of 0.05. The statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

Results. Data analysis included 56 patients with hematologic malignancy who were treated for IA between February, 2012 and March, 2018 from three countries: Brazil (n=20), Japan (n=10), and Lebanon (n=26). Thirty-five patients received primary anti-fungal therapies containing voriconazole (Vori group) and 21 received therapies without voriconazole (Non-Vori group) of whom 90% were treated with Amphotericin B based regimen. Demographic, clinical and laboratory data (**Table 1**) as well as treatment outcomes were compared between the two groups (**Table 2**).

Most baseline characteristics were comparable between the two groups including age, gender, underlying disease, steroid treatment prior to infection and neutropenia at infection onset (**Tables 1** and **2**). However, patients treated with voriconazole-containing regimens were more likely to have had a HSCT in the year preceding aspergillosis infection (34% vs 10%, p=0.04). All patients who received Computed Tomography (CT) scans (chest or sinus) in both groups had positive findings. Similarly, among patients with galactomannan tests, e.g. serum GM index was > 0.5 in all patients while BAL GM index was > 1. Overall, 11% of patents in the Vori-group and 10% in the non-Vori group had definite aspergillosis while all others were diagnosed as probable cases (p >.99). The infection type was also similar between the Vori- and

Table 1. Characteristics of patients with different primary therapies.

Characteristics	Non-Voriconazole containing regimen*	Voriconazole containing regimen**	*p*-value
	(n=21)	(n=35)	
	N (%)	N (%)	
Clinical center			0.12
Brazil	10 (48)	10 (29)	
Japan	5 (24)	5 (14)	
Lebanon	6 (29)	20 (57)	
Age (years), median (range)	55 (18-76)	54 (19-81)	0.85
Sex, male	18 (86)	24 (69)	0.15
Diagnosis of Asp infection			> .99
Definite	2 (10)	4 (11)	
Probable	19 (90)	31 (89)	
Type of Asp infection			0.86
Invasive pulmonary infection	17 (81)	30 (86)	
Disseminated infection	2 (10)	3 (9)	
Sinus infection	2 (10)	2 (6)	
Underlying disease			0.66
AML	7 (33)	14 (40)	
ALL	4 (19)	7 (20)	
CML	2 (10)	1 (3)	
Lymphoma	3 (14)	8 (23)	
Myeloma	5 (24)	4 (11)	
Other	0 (0)	1 (3)	
BMT in the year preceding IA	2 (10)	12 (34)	0.04
Type of BMT			> .99
Auto	0/2 (0)	4/12 (33)	
Allo	2/2 (100)	8/12 (67)	
GVHD	0/2 (0)	2/11 (18)	> .99
Neutropenia at onset of IA infection	14 (67)	15/34 (44)	0.10
Recovery from neutropenia	9/14 (64)	12/15 (80)	0.43
Positive findings of chest CT	21 (100)	33/33 (100)	
Positive findings of sinus CT	15/15 (100)	19/19 (100)	
Maximum GM value ≥ 0.5	20/20 (100)	35/35 (100)	
BAL	10/10 (100)	15/15 (100)	
Co-infection	15 (71)	24 (69)	0.82

* In the group treated with non-voriconazole containing regimen, 17 patients (81%) were treated with amphotericin B alone, 2 (10%) treated with amphotericin B in combination with echinocandin, and 2 (10%) treated with echinocandin alone.
** In the group treated with voriconazole containing regimen, 26 patients (74%) were treated with voriconazole alone, 8 (23%) treated with voriconazole in combination with amphotericin B, and 1 (3%) treated with voriconazole in combination with amphotericin B and echinocandin.

non-Vori groups respectively: 86% vs 81% for invasive pulmonary infections, 9% vs 10% for disseminated infections and 6% vs 10% for sinus infections.

The majority of patients in this study (63%) received antifungal prophylaxis prior to the diagnosis of IA including prophylactic fluconazole (45%) and mold-active azoles (16%) (**Table 2**). Regarding primary therapy, in the non-Vori group, 17 patients (81%) were treated with amphotericin B alone, 2 (10%) treated with amphotericin B in combination with echinocandin, and 2 (10%) treated with echinocandin alone. In the Vori group, 26 patients (74%) were treated with voriconazole alone, 8 (23%) treated with voriconazole in combination with amphotericin B, and 1 (3%) treated with voriconazole in combination with amphotericin B and echinocandin. Data on resistance against the antifungal regimens in primary therapy was unknown.

Table 2. Comparing the intervention and outcomes of patients receiving voriconazole vs mon-voriconazole regimen.

Intervention and outcomes	Non-Voriconazole containing regimen	Voriconazole containing regimen	*p*-value
	(n=21)	(n=35)	
	N (%)	N (%)	
Received cumulative steroids ≥ 600 mg	3 (14)	11 (31)	0.15
ICU stay during infection	6/20 (30)	9 (26)	0.73
Mechanical ventilation during infection	7/19 (37)	9/34 (26)	0.43
GMSF or GCSF	12 (57)	12 (34)	0.11
Prophylaxis	14 (67)	21 (60)	0.62
AmBisome B	2 (10)	0 (0)	0.14
Mold-active azoles*	4 (19)	5 (14)	0.72
Fluconazole	9 (43)	16 (46)	0.84
Echinocandin	0 (0)	1 (3)	>.99
Primary therapy			0.26
Empiric	7 (33)	7 (20)	
Diagnosis-driven	14 (67)	28 (80)	
Duration of primary therapy (days), median (IQR)	19 (10-47)	45 (24-92)	0.01
Duration of overall therapy for Asp infection (days), median (IQR)	80 (22-132)	58 (32-152)	0.87
Response to primary therapy	5/13 (38)	19/34 (85)	0.003
Final response at the end of overall therapy	12 (57)	27 (77)	0.12
Adverse events related to primary therapy	1 (5)	6 (17)	0.24
Hypokalemia	1	1	
Elevated liver function tests (LFTS)	0	4	
Hallucinations	0	1	
Death within 6 months of infection diagnosis	14/20 (70)	10/32 (31)	0.006
IA attributable death within 6 months of infection diagnosis	8/18 (44)	3/32 (9)	0.01

Abbreviations: IQR = Interquartile range.
* Mold-active azoles here included itraconazole, posaconazole and voriconazole

Patients in the Vori-group had a significantly longer duration of primary therapy compared to those in the non-Vori group (median: 45 vs 19 days, *p*=0.01). However, there was no significant difference in the duration of the overall therapy (primary and salvage) for their infections (median: 58 vs 80 days, p=0.87). Overall patients in Vori-group had better outcomes. They had higher rates of response to primary therapy compared to those in non-Vori group (85% vs 38%, *p*=0.003) (**Table 2**), had lower mortality rates within 6 months of diagnosis of IA (31% vs 70%, *p*=0.006) and lower aspergillosis-attributable mortality rate during the same time period (9% vs 44%, *p*=0.01). On the other hand, 5% of the patients in non-Vori group and 17% in Vori-group had adverse events related to their primary therapy (*p*=0.24). Lastly, we performed multivariate analysis to identify the independent predictors of response to primary therapy and all-cause mortality, respectively. Data showed that patients receiving mechanical ventilatory support were less likely to respond to primary therapy (odds ratio (OR)=0.11, *p*=0.024) and patients receiving a primary therapy containing voriconazole were more likely to have a successful response (OR=18.1, *p*=0.002) (**Table 3A**). Regarding mortality, we found that patients with leukemia (OR=4.9, *p*=0.038) or those receiving mechanical ventilation support (OR=5.3, *p*=0.026) were more likely to die within 6 months after IA diagnosis while those receiving primary therapy with voriconazole were less likely to die within this time period (OR=0.14, *p*=0.011) (**Table 3B**).

Discussion. In this retrospective international multicenter trial we compared the efficacy of voriconazole containing regimen to non voriconazole containing regimen for the treatment of invasive aspergillosis. Primary therapy with voriconazole containing regimen was a predictor of better outcomes in patients with IA. This finding derived from academic medical centers in the Middle East, Far East and Brazil confirms what has been shown in the studies conducted in US and Europe[4-8] that voriconazole is a

Table 3. Predictors of outcomes by multivariate logistic regression analysis.

A) Predictors of response to primary therapy.

Predictors	**Odds Ratio**	**95% CI**	***p*-value**
Mechanical ventilation	0.11	0.02 to 0.75	0.024
Primary therapy			
Voriconazole containing regimen	18.1	2.9 to 114.7	0.002
Non-voriconazole contaning regimen	Reference		

B) Predictors of mortality within 6 months after infection diagnosis.

Predictors	**Odds Ratio**	**95% CI**	***p*-value**
Type of cancer			0.038
Leukemia	4.9	1.1 to 22.2	
Other hematologic malignancy	Reference		
Mechanical ventilation	5.3	1.2 to 23.3	0.026
Primary therapy			
Voriconazole containing regimen	0.14	0.03 to 0.64	0.011
Non-voriconazole containing regimen	Reference		

suitable treatment option even in high risk patients with hematologic malignancy. The high risk patients include those with leukemia patients and induction chemotherapy as well as HCT recipients including patients who developed GVHD as transplant complication.

These findings are also in accordance with the international guidelines that recommend Voriconazole as primary treatment for invasive aspergillosis.[13-15]

Our study showed higher response rate to primary therapy for IA in patients on initial therapy with voriconazole. In addition voriconazole was an independent predictor of successful response, by multivariate analysis (OR=18.1, p=0.002). Similar findings were reported by Herbrecht *et al*, 2002, in a randomized, unblinded trial, where successful treatment outcomes at 12 weeks were observed in 52.8% of the patients receiving voriconazole (144 patients) compared to 31.6 % of those receiving amphotericin B (133 patients) . Furthermore, in the setting where the antifungal were giving empirically, and despite that, voriconazole group had favorable outcome compared to the non-vori group. It is to note that 90% of the patients in the non vori group were treated with Amphotericin B based regimen.

In a randomized, multicenter trial Walsh *et al* compared voriconazole, versus liposomal amphotericin B as empirical antifungal therapy in a total of 837 patients. Voriconazole was shown to be reasonable alternative to amphotericin B in patients with neutropenia and persistent fever, which is in accordance with our results.[16] Furthermore, in a study by Ramos et al from MD Anderson Cancer Center showed that the anti- mold active azole agents such as voriconazole in their uses as primary or salvage therapy were associated with improves overall clinical outcome as well as overall mortality.[6]

Invasive aspergillosis is a common cause of infection-related mortality in hematologic and hematopoietic cell transplant (HCT) recipients. The overall mortality, one year after diagnosis, ranges from 70% to 93%.[7,17,18] In our study, the treatment of IA with an antifungal regimen containing voriconazole was associated with significantly lower overall mortality rate and aspergillosis-attributable mortality rate within 6 months of IA diagnosis despite the relatively small number of patients included in this current study. Similar results were reported by Upton *et al*, in a retrospective clinical chart review of 405 cases of proven and probable IA diagnosed in HCT recipients. Their study showed that treatment with voriconazole was independently associated with reduce risk of IA-related death.[5] Moreover, another study by Nivoix et al showed that voriconazole was associated with increase probability of survival compared with all other therapy.

Conclusions. Our international, multicenter retrospective study presents a real world experience from the Far East, Middle East and South America (Brazil) demonstrating of the efficacy of voriconazole-containing regimen as a primary treatment for invasive aspergillosis in immunocompromised cancer patients. Voriconazole was associated with a better outcome and lower mortality rate compared to other antifungal therapies in this subgroup of patients.

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