Improving outcomes of acute invasive *Aspergillus rhinosinusitis* in patients with hematologic malignancies or aplastic anemia: the role of voriconazole

We evaluated the outcomes of patients with hematologic diseases diagnosed with acute invasive *Aspergillus rhinosinusitis* comparing a group of patients diagnosed after voriconazole was available at our center with a historical group of patients diagnosed before voriconazole was available. Voriconazole use was associated with a decrease in mortality and earlier clinical response.

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Acute invasive *Aspergillus rhinosinusitis* (AIAR) is a life-threatening fungal infection which appears almost exclusively in leukemia or aplastic anemia.[1-4] Voriconazole is a drug of choice in the treatment of invasive aspergillosis. However, clinical experiences mainly concerned pulmonary localization of this infection and included only a few cases of AIAR.[5,6] Before May 2003, deoxycholate amphotericin B (d-AmB) and liposomal amphotericin B (lip-AmB) were the drugs of choice in AIAR therapy at our center. Voriconazole became available in May 2003 and was considered the first line therapy in microbiologically documented AIAR. In cases of possible fungal rhinosinusitis without microbiologic isolation of the pathogen, an AmB formulation was used as first line therapy. In the event of a subsequent microbiologic diagnosis of aspergillosis, AmB was replaced with intravenous voriconazole, unless a clear improvement in the infection had already been observed with AmB therapy.

The aim of our study was to analyze the outcomes of 22 patients with hematologic diseases diagnosed with AIAR after voriconazole was available at our center (Voriconazole period group) compared with a historical group of 17 patients with AIAR who received AmB before voriconazole was available (Control group). The two groups were compared in an intention to treat analysis regardless of the initial antifungal drug employed. Only patients with AIAR defined as proven or probable according to standardized composite criteria were included.[7] Characteristics of the two groups are shown in Table 1.

The 17 *control* patients received primary therapy with d-AmB (12 cases) and lip-AmB (5 cases). Four patients who received AmB-d switched to lip-AmB due to renal toxicity.

Patients included in the *voriconazole period group* had received the triazole since the first day of treatment in 12 cases. The other 10 patients received primary therapy with d-AmB (4 cases) or lip-AmB (6 cases). In 7 of them, treatment was replaced with voriconazole, and the other 3 patients did not receive voriconazole due to early death in one case and early response to primary AmB therapy in two cases.

At 3 months from the diagnosis of infection, 6 patients (27%) of the *voriconazole period group* had died at a median of 20.5 days, and 9 patients (53%) of the *control group* died at a median of 25 days. Overall survival at 3 months after the day of diagnosis of AIAR was highest among the patients of the *voriconazole period group* although this was not statistically significant (hazard ratio [HR] 0.46; 95% CI, 0.16–1.3; p=0.15). Univariate Cox regression model to identify risk of death showed that only the variable *focal sinonasal infection* compared to *disseminated disease* was significantly associated with longer survival. At multivariable analysis, survival was significantly associated to the variables *voriconazole period group* (HR 0.16; 95% CI 0.04 – 0.57; p=0.005) and *focal sinonasal infection* (HR 0.12; 95% CI 0.03–0.46; p=0.002).

Time to clinical improvement within two weeks of the start of antifungal therapy was also compared. The day of

Table 1. Demographic and clinical characteristics of patients with AIAR receiving antifungal therapy between May 2003 and December 2006 (voriconazole period group) or between January 1997 and May 2003 (control group).

Variable	*Voriconazole period group (n=22)*	*Control group (n=17)*	*p*
Age, median years (range)	37 (7-69)	36 (16-75)	0.8
Female sex	5 (22.7)	3 (18)	1.0
Type of previous treatment for the underlying disease			
Allogeneic HSCT	8 (36)	3 (18)	0.2
Autologous HSCT	0	1 (6)	
Cytotoxic chemotherapy	14 (64)	11 (65)	
Immunosuppressive therapy	0	2 (12)	
Hematologic disease			
Acute myeloid leukemia	11 (50)	9 (53)	0.8
Chronic myeloid leukemia in blast crisis	2 (9)	2 (12)	
Acute lymphocitic leukemia	5 (23)	3 (18)	
Severe aplastic anemia	1 (4)	2 (12)	
Lymphoma/chronic lymphocitic leukemia	3 (14)	1 (6)	
Phase of the hematologic disease			
Disease at onset or in first complete remission	11 (50)	7 (41)	0.7
Disease relapsed or resistant to treatment	11 (50)	10 (59)	
Duration of previous corticosteroid treatment			
>10 - <20 days	6 (27.3)	4 (23)	1.0
≥20 days	16 (72.7)	13 (77)	
Stage of AIAR			
Focal	9 (41)	12 (71)	0.1
Disseminated	13 (59)	5 (29)	
Pansinusitis	17 (77)	12 (71)	0.7
Clinical/radiological signs and symptoms of AIAR			
Periorbital/facial swelling	20 (91)	17 (100)	0.5
Erosion of sinus walls at CT scan	9(41)	10 (59)	0.3
Nasal discharge	19 (86)	16 (94)	0.6
Nose ulceration or eschar of nasal mucosa	5 (23)	8 (47)	0.2
Pain	20 (91)	17 (100)	0.5
Certainty of diagnosis of fungal infection			
Proven	4 (18)	6 (35)	0.2
Probable	18 (82)	11 (65)	
Aspergillus species			
A. fumigatus	3 (14)	8 (47)	0.1
A. flavus	14 (64)	6 (35)	
A. terreus	3 (14)	3 (18)	
A. niger	1 (4)	0	
A. versicolor	1 (4)	0	
PMN < 500/mm^3, n. of patients (%)	12 (54)	14 (82)	0.1
PMN <100/mm^3, n. of patients (%)	10 (45)	10 (59)	0.5
Duration of neutropenia (PMN≤500) after AIAR diagnosis, mean days (range)	7 (0-30)	10 (0-27)	0.3

Data are n. (%) of patients, unless otherwise indicated. AIAR: acute invasive Aspergillus rhinosinusitis; CT: computed tomography.

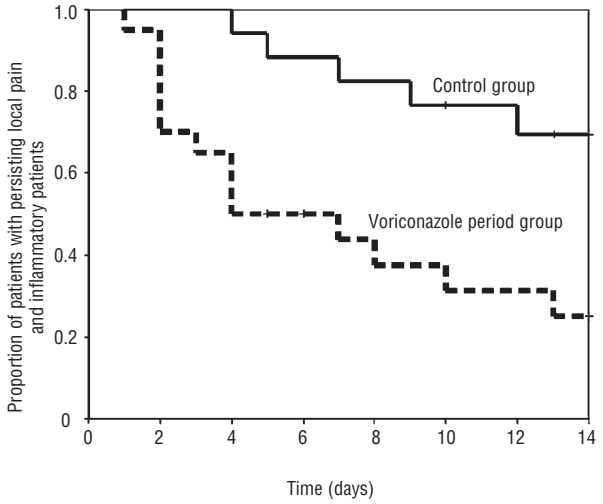

Figure 1. Kaplan-Meier curve. Time to clinical improvement comparing patients with acute invasive A*spergillus rhinosinusitis* observed after May 2003 (*voriconazole period group*) or before May 2003 (*control group*). *p*=0.009, calculated from the likelihood ratio test using Cox regression.

clinical improvement was considered as the first day of a clinically significant reduction of both pain and local inflammatory signs. Clinical improvement had to be persistent in the following days and independent of analgesic treatments. Overall, time to clinical improvement was significantly shorter in patients of the *voriconazole period group* (HR, 3.97; 95% CI 1.41–11.16; *p*=0.009) (Figure 1).

This study evaluated the clinical characteristics and response to therapy of the largest cohort of patients with hematologic diseases and AIAR reported to our knowledge. In agreement with the overall improved outcome in invasive aspergillosis reported in several experiences,[8,9] our study shows a decrease in mortality in patients with a diagnosis of AIAR in recent years. Although multiple chances in clinical practice could account for the differences in outcome, the inclusion of voriconazole in the antifungal strategy was independently associated with improved survival. The efficacy of this drug was also confirmed by the observed early clinical improvement of the sinonasal infection. The reasons for the dramatic activity of voriconazole observed in patients with AIAR are difficult to assess. Different antimicrobial activity of the drugs could be considered. The pharmacokinetic differences in the antifungals could be a further justification of the difference in efficacy. More than all other anti-Aspergillus drugs, voriconazole exhibits significant transport across the blood-brain and blood-eye barriers.[10] Therefore, we can hypothesize that the diffusion of the drug from the CNS and eyes into the contiguous periorbital and sinonasal tissues could have an important role.

Our study confirms the primary role of voriconazole in the treatment of sinonasal localizations of invasive aspergillosis.

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