Voriconazole for secondary prophylaxis of invasive fungal infections in allogeneic stem cell transplant recipients: results of the VOSIFI study

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ABSTRACT

Background
Recurrence of prior invasive fungal infection (relapse rate of 30-50%) limits the success of stem cell transplantation. Secondary prophylaxis could reduce disease burden and improve survival.

Design and Methods
A prospective, open-label, multicenter trial was conducted evaluating voriconazole (4 mg/kg/12 h intravenously or 200 mg/12 h orally) as secondary antifungal prophylaxis in allogeneic stem cell transplant recipients with previous proven or probable invasive fungal infection. Voriconazole was started 48 h or more after completion of conditioning chemotherapy and was planned to be continued for 100-150 days. Patients were followed for 12 months. The primary end-point of the study was the incidence of proven or probable invasive fungal infection.

Results
Forty-five patients were enrolled, 41 of whom had acute leukemia. Previous invasive fungal infections were proven or probable aspergillosis (n=31), proven candidiasis (n=5) and other proven or probable infections (n=6); prior infection could not be confirmed in three patients. The median duration of voriconazole prophylaxis was 94 days. Eleven patients (24%) died within 12 months of transplantation, but only one due to systemic fungal disease. Three invasive fungal infections occurred post-transplant: two relapses (one candidemia and one fatal scedosporiosis) and one new zygomycosis in a patient with previous aspergillosis. The 1-year cumulative incidence of invasive fungal disease was 6.7±3.6%. Two patients were withdrawn from the study due to treatment-related adverse events (i.e. liver toxicity).

Conclusions
Voriconazole appears to be safe and effective for secondary prophylaxis of systemic fungal infection after allogeneic stem cell transplantation. The observed incidence of 6.7% (with one attributable death) is considerably lower than the relapse rate reported in historical controls, thus suggesting that voriconazole is a promising prophylactic agent in this population. (*ClinicalTrials.gov identifier: NCT00143312*).

Key words: voriconazole, prophylaxis, fungal, allogeneic, transplant.

Citation: Cordonnier C, Rovira M, Maertens J, Olavarria E, Faucher C, Bilger K, Pigneux A, Cornely OA, Ullmann AJ, Bofarull RM, de la Cámara R, Weisser M, Liakopoulou E, Abecasis M, Heussel CP, Pineau M, Ljungman P, and Einsele H on behalf of the Voriconazole for Secondary Prophylaxis of Invasive Fungal Infections in Patients With Allogeneic Stem Cell Transplants (VOSIFI) study group and the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Voriconazole for secondary prophylaxis of invasive fungal infections in allogeneic stem cell transplant recipients: results of the VOSIFI study. Haematologica 2010;95(10):1762-1768. doi:10.3324/haematol.2009.020073

Acknowledgments: the authors thank Ian McKenzie and Paul Miller for their assistance with the statistical analyses. The authors also thank Myriam Labopin, Virginie Chesnel and Benedicte Samey of the Paris EBMT office for providing the data on the patients' conditioning regimens, graft-versus-host disease, and cumulative incidence curves of invasive fungal infections.

Funding: this study was sponsored by Pfizer Inc. Editorial support was provided by D. Wolf, MSc, of PAREXEL and was funded by Pfizer Inc.

Manuscript received on November 25, 2009. Revised version arrived on May 7, 2010. Manuscript accepted on May 17, 2010.

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A complete list of the members of the VOSIFI Study Group is provided in the Appendix.

Introduction

Patients with hematologic malignancies are at high risk of invasive fungal infections, predominantly aspergillosis and candidiasis, due to prolonged chemotherapy-induced neutropenia. The risk period following an allogeneic hematopoietic stem cell transplant (HSCT) even extends beyond the neutropenic phase, particularly in cases of graft-*versus*-host disease.[1-3] Despite appropriate treatment and an initially favorable outcome, the risk of recurrence of an invasive fungal infection following HSCT is high (30-50%).[4] Documented previous invasive fungal infections may be a major obstacle to the success of HSCT and may affect patients' survival[5-7] to such an extent that transplant centers have been unwilling to carry out HSCT in patients with a history of an invasive fungal infection.[5] Although no randomized study has investigated this issue, effective secondary prophylaxis for invasive fungal infections may significantly improve outcomes, including reduced transplant-related mortality.[5-7] Consequently, most patients with a previous invasive fungal infection who are referred for HSCT now receive some form of secondary antifungal prophylaxis,[7] although the optimal agent and the regimen and duration of such prophylaxis are not well defined.[8]

Fluconazole has been the standard agent for prophylaxis before and after HSCT. However, its inactivity against molds as well as increasing resistance among *Candida spp.* are limiting its use in this setting.[9] Second-generation triazole antifungals, on the other hand, have been shown to be effective for prophylaxis after engraftment.[10] Voriconazole is a broad-spectrum second-generation triazole, available in both oral and intravenous formulations, with potent activity against a wide variety of clinically significant molds and yeasts.[11,12] In a large, prospective, randomized trial, voriconazole was shown to provide a significant survival benefit, as well as superior efficacy and safety, over amphotericin B as first-line treatment of proven or probable invasive aspergillosis.[13] Furthermore, exploratory studies have shown that voriconazole is effective as secondary prophylaxis of invasive fungal infections in leukemia patients and HSCT recipients.[4,14] To further evaluate voriconazole for secondary prophylaxis of previous proven or probable invasive fungal infections, a 12-month, open-label, non-comparative study was conducted in patients undergoing allogeneic HSCT.

Design and Methods

This was a phase III, prospective, non-comparative, open-label, international multicenter trial designed and supported by the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT). The study was conducted at 17 centers in eight countries (Belgium, France, Germany, Portugal, Spain, Sweden, Switzerland and the United Kingdom) and was carried out in accordance with the Declaration of Helsinki, the International Conference on Harmonisation's Good Clinical Practices Guidelines and US Food and Drug Administration regulations. Full ethical approval was obtained at each participating center, and all patients provided prior written informed consent. The trial was registered at clinicaltrials.gov (NCT00143312).

Patients

The study population comprised men and women, aged 18 years or older, with proven or probable invasive fungal infection in the previous 12 months, who were undergoing allogeneic HSCT for any hematologic disease and with any conditioning regimen. Previous invasive fungal infection was assessed according to the 2002 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 criteria,[15] which were modified to include patients with a "halo" sign on chest imaging plus appropriate host and minor clinical criteria, but no microbiology, into the category of those with a probable invasive fungal infection. These modifications were in accordance with diagnostic criteria utilized in previous clinical trials in invasive aspergillosis[13,16] and also served to enhance the recruitment of patients. Patients were excluded from the study if they had: (i) severe disease other than their underlying condition; (ii) a history of zygomycosis; (iii) a positive serum galactomannan antigen test (ratio ≥1.0), evidence of active fungal disease (defined as the persistence of clinical symptoms, i.e., fever, or clinical respiratory symptoms or cutaneous lesions) related to the previous systemic fungal disease), or persistent candiduria just before HSCT; (iv) previous failure of voriconazole in the treatment of invasive fungal infection; (v) liver tests five times the upper limit of normal; or (vi) a creatinine clearance below 50 mL/min.

Study treatment

All patients received prophylactic voriconazole, either intravenously with a loading dose of 6 mg/kg every 12 h (for two doses) followed by maintenance doses of 4 mg/kg every 12 h, or orally with a loading dose of 400 mg every 12 h (for two doses) followed by maintenance doses of 200 mg every 12 h. Patients could be started on either intravenous or oral voriconazole and switched between the formulations after completion of the loading dose at the discretion of the investigator. The first loading dose was given at least 48 h after completion of conditioning chemotherapy and in the time period of 3 days prior to HSCT and the day of HSCT. Voriconazole prophylaxis was to be maintained for at least 100 days after transplantation and could be extended by up to 50 days if at day 100 the patient was receiving prednisone (≥0.2 mg/kg), muromonab (OKT3) or mycophenolate mofetil, had been receiving antithymocyte globulin within the 4 weeks prior to day 100, or had been neutropenic (polymorphonuclear neutrophil leukocytes <500/mm^3) within the 10 days prior to day 100.

Analysis

The efficacy and safety of voriconazole were assessed at screening and baseline and at regular intervals throughout the study, including during follow-up visits 6 months and 12 months after transplantation. In all patients the diagnosis of proven or probable invasive fungal infection was verified by a Data Review Committee; verification of a probable invasive fungal infection was partially based on digital radiological images (including computed tomography scans of the chest). The intent-to-treat population consisted of all patients who had received at least one dose of study medication and underwent at least one post-enrollment efficacy assessment. Efficacy was also evaluated in a modified intent-to-treat population which comprised those patients in the intent-to-treat population whose previous diagnosis of proven or probable invasive fungal infection was confirmed by the Data Review Committee. All patients who received at least one dose of study medication were included in the safety population.

The primary efficacy end-point was the proportion of patients who developed a proven or probable invasive fungal infection

between the start of prophylaxis and the 12-month follow-up visit. Secondary efficacy end-points were the proportion of patients developing a proven or probable invasive fungal infection (recurrent or new) from the start of voriconazole prophylaxis until the end of prophylaxis or the 6-month follow-up visit; the time to occurrence of proven or probable invasive fungal infection from the start of voriconazole prophylaxis; and the proportion of patients who survived free of proven or probable invasive fungal infection at 12 months. The 1-year cumulative incidence of invasive fungal infection was estimated in a competing risks setting, since death without invasive fungal infection was a competing event.[17] All patients were censored at the follow-up visit. The safety and tolerability of voriconazole prophylaxis in the safety population were assessed at each study visit; the *Medical Dictionary for Regulatory Activities* (Version 11.0) was used to code adverse events.

At the time the study was designed, the only large, retrospective study of previous invasive fungal infections in allogeneic HSCT recipients reported a 33% incidence of invasive fungal infections after transplantation.[5] Results of a small pilot study[4] suggested that secondary prophylaxis with voriconazole could significantly reduce this incidence. In order to estimate the required sample size, three different hypotheses were evaluated, assuming rates of invasive fungal infections of 10%, 20% and 30% after transplantation. With a sample size of 56 patients, the 95% confidence interval limits were calculated as ±7.9%, ±10.5% and ±12.0% for assumed invasive fungal infections rates of 10%, 20% and 30%, respectively. Presuming that approximately 10% of patients would not be evaluable, the protocol initially called for 63 to 70 patients to be recruited into the study. Because a sufficient number of participants could not be enrolled within the planned timelines, the target sample size was reduced to 45 patients.

Results

Patients' characteristics

Forty-six patients were screened for inclusion, 45 of whom were assigned to treatment between February 2005 and March 2007. Of these 45, assessment of invasive fungal infection at the 12-month follow-up visit was not available for 16 patients, including 11 who died; a summary of the patients' disposition is provided in Figure 1. The median follow-up of participants was 360 days (range, 5-469 days) and the median duration of voriconazole prophylaxis was 94 days (range, 5-180 days). Most of the patients enrolled in the study had acute myeloid leukemia (31; 69%). The patients' underlying conditions are listed in detail in Table 1. Hematologic disease was in first complete remission in 24 (53%) patients at the time of HSCT.

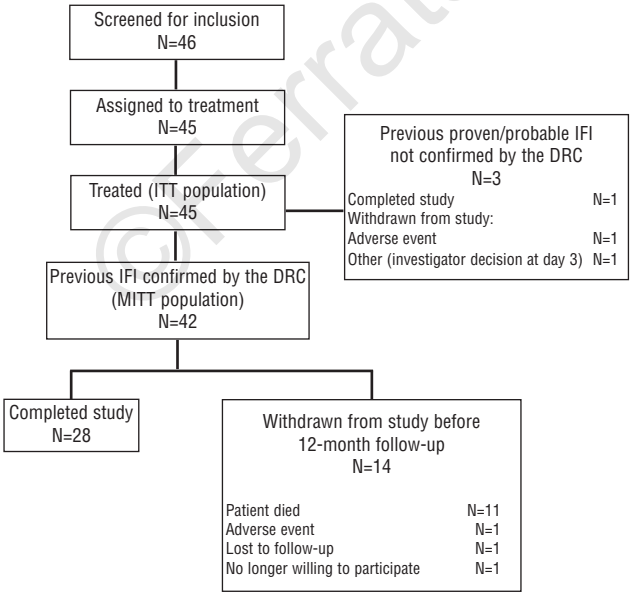

Figure 1. Patient disposition. ITT, intent-to-treat; IFI, invasive fungal infection; DRC, data review committee; MITT, modified ITT.

The previous invasive fungal infections were aspergillosis in 31 cases (69%; 6 proven, 25 probable), proven candidiasis in five cases (11%), other invasive fungal infections in six (13%; 3 proven and 3 probable). In three cases (7%) previous invasive fungal infections could not be confirmed by the Data Review Committee due to missing information or insufficient criteria to validate the diagnosis. Had the unmodified EORTC-MSG definitions for probable invasive fungal infection been applied, five patients in the group with probable infections would have been classified as possible cases on the basis of a halo sign, associated with minor criteria. Thirty-five patients had received voriconazole as therapy for their previous invasive fungal infection. The median time between the end of the most recent previous invasive fungal infection and the date of HSCT was 59 days (range, 3-311 days). Only one patient continuously received antifungal treatment over the time period between the previous invasive fungal infection and HSCT. For those who had stopped taking antifungal agents before inclusion, the mean number of days without antifungal treatment prior to transplantation was 39 (range, 2-278 days). Post-hoc analysis of the last available computed tomography results from the period of 30 days prior to start of study treatment indicated that in patients with previous aspergillosis (n=31) chest computed tomography scans were normal in 14 cases (i.e., showed no pulmonary/lymph node lesions evocative of active pulmonary aspergillosis), showed residual lesions in five cases, and were not recorded in 12 cases. In patients with other previous invasive fungal infections due to filamentous fungi, chest computed tomography was normal in one case and not available for two patients. Of the five patients with previous *Candida* infection, one had normal chest and abdominal computed tomography scans, one had residual hypodense hepatic lesions on abdominal scans, and data were not available for three patients. For the three remaining patients, imaging data were only available for the patient with previous *Scedosporium* infection, who had an abnormal chest computed tomography scan.

The most common source of stem cells for HSCT was the peripheral blood (n=38; 84%), followed by bone marrow (n=6; 13%) and cord blood (n=1; 2%). Twenty-four patients (53%) were transplanted from a family donor, including HLA-identical siblings (18 patients), HLA-mismatched relatives (5 patients) and an identical twin (1 patient); 21 patients (47%) were transplanted from an unrelated donor. The conditioning regimen was myeloablative in 27 patients (60%), including 14 patients who received total body irradiation, and non-myeloablative in 18 (40%), including seven given total body irradiation. Among the 45 patients, 29 started with an oral formulation of voriconazole, and 16 started on the intravenous form. Twenty-six patients (58%) developed at least one

episode of graft-*versus*-host disease during the 12-month follow-up period: acute graft-*versus*-host disease (grade I, n=6; grade II, n=7; grade III, n=5) and/or chronic limited (n=5) or extensive (n=8) graft-*versus*-host disease.

The efficacy of voriconazole

Of the 45 patients enrolled in the study, 42 were included in the modified intent-to-treat population. The crude survival rate at 12 months was 75.6% (34/45 patients), assuming that all patients lost to the 12-months' follow-up (n=5) were still alive at that time.

The 1-year cumulative incidence of invasive fungal infections with death as a competing risk in the modified intent-to-treat population was 6.7±3.6% (Figure 2).Three patients in the modified intent-to-treat population (n=42) developed an invasive fungal infection during the course of the study, all occurring within 6 months after transplantation. One of the infections was a proven recurrence of a previous proven *Candida albicans* candidemia, one was a proven recurrence of a previous probable *Scedosporium prolificans* infection, which ultimately led to death, and the third case was a new probable *Mucor spp.* zygomycosis in a patient with previous probable aspergillosis. These infections occurred at days 3, 16, and 66 post-transplant, respectively. The patient who experienced a recurrent episode of candidemia (following a myeloablative transplant) received an intravenous loading dose of voriconazole during the first 24 h and was then switched to the oral formulation. Minimum inhibitory concentrations of azoles for the causative *C. albicans* strain were not available. The patient who had a relapse of scedosporiosis had undergone myeloablative HSCT and did not develop any graft-*versus*-host disease. This patient transiently had blood cultures positive for *Scedosporium spp*. on day 16 post-transplant, prompting addition of terbinafine to the voriconazole. The patient's leukemia relapsed on day 75 post-transplant, and she was retreated with chemotherapy. She died with a proven recurrence of scedosporiosis (blood, lung and skin) during the neutropenic phase following salvage chemotherapy. Of note, the causative *Scedosporium* strain was found to be resistant to amphotericin B, itraconazole, voriconazole, posaconazole, terbinafine, and caspofungin, both during the pre- and post-transplant episode of the scedosporiosis infection; the combination of voriconazole plus terbinafine did not appear to have either a synergistic or an antagonistic effect. The patient who developed zygomycosis had received a reduced-intensity conditioning regimen and developed acute graft-*versus*-host disease followed by extensive chronic graft-*versus*-host disease.

The safety of voriconazole

The safety and tolerability of voriconazole were evaluated in all enrolled patients (n=45). Eleven patients (24%) died during the study (median, 136 days after the start of prophylaxis). Causes of death were relapse of leukemia (four patients), respiratory failure or lung disease of unknown origin (three patients; an autopsy was carried out in one of them. This patient died on day 203 after stopping voriconazole on day 101 and the autopsy showed no evidence of invasive fungal infections, and a diffuse, bilateral, congestive pulmonary edema, graft-*versus*-host disease (two patients), scedosporiosis in the setting of leukemia relapse (one patient), and sepsis (one patient; he died on day 93 after stopping voriconazole on day 38: the autopsy showed multi-visceral organ failure without evidence of an invasive fungal infection, but the causative pathogen could not be identified). Overall 445 adverse events were reported, the most common of which are shown in Table 2. Most

Table 1. Patients' demographic and baseline characteristics.

Demographics	Patients (N=45)
Male, n. (%)	28 (62)
Mean age (range), years	48 (22-72)
Mean body mass index (range)	24.6 (18.1-35.5)
Primary diagnosis, n.	
Acute myeloid leukemia	31
Acute lymphoblastic leukemia	7
Acute leukemia, unspecified	3
Chronic myeloid leukemia transformation	2
Chronic lymphocytic leukemia	1
Mycosis fungoides	1
Previous invasive fungal infection, n.	
Probable aspergillosis	25
Proven aspergillosis	6
Proven candidiasis	5
Other proven fungal infection	3
Filamentous infection of lung (biopsy proven, culture negative)	1
Rhodotorula mucilaginosa fungemia	1
Filamentous infection of ethmoidal sinus (biopsy proven, culture negative)	1
Other probable fungal infection	3
Pulmonary *Scedosporium* infection	1
Pulmonary infection (imaging documented)	1
Pulmonary filamentous infection	1
Previous IFI not validated by the DRC due to insufficient data or insufficient criteria*	3

*One of these three patients was withdrawn from the study by the investigator on day 3. DRC: data review committee; IFI: invasive fungal infection.

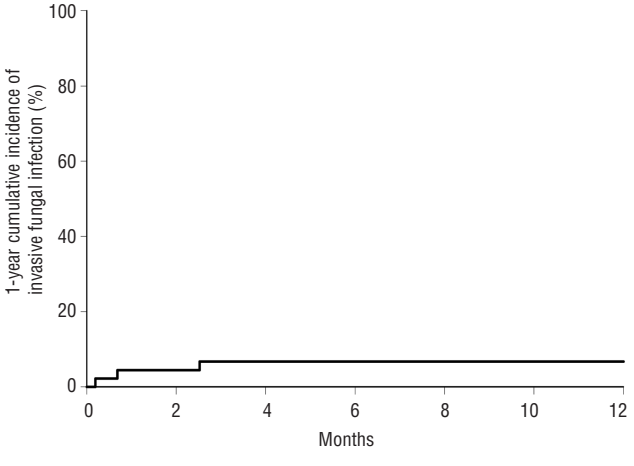

Figure 2. Cumulative incidence of invasive fungal infection (%) over the course of 12 months post-transplantation, with death as a competing risk.

of the adverse events were described as being of mild or moderate intensity. Adverse events were reported as severe in 24 (53%) patients, and serious in 23 (51%). Two patients discontinued the study as a result of adverse events, in both cases hepatotoxicity. The majority of the adverse events were considered to be unrelated to voriconazole. Treatment-related adverse events (59 in total) were reported for 26 (58%) patients, the most common being hepatotoxicity (four patients), headache (three patients), and visual hallucinations (three patients); most of these were mild or moderate in intensity.

Table 2. Most common all-causality adverse events (occurring in more than five patients).

Preferred term	N. of patients	Percentage of patients
Mucosal inflammation	17	37.8
Diarrhea	16	35.6
Vomiting	16	35.6
Pyrexia	15	33.3
Headache	14	31.1
Graft-*versus*-host disease	13	28.9
Hypertension	9	20.0
Febrile neutropenia	8	17.8
Thrombocytopenia	8	17.8
Abdominal pain	8	17.8
Anemia	7	15.6
Insomnia	7	15.6
Abdominal pain, upper	6	13.3
Nausea	6	13.3
Rash	6	13.3

Discussion

Based on the results of this open-label non-comparative study, which was the first prospective clinical trial of antifungal prophylaxis in allogeneic HSCT recipients with prior invasive fungal infections, voriconazole appears to be safe and effective in protecting such patients from recurring or new systemic fungal disease.

Fifteen years ago, many hematology centers were reluctant to administer high-dose consolidation chemotherapy or perform HSCT in patients with a history of invasive aspergillosis.[18] Although such patients are still considered to be at a high risk of recurrent invasive fungal infection, several retrospective studies have shown that the benefit of HSCT may outweigh the risk of fungal relapse.[5,6,8,19,20] In two large studies of allogeneic HSCT recipients with previous aspergillosis, the risk of fungal relapse was estimated to be 33% and 29%, with similar ranges for previous candidiasis.[19,21] From the major studies of patients with previous aspergillosis, it appears that resolution of fungal infiltrates before transplantation, reduced intensity of the conditioning regimen, absence of total body irradiation, and administration of secondary prophylaxis are the main factors that protect against recurrent invasive fungal infection.[5-7] Therefore, although no randomized study has directly evaluated secondary antifungal prophylaxis in such high-risk patients, most transplant centers recognize its potential to decrease the risk of invasive fungal infections after HSCT. However, until now no clear evidence has been available to define optimal therapy for this indication. Due to this lack of a standard agent for secondary invasive fungal infections prophylaxis, as well as of previous prospective studies, our trial had to be designed as an open-label study. Implementation of a comparative trial is further complicated by the relative scarcity of target patients: Fukuda *et al.*[6] were only able to identify 45 individuals with previous invasive aspergillosis among a retrospective consecutive cohort of 2319 HSCT recipients between 1992 and 2001 at a single institution.

The positive results of this trial in 45 patients support those from previous retrospective studies in smaller numbers of patients. Several centers have reported their experience with voriconazole for secondary prophylaxis, with encouraging results.[4,22,23] In a retrospective EBMT study of 129 allogeneic HSCT recipients with a history of proven or probable invasive aspergillosis, the use of voriconazole monotherapy as initial secondary prophylaxis in 31 of those patients showed a trend toward reducing the risk of disease progression.[7] Caspofungin was also evaluated for this indication (n=18 patients) and was found to reduce relapse or progression of invasive fungal infections.[24] Other research suggests that secondary prophylaxis with liposomal amphotericin B may be beneficial for pediatric HSCT recipients, but the fungal relapse rate may be as high as 32% among patients with previous proven or probable infections.[19] Although primary prophylaxis with posaconazole has been shown to prevent invasive fungal infections in allogeneic HSCT recipients with graft-*versus*-host disease[10] and in patients with acute myeloid leukemia in the remission induction phase,[25] reports of secondary prophylaxis with this agent are limited. Unfortunately, many published retrospective studies of secondary antifungal prophylaxis mixed allogeneic HSCT recipients and other populations at risk (e.g., patients undergoing chemotherapy for acute leukemia) and often included many cases of possible invasive fungal infection, without having the level of diagnosis confirmed by a Data Review Committee. Some studies were also performed in patients with an active invasive fungal infection at the time of HSCT,[22] thus ruling out a direct comparison with a true secondary prophylaxis approach. Of note, the retrospective design of these previous reports precludes any objective assessment of the protective effect of the evaluated drugs.

Although opportunistic molds and yeast-like fungi such as zygomycetes and *Fusarium spp*. are increasingly important in HSCT recipients,[2,26] *Candida spp*. and *Aspergillus spp*. remain the most common causative agents of invasive fungal infections after HSCT. In this respect it is important to point out that we did not observe any case of proven or probable aspergillosis in our cohort of patients over the 12-month follow-up period. Among the new broad-spectrum azoles, voriconazole has demonstrated favorable results in candidemia,[27] and is a standard for the first-line treatment of acute invasive aspergillosis.[13,28-31] Extensive clinical experience has also shown that voriconazole is effective against *Scedosporium spp*. and *Fusarium spp*.;[32,33] furthermore, it possesses potent *in vitro* activity against a wide range of other molds.[12] Voriconazole is available in both oral and intravenous formulations, which allows continuation of therapy in patients who have difficulty in swallowing (due to

severe mucositis, for example) and can, therefore, cover the entire risk period of invasive fungal infections in HSCT patients, unlike other azoles that are only available as oral formulations. The availability of oral voriconazole makes the agent convenient for outpatient use, for example, in patients recovering from neutropenia.

Our study has both strengths and limitations that deserve discussion. Its main limitation is the open-label design; however, since it was the first prospective study in secondary antifungal prophylaxis and given the scarcity of suitable patients, no other design was deemed pertinent. The inclusion of one case of prior *S. prolificans* infection may be debated, as this fungus exhibits reduced susceptibility to voriconazole *in vitro*. However, the affected patient responded clinically to voriconazole before transplantation and did not, therefore, fulfill exclusion criteria; furthermore, a favorable outcome to vorinoconazole treatment in *S. prolificans* scedosporiosis, although unusual, has been reported.[32] The main strengths of our study are its prospective design and the extensive 1-year post-transplant follow-up, as well as the high level of certainty of the diagnosis of invasive fungal infections. Of note, had the EORTC criteria not been modified to accept a halo sign as a diagnosis of probable aspergillosis, only five of 45 (11%) patients would have been considered possible cases. While our positive results justify future comparative studies of voriconazole in this setting, recruiting adequate numbers of patients into randomized controlled trials may be quite difficult.

Although the prospective design of our study may have selected patients in a better clinical condition than those previously reported in retrospective studies, the observed cumulative incidence of 6.7% of new or recurrent invasive fungal infections at 12 months post-HSCT, with only one invasive fungal infection recurrence leading to death in the setting of a leukemia relapse and no case of aspergillosis after transplantation, compares favorably with an expected rate of more than 30%.[5,6,8] In addition, despite many complications as a result of the seriousness of the underlying conditions, treatment-related adverse events were acceptable and consistent with clinical experience in this high-risk patient population. Thus, voriconazole may be a promising prophylactic agent in adults undergoing HSCT for a hematologic disease.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

Financial and other disclosures provided by the authors using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are also available at www.haematologica.org.

Appendix

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