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Antifungal Agents for Secondary Prophylaxis Based on Response to Initial Antifungal Therapy in Allogeneic Hematopoietic Stem Cell Transplant Recipients with Prior Pulmonary Aspergillosis

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A B S T R A C T

We performed a prospective study to evaluate the efficacy and safety of secondary antifungal prophylaxis (SAP) for patients with a history of invasive pulmonary aspergillosis (IPA) in allogeneic hematopoietic stem cell transplantation (allo-HSCT). In this study, the prophylactic agents used were chosen based on treatment response to initial antifungal therapy. One hundred and thirty-six patients undergoing allo-HSCT with prior IPA were enrolled in this multicenter study. The agents of SAP included itraconazole in 24, voriconazole in 74, caspofungin in 32, and liposomal amphotericin B in 6. Eighty-eight patients had stable IPA and 48 had active IPA at the time of transplantation. The success rate of SAP was 91.2%. Twelve patients developed breakthrough invasive fungal disease (IFD), and none discontinued antifungal agents because drug-related adverse events. The incidence of breakthrough IFD was neither different among the different antifungal agents ($P = .675$) nor between patients with active and stable IPA ($P = .080$). The 1-year cumulative incidence of IFD and IPA relapse was 27.3% ± 4.5% and 24.7% ± 4.4%, respectively. Our data indicate that SAP with antifungal agents based on initial antifungal therapy has favorable efficacy and safety in allo-HSCT recipients with prior IPA. Active IPA might not increase the risk of breakthrough IFD after transplantation.

INTRODUCTION

Invasive fungal disease (IFD) is a serious and common complication in patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT), leading to considerable morbidity and mortality. Patients with prior IFD, especially with a history of invasive pulmonary aspergillosis (IPA), are subject to an unacceptable risk of infection relapse and death after transplantation [1-3]. Historically, prior IPA constituted a relative contraindication to allo-HSCT [4,5]. Recently, new antifungal agents, with advances in activity against *Aspergillus* and side effects have significantly improved the outcomes of fungal infection [6]. A growing body of clinical evidence shows that secondary antifungal prophylaxis (SAP) could reduce the risk of IFD recurrence and transplantation-related mortality [3,7-10]. Consequently, most patients with prior IFD now might receive allo-HSCT in the context of SAP [8,9,12-14]. However, the optimal agents for SAP have not been well defined until now. In addition, it is still a matter of discussion whether transplantations can be performed in patients with active IPA. In this prospective study, antifungal agents for SAP were chosen based on treatment response to initial antifungal therapy. The efficacy and safety of this strategy were assessed. Moreover, we compared the outcome of SAP between patients with stable IPA and active IPA.

METHODS

IFD Diagnosis and Entry Criteria

This was a prospective, open-labeled, multicenter study. According to the revised European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group; National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria [11], *IPA* was defined as radiographic findings compatible with IFD on computed tomography (CT) scan plus 1 of the following: (1) *Aspergillus* identified by biopsy, (2) *Aspergillus* identified from culture of bronchoalveolar lavage fluids, or (3) positive finding of serum galactomannan (GM) test (>.5 ng/mL^{-1}). Patients with a history of proven or probable IPA before transplantation were eligible for this study. Patients were excluded if they had 1 of the following: (1) no response to initial antifungal treatment, (2) drug-related toxicity caused by the antifungal agent used in initial antifungal treatment or intolerance to the agents, (3) liver dysfunction (bilirubin or transaminase level > 3 times the upper limit of normal) or renal impairment (creatinine clearance rate < 30 mL/minute), or (4) possible IPA. The study was performed in accordance with the modified Helsinki Declaration, and the protocol was approved by Nanfang Hospital ethical review boards before study initiation. All patients and donors provided written informed consent.

Patients and Transplantation

Between January 2007 and June 2013, 136 patients with a history of IPA were enrolled in this study at Nanfang Hospital, Guangzhou General Hospital of Guangzhou Command, and SUN Yat-sen Memorial Hospital. Fifty were female and 86 were male. The median age was 33 (range, 14 to 57)

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years and the mean weight was 60 (range, 42 to 83) kilograms at the time of transplantation. The underlying primary diseases included leukemia in 122, lymphoma in 7, myelodysplastic syndrome in 6, and severe aplastic anemia in 1. For their initial treatment of IPA, 21 patients received itraconazole, 72 received voriconazole, 31 received caspofungin, 6 received liposomal amphotericin B (L-AmB), and 6 received a combination of 2 agents (ie, itraconazole and L-AmB in 3, voriconazole and L-AmB in 2, caspofungin and L-AmB in 1). The median duration of antifungal treatment before transplantation was 98 days (range, 20 to 338 days).

Ninety-four patients underwent transplantation from a related donor and 42 from an unrelated donor. HLA-matched transplantations were conducted in 94 patients and HLA-mismatched transplantations were conducted in 42. In the patients with unrelated donors, 24 received HLA-matched and 18 received HLA-mismatched transplantations. Sixty-six patients received standard conditioning and 70 received intensified conditioning. The regimens of conditioning had been described in previous study [12]. Graft-versus-host disease (GVHD) prophylaxis and treatment were administered according to the strategy previously described [12].

Antifungal Prophylaxis and Treatment

The SAP agents were chosen based on the treatment responses to initial antifungal therapy: the same antifungal agent that was previously used and proven effective in initial antifungal therapy was administered as the SAP agent. Itraconazole was given intravenously with a loading dose of 200 mg every 12 hours for 4 doses, followed by maintenance doses of 200 mg every 24 hours until neutrophil engraftment and then switched to 200 mg every 12 hours orally. Voriconazole was given intravenously with a loading dose of 6 mg/kg every 12 hours (for 2 doses), followed by maintenance doses of 4 mg/kg every 12 hours until neutrophil engraftment and then switched to 200 mg every 12 hours orally. Caspofungin was given intravenously at a loading dose of 70 mg every 24 hours (for 1 dose) followed by maintenance doses of 50 mg every 24 hours. L-AmB was given at a dose of 150 mg daily. For patients with itraconazole, voriconazole, or caspofungin, the dose was reduced by one half if bilirubin was above the normal threshold but < 2 times the upper limit of normal; the agent was switched to another antifungal agent, as deemed appropriate by the attending physician, if bilirubin was > 2 times the upper limit of normal. For patients with L-AmB, the dose was reduced to 50 mg if creatinine was above the normal threshold but < 2 times the upper limit of normal; L-amB was changed to another antifungal agent if creatinine was > 2 times the upper limit of normal. SAP was given from the start of the conditioning until 90 days after transplantation in patients with stable IPA before transplantation or until eradication or stability of residual foci in the patients with active IPA. The agent that was used in SAP was given for prophylaxis again when patients developed acute GVHD (aGVHD) were treated with corticosteroids and/or monoclonal anti-T cell antibodies. Generally, antifungal prophylaxis was not administered in patients receiving immunosuppressive treatment for chronic GVHD (cGVHD). Once breakthrough IFD was diagnosed, antifungal therapy would be modified. The patients using triazoles for prophylaxis were switched to echinocandins or L-AmB (3 mg/kg) for treatment, and those with prophylactic echinocandins or L-AmB were switched to one of the other 2 kinds of antifungal agents. If IFD occurred after the end of prophylaxis, patients were treated with the antifungal agent that was used for prophylaxis.

Monitoring

Generally, serum concentration of GM and β-D-glucan (G test) of all patients were monitored once each week and a CT scan was done once each month during the SAP. The GM test was performed in the Department of Laboratory Medicine, Nanfang Hospital and the G test was performed in the respective hospitals. If a patient was suspected of developing IFD during the prophylaxis or after the end of prophylaxis, a G test, GM test, and CT were performed. A blood culture, bronchoalveolar lavage of fluids, and biopsy of involved areas were performed according to clinical indications.

Definitions

Responses to treatment were classified into complete responses (CR), partial responses (PR), stable responses, and failure of therapy, as evaluated in the clinical trials [13,14]. CR and PR were considered effective. Patients with stable IPA at transplantation were those who achieved CR after initial antifungal treatment—no fungal lesion by CT detection or no 18 F-fluorodeoxyglucose high uptake in residual pulmonary lesion by positron emission tomography/CT [15-17], as well as negative GM test. *Active IPA* was defined as PR or stable responses to prior IFD at transplantations. *Breakthrough IFD* was defined as a new episode of fungal infection or the recurrence of fungal infection during the SAP [18]. *IPA relapse* was defined as the recurrence of IPA, which occurred during and after prophylaxis, caused by the same *Aspergillus,* including expansion of residual lesion or occurrence of new lesion other than historic lesion. A positive finding of GM test without clinical sign was not considered IPA relapse. IFD-related mortality was death due to IFD or toxicity of antifungal agents. The stages of the underlying primary diseases were evaluated according to consensus criteria [19-23]; patients with severe aplastic anemia were considered in non-CR (complete remission) stage at transplantation.

Table 1
Demographic and Clinic Characteristics of the Patients

Characteristic	Stable IPA (n = 88)	Active IPA (n = 48)	*P* Value
Age, median (range), yr	30 (14-53)	36 (20-57)	.074
Gender			.896
Male	56 (63.6%)	30 (62.5%)	
Female	32 (36.4%)	18 (37.5%)	
Stage of underlying primary diseases			<.001
CR	70 (79.5%)	17 (35.4%)	
Non-CR	18 (20.5%)	31 (64.6%)	
Diagnosis of prior IPA			.770
Proven	13 (14.8%)	8 (16.7%)	
Probable	75 (85.2%)	40 (83.3%)	
Duration of initial treatment of IPA			.992
Median (range), d	98 (22-338)	92 (20-220)	
Donor			.945
Related	61 (69.3%)	33 (68.8%)	
Unrelated	27 (30.7%)	15 (31.2%)	
HLA type			.217
Matched	64 (72.7%)	30 (62.5%)	
Mismatched	24 (27.3%)	18 (37.5%)	
Conditioning regimen			.009
Standard	50 (56.8%)	16 (33.3%)	
Intensified	38 (43.2%)	32 (66.7%)	
ATG for aGVHD prophylaxis	40 (45.5%)	26 (54.2%)	.331

IPA indicates invasive pulmonary aspergillosis; ATG, antithymocyte globulin; CR, complete remission; aGVHD, acute graft-versus-host disease.
Data presented are n (%), unless otherwise indicated.

STATISTICAL CONSIDERATIONS

The data were analyzed on December 31, 2013. The primary endpoint, success of SAP, was defined as absence of breakthrough IFD (proven, probable, and possible) during SAP and no premature discontinuation of study agents because of drug-related adverse events. Secondary endpoints consist of the incidence of post-transplantation IFD (including breakthrough IFD and IFD that occurred after the end of SAP), adverse events, IFD-related mortality, and survival. IFD that occurred after salvage therapy for relapse of underlying primary disease was not included as post-transplantation IFD. Continuous variables were compared by the Mann-Whitney test. For categorical variables, the chi-square statistic or Fisher exact test were used to establish the difference of distribution between groups. Cumulative incidence of IPA and overall survival (OS) were estimated by the Kaplan-Meier procedure and comparison was done by a log-rank test. A Cox proportional hazards regression model was used for analysis of risk factors for breakthrough and post-transplantation IFD as well as for OS. All *P* values were 2-sided. *P* values $< .05$ were considered to indicate statistical significance. The statistics was performed by the software SPSS (Chicago, IL).

RESULTS

Baseline Characteristics of the Patients and Prior IPA

Of the 136 patients enrolled in study, IPA was proven in 21 and probable in 115 patients. Eight-eight patients had stable IPA and 48 had active IPA at the time of their transplantation. Fourteen patients had cavity lesions or a nodule more than 2 cm in diameter, and 8 of these patients received