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Original Article

Secondary antifungal prophylaxis in allogeneic hematopoietic stem cell transplant recipients with invasive fungal infection

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Abstract

Introduction: Invasive fungal infection (IFI) is a major cause of morbidity and mortality in allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients. A previous history of IFI is not an absolute contraindication for allo-HSCT, particularly in the era of secondary antifungal prophylaxis (SAP). Prompt diagnosis and therapy are essential for HSCT outcome.

Methodology: The charts of 58 allo-HSCT recipients [median age:29.5 (16-62); M/F:41/17] who had a previous history of IFI were retrospectively reviewed.

Results: Possible IFI was demonstrated in 32 (55.2%), probable in 13 (22.4%) and proven in 13 patients (22.4%). All patients received SAP [liposomal amphoterisin B (n = 35), voriconazole (n = 17), caspofungin (n = 2), posaconazole (n = 1), combination therapy (n = 3)] which was started on the first day of the conditioning regimen. Treatment success was better in the voriconazole group when compared to the amphotericin B arm (100% vs 69.2%; p = 0.029). Development of breakthrough IFI was more frequent in patients on amphotericin B prophylaxis (42.4% vs 23.1%; p = 0.036). Clinical and radiological response were achieved in 13 of 18 patients (72.2%) who developed breakthrough infection. Overall survival of the study population was 13.5% at a median follow-up of 154 (7-3285) days. Fungal mortality was found to be 23%. Overall survival was better in the voriconazole arm, without statistical significance (90% vs 65.8%, p > 0.05).

Conclusions: Secondary antifungal prophylaxis is considered to be an indispensible strategy in patients with pre-HSCT IFI history. Voriconazole seems to be a relatively better alternative despite an underlying necessity of larger prospective trials.

Key words: invasive fungal infection; antifungal prophylaxis; voriconazole; amphotericin B.

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Introduction

Invasive fungal infections (IFI) remain to be a leading cause of morbidity and mortality in patients with hematological malignancies, particularly in allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients [1-4].

Several factors, including age, prolonged neutropenia, corticosteroid treatment, graft versus host disease (GvHD), HLA mismatch, T-cell depletion, cytomegalovirus infection, iron overload and prior IFI, have been identified to determine the risk of breakthrough and recurrent IFI during HSCT course [3,5-20]. As novel prophylactic and therapeutic strategies have improved the dismal course of fungal infections, a previous history of IFI is no longer considered as an absolute contraindication, even though the relapse rate remains to be 19-33% after allo-HSCT [5,6,21,22].

In general, fluconazole, itraconazole and voriconazole are recommended for antifungal prophylaxis in low-risk allo-HSCT recipients with no additional risk factors and posaconazole in patients with GvHD. In high-risk patients, mold-active triazoles such as itraconazole, posaconazole and voriconazole should be used for primary prophylaxis. Secondary prophylaxis is mandatory to prevent recurrence and breakthrough infection in patients with a prior history of IFI [17,18]. Patients, who had a previous IFI and do not receive secondary antifungal prophylaxis (SAP), are more likely to experience a breakthrough fungal infection in the early course of allo-HSCT [23]. Even though the use of SAP reduces systemic antifungal use

and IFI frequency, it may also increase the risk of colonization and infection with azole-resistant fungal strains [24].

Although primary prophylaxis has a relatively definite course, an optimal preventive strategy has not been improved for SAP in allo-HSCT recipients with prior IFI. Voriconazole, itraconazole, liposomal amphotericin B (L-AmB) and caspofungin have been found to be effective in retrospective studies, although specific recommendations have not been developed yet [1,3,6,8-10,12,13,15,25-27].

This retrospective study was planned in order to share our SAP experience in allo-HSCT recipients with prior IFI, as a more standardized approach is precisely required to overcome IFI-associated morbidity and mortality in high-risk patients.

Methodology

Patients

A total of 58 allo-HSCT recipients [median age: 29.5 (16-62) years; male/female: 41/17] with a prior history of IFI were included in this study. A total of 31 patients (53.5%) were diagnosed as acute myeloid leukemia (AML), 15 patients (25.9%) acute lymphoblastic leukemia (ALL), 2 patients (3.4%) non Hodgkin's lymphoma (NHL), 6 patients (10.4%) severe aplastic anemia, 2 patients (3.4%) myelodysplastic syndrome (MDS) and 2 patients (3.4%) chronic lymphocytic leukemia (CLL). Complete remission was achieved in 35 patients (92.1%) and 3 patients (7.9%) were evaluated as progressive disease. Patient characteristics are summarized in Table 1.

Transplantation

Of 58 allo-HSCTs which were performed at Gazi University Stem Cell Transplantation Unit between 2003 and 2016, 50 (86.2%) were assigned as related, 1 haploidentical (1.7%) and 7 unrelated (12.1%). Conditioning regimens were myeloablative in 40 (69%) and reduced-intensity in 18 (31%) patients. Cyclosporine/methotrexate and cyclosporine/mycophenolate mofetil were used in 50 patients (86.2%) and 8 patients (13.8%) for GvHD prophylaxis respectively. Concomittant GvHD and IFI were reported in 9 patients (15.5%) and steroid treatment was administered in 8 patients (13.7%).

Risk Stratification, Monitoring and Diagnosis of Invasive Fungal Infection

Pre-HSCT high-resolution computerized tomography (HRCT) was performed in all patients and repeated in case of refractory neutropenic fever or unexplained respiratory symptoms. Serum concentration of galactomannan was monitored once a week. Blood, urine and sputum cultures, cultures from infected sites and catheters, radiological scans and invasive procedures such as bronchoscopic examination were performed based on certain clinical

Table 1. Patient Characteristics.

Characteristics	n (%)
Age (years) median(range)	**29.5 (16-62)**
Gender	
Male	41 (70.6)
Female	17 (29.4)
Diagnosis	
Acute myeloid leukemia	31 (53.5)
Acute lymphoblastic leukemia	15 (25.9)
Non Hodgkin lymphoma	2 (3.4)
Aplastic anemia	6 (10.4)
Myelodysplastic syndrome	2 (3.4)
Chronic lymphocytic leukemia	2 (3.4)
ECOG performance status median(range)	1 (0-4)
EBMT score median(range)	4 (0-6)
Sorror's comorbidity index median(range)	2 (0-7)
C-reactive protein(CRP) (g/L)median(range)	16 (1-353)
Erythrocyte sedimentation rate (mm/h)median(range)	55 (2-160)
Galactomannan median(range)	0.26(0.1-0.9)
Ferritin (ng/mL) median(range)	165 (4.7-26000)
Pre-transplant disease status (n=38)	
Complete remission	35 (92.1)
Progressive disease	3 (7.9)
Donor type	
Related	50 (86.2)
Unrelated	7 (12.1)
Haploidentical	1 (1.7)
Conditioning regimen	
Myeloablative	40 (69)
Reduced intensity	18 (31)
GvHD prophylaxis	
Cyclosporine A / methotrexate	50 (86.2)
Cyclosporine A / mycophenolate mofetil	8 (13.8)
Infused CD34 cell count (10^6/kg)median(range)	4.2 (0.9-8.2)
Duration of neutropenia (days) median(range)	17 (8-53)
Neutrophil engraftment (day) median(range)	19 (10-43)
Platelet engraftment (day) median(range)	19 (11-200)
Concurrent GvHD	
Yes	9 (15.5)
No	49 (84.5)
Corticosteroid Therapy	
Yes	8 (13.7)
No	50 (86.3)

EBMT: European Society for Blood and Marrow Transplantation; ECOG:*Eastern Cooperative Oncology Group;* HSCT: Hematopoietic Stem Cell Transplantation; GVHD: Graft versus Host Disease.

indications. Invasive fungal infections were defined and classified according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group guidelines[28].

Secondary Antifungal Prophylaxis

Secondary antifungal prophylaxis, which was started on the first day of the conditioning regimen, was identified based on the initial treatment response. The same antifungal agent, which was previously used and proven to be effective, was administered. Voriconazole was given intravenously with a loading dose of 6 mg/kg every 12 hours, followed by 4 mg/kg every 12 hours until neutrophil engraftment. After neutrophil recovery, voriconazole treatment was switched to oral formulation as 200 mg every 12 hours. Caspofungin was given intravenously at a loading dose of 70 mg/day and then a maintenance dose of 50 mg/day. Posaconazole was given 400 mg every 12 hours as oral suspension. Liposomal AmB was given intravenously at a dose of 1 mg/kg/day. In case of breakthrough or recurrent infection, antifungal regimen was modified or switched to combination therapy. Details of SAP are represented in Table 2. Treatment success was defined as the absence of IFI recurrence, any breakthrough or new infection, while treatment failure was a recurrence of previous IFI or occurrence of new infection. Invasive fungal infection related mortality was described as death due to IFI or toxicity of antifungal therapy.

Statistical analysis

Continuous and categorical variables were compared with Mann Whitney U and χ^2 test, respectively. Correlations were analyzed with Spearman test. Kaplan Meier analysis was used for survival analysis and risk factors for survival were evaluated by Cox Regression and Log Rank tests. SPSS 16.0 programme was used for statistical analysis (SPSS Inc, Chicago, IL, USA). $p < 0.05$ was considered to be statistically significant.

Results

Demographics and Clinical Characteristics

Possible IFI was demonstrated in 32 patients (55.2%), probable in 13 patients (22.4%) and proven in 13 patients (22.4%). Pneumonia was the most common presentation which was observed in 44 patients (75.9%). A total of 12 patients (20.7%) had active IFI at the time of HSCT. Tissue or blood cultures yielded positive results in 10 patients (17.2%) [Aspergillus in 7, Candida in 2 and Rhizopus in 1 patient]. Galactomannan test was found to be positive in 6 patients (10.3%).

Secondary antifungal prophylaxis was administered in 58 patients [median age: 29.5(16-62); M/F: 41/17]. Liposomal AmB was used in 35 patients (60.3%), voriconazole in 17 patients (29.3%), caspofungin in 2 patients (3.5%) and posaconazole in 1 patient (1.7%). Combination therapy was given to 3 patients (5.2%) with active IFI.

Efficacy of Secondary Antifungal Prophylaxis

Breakthrough IFI was observed in 18 patients (31%). Of these, a total of 10 patients (55.5%) were treated with L-AmB, 3 patients (16.7%) with caspofungin and 5 patients (27.8%) with combination therapy. Median duration of the treatment was 25 (6-96) days. Clinical response with radiological resolution was achieved in 13 (72.2%) patients. Breakthrough IFI was more frequent in patients on L-AmB prophylaxis (42.4% vs 23.1%; $p = 0.036$). However, unrelated (14.3% vs 5.9%; $p = 0,013$) and myeloablative HSCTs (74.3% vs 53%; $p = 0.004$) were also found to be more common in L-AmB group.

Patients were divided into two main groups as voriconazole and L-AmB arms. Age, European Society for Blood and Marrow Transplantation (EBMT) score, Sorror comorbidity index, Eastern Cooperative Oncology Group (ECOG) performance status, C reactive protein levels, ferritin levels and duration of neutropenia were not statistically different between two groups ($p > 0.05$). Treatment success was significantly

Table 2. Secondary Antifungal Prophylaxis Regimens Based on Invasive Fungal Infection Types.

	Possible IFI n(%)	Probable IFI n(%)	Proven IFI n(%)
Liposomal Amphotericin B	21 (65.7)	8 (61.5)	6 (46.1)
Voriconazole	9 (28.1)	3 (23.1)	5 (38.5)
Caspofungin	1 (3.1)	-	1 (7.7)
Posaconazole	1 (3.1)	-	-
Combination Therapy	-	2 (15.4)	1 (7.7)
Total	**32**	**13**	**13**

IFI Invasive Fungal Infection.

better in the voriconazole group (100% vs 69.2%; p = 0.029). Overall survival (OS) was longer in patients who received voriconazole [OS: 90%; follow-up: 320 (23-2466) days], when compared to L-AmB arm [OS: 65.8%; follow-up: 145 (7-3285) days], without statistical significance (p > 0,05). Fungal infection related mortality was observed in 8 patients (23%). Three of these were stated to have pre-HSCT active IFI.

Discussion

In the current study, the efficacy of SAP was evaluated in 58 allo-HSCT recipients with previous IFI history. Breakthrough IFIs were less frequent in the voriconazole group, however the percentage of unrelated and myeloablative HSCTs were relatively higher in the L-AmB arm. Treatment success was significantly better in the voriconazole group. Overall survival was longer in patients who received voriconazole, without statistical significance.

As IFI remains to be a prominent cause of mortality in HSCT recipients, novel preventive strategies are being developed to overcome this obstacle. The substantial risk of recurrent IFI after HSCT is 16-33% in patients who had survived the first IFI episode while IFI-related mortality reaches up to 88% in high-risk patients. Through the widespread use of SAP, a prior history of IFI is no longer considered as an absolute contraindication for HSCT. However, the incidence of IFI remains to be as high as 22-29% in allo-HSCT recipients who had received SAP. Breakthrough IFI was found to be less common in patients who had received SAP than those who had not [1,3,5,6,8,9,29,30].

In a study by Fukuda *et al.*, in which 2319 HSCT recipients were retrospectively reviewed for a history of IFI, 45 patients were found to have prior IFI history. A total of 13 patients (29%), who experienced post-HSCT IFI, had lower OS and higher transplant related mortaliy (TRM) [29]. In another retrospective study by Liu *et al.*, SAP was given to 121 of 164 patients who underwent chemotherapy or HSCT. Recurrence of IFI was reported to be 16.5% and 46.5% in SAP and non-SAP groups, respectively. Recurrence rate was significantly higher in patients with allo-HSCT when compared to autologous HSCT or chemotherapy [3]. El-Cheikh *et al.* evaluated the impact of pre-HSCT invasive aspergillosis (IA) on the outcome of RIC allo-HSCT. Voriconazole was used in 71% of patients, itraconazole in 14% and combination in 14%. Only 3 patients (11%) had reactivation of IA and one patient developed disseminated fusariosis [31]. In our study, breakthrough IFI was demonstrated in 18 patients (31%), which may be attributed to the higher percentage of patients (20.7%) who had active IFI at the time of HSCT. Invasive fungal infection related mortality was found to be 23% in our cohort, which is compatible with the previously reported data.

The European Conference on Infections in Leukemia (ECIL) guidelines, which recommend SAP with an evidence level of AII, underline the importance of primary treatment success and fungus type in antifungal drug selection. The optimal agent, regimen and duration of prophylaxis are not well-defined [3,9,12,15,32,33]. Secondary antifungal prophylaxis with fluconazole, voriconazole, itraconazole, echinocandins and L-AmB has been shown to be effective in reducing the risk of breakthrough infection in several retrospective studies. Although posaconazole prevents IFI in allo-HSCT recipients with GvHD and in patients with AML in the remission induction phase, there is limited data on its role in SAP [2,12,13,34-37].

In the current study, voriconazole was found to be superior to L-AmB for SAP in allo-HSCT recipients, which emphasizes the efficacy of voriconazole in SAP in concordance with previous studies [8,10,13,15,21,25,26]. In a prospective study by Cordonnier *et al*., 45 patients with prior IFI had received voriconazole for SAP. It was reported that only 6.7% of patients has developed IFI during the first year of HSCT. Voriconazole was considered to be safe and effective for secondary prophylaxis of systemic IFI after allo-HSCT [12]. In another report of the same group, 11 leukemia patients with previous aspergillosis or candidiasis, who had received secondary prophylaxis with voriconazole were evaluated. None of the patients had recurrent infection and the drug was well-tolerated [25]. In a case-series reported by Masamoto *et al*., 15 patients with previous pulmonary IFI received SAP with voriconazole during chemotherapy for acute leukemia. No progressive disease was observed and toxicity profile was tolerable [15]. To our knowledge, there is limited data which compares the efficacy of antifungal agents for SAP in allo-HSCT recipients. A prospective multicenter trial assessed efficacy and safety of SAP with voriconazole, itraconazole, caspofungin or L-AmB in HSCT recipients with a history of IFI. The 1-year cumulative incidence of IFI was 8.8%, with no discontinuation due to adverse events. No differences in the incidence of breakthrough IFIs were observed among the antifungal agents [9]. In another study, Kikuchi *et al*. found that voriconazole

was more effective than micafungin or L-AmB in a retrospective review of 46 hematology patients [38].

Although voriconazole represented better efficacy and a significant survival benefit in the first-line treatment of IFI, current data is inadequate to introduce a definite conclusion for the role of voriconazole in SAP. Nonetheless, voriconazole seems to be more advantageous in several circumstances including broad-spectrum of action, low toxicity and clinical efficacy. Drug interactions should be considered in order to maintain the optimal dose and avoid drug toxicity [12,25].

Conclusion

This study, despite its small sample size and retrospective nature, aimed to identify the efficacy of SAP in allo-HSCT recipients with prior IFI by comparing certain antifungal agents. Similarity of several risk parameters between two groups including age, EBMT score, Sorror comorbidity index, ECOG performance status, C reactive protein and duration of neutropenia strengthens the reliability of the results. Severe toxicity was not reported, however lack of satisfactory data on drug side effects, interactions and toxicity may be considered as the weak part of the study. As a result, voriconazole seems to be a feasible antifungal agent which can be used safely in HSCT recipients who have experienced IFI. Nevertheless, large randomized studies would help to improve our understanding about the significance of proper antifungal prophylaxis which may be life-saving for high-risk HSCT survivors by altering the course of breakthrough infection. Prospective data is mandatory in order to standardize a feasible approach for SAP in high-risk patients.

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