Hematological Malignancy

Invasive Fungal Infection in Hematopoietic Stem Cell Transplant Recipient from an Indian Oncology Setting

Abdul Ghafur[1]   Bikram Das[1]   T. Raja[2]   Jose Easow[2]   Radhika Kartikeyan[1]   Benjamin M. Easow[1]
S. G. Ramanan[2]

[1] Department of Infectious Diseases, Apollo Cancer Institute, Chennai, Tamil Nadu, India
[2] Department of Oncology, Apollo Cancer Institute, Chennai, Tamil Nadu, India

Address for correspondence Abdul Ghafur, MD, MRCP, FRCPath, Apollo Cancer Institute, Chennai, Tamil Nadu 600035, India (e-mail: drghafur@hotmail.com).

Abstract

Abdul Ghafur

Objective Invasive fungal infections (IFI) are one of the major causes of morbidity and mortality in post-hematopoietic stem cell transplant (HSCT) recipients. Data from India is limited. The objective of this study was to analyze the incidence, risk factors, and outcomes associated with IFI in our center.

Materials and Methods Adult patients, who underwent marrow/stem cell transplantation between 2014 and 2018, in an oncology center in India, were included in this single-center retrospective observational study. The revised European Organization for Research and Treatment of Cancer/ Mycoses Study Group (EORTC/MSG) consensus group 2008 definition for IFI was considered to define cases. Incidence, risk factors, and outcomes associated with IFI were analyzed.

Statistical Analysis All continuous variables were represented by mean ± standard deviation and categorical variables as percentage. Comparison of categorical variables was done by either the chi-squared test or Fisher's exact test. All "p" values less than 0.05 were considered statistically significant.

Results Out of the 126 patients who underwent HSCT between January 2014 and December 2018, 56 (44.4%) patients had allo-HSCT, 64 (50.8%) had auto-HSCT, and 6 (4.8%) had haplo-identical HSCT. Eighty-three (63%) patients were male and 43 (34%) females, and 113 (83.9%) Asians and 13 (10.3%) Africans. Total 111 (88%) patients received myeloablative conditioning and 24 (19%) received total body irradiation. The hematological conditions were acute myeloid leukemia ($n=23$; 18.25%), acute lymphoblastic leukemia ($n=16$; 12.69%), chronic myeloid leukemia ($n=4$; 3.17%), Hodgkin lymphoma ($n=17$; 13.4%), non-Hodgkin lymphoma ($n=11$; 8.73%), myeloma ($n=35$; 27.7%), sickle cell disease ($n=13$; 10.31%), etc. Most patients received fluconazole (78; 61.9%) followed by micafungin (23; 18.25%), posaconazole (20; 15.87%), voriconazole (4; 3.17%), and liposomal amphotericin B (1; 0.79%) as antifungal prophylaxis. The overall rate of IFI (possible cases included) was auto-HSCT ($n=5$; 7.81%), and allo-HSCT ($n=5$; 8.92%). Among auto-HSCT, the IFI was proven = 0,

Keywords
► hematopoietic stem cell transplant
► India
► invasive fungal infection
► antifungal prophylaxis

probable $n = 1$ (1.5%), and possible $n = 4$ (6.25%) and among allo-HSCT the IFI was proven $= 0$, probable $n = 2$ (3.57%), and possible $n = 3$ (5.35%). No patients in haplo-HSCT had IFI. The 1-year survival rate among the IFI cases was 8/10(80%). A meaningful comparison of the risk factors and the impact of prophylactic regimens were difficult because of the very low number of IFI cases.

Conclusion   The overall rate of IFI in HSCT patients in our setting was low compared to global data on IFI in HSCT.

Introduction

Invasive fungal infection (IFI) is one of the major causes of morbidity and mortality among hematopoietic stem cell transplant (HSCT) recipients due to their immunocompromised state. There are several risk factors for IFI in HSCT recipients like the type of malignancy, conditioning regimen, extensive chronic graft versus host disease (GVHD), secondary neutropenia, and relapse after transplant.[1,2] Mold infection is more common than yeast infection in some studies.[2] Prophylaxis with antifungals has reduced the incidence of IFI as well as morbidity and mortality. There is limited data available from the Indian oncology setting on IFI epidemiology in HSCT recipients in the current era of evolving antifungal prophylaxis. Our study aimed to analyze the incidence, risk factors, and the outcome associated with IFI in post HSCT recipients in the setting of different antifungal prophylaxis in a single-center in South India.

Materials and Methods

Adult patients (>18 years), who underwent marrow/stem cell transplantation during the period 2014 to 2018, in our oncology center, were included in the study. Patients were diagnosed to have IFI as proven, probable, or possible according to the revised EORTC/MSG consensus group 2008 definition. The criteria for nonendemic IFI were applied and it did not include pneumocystis pneumonia. Patients with prior evidence of IFI were excluded. In this single-center retrospective observational study, the hospital records of patients and clinical details were analyzed. The case definitions were as follows. The aspergillosis galactomannan antigen was measured by Platelia Aspergillus Ag assay by BIO-RAD (a one stage immunoenzymatic sandwich microplate assay). The cutoff value of galactomannan antigen in plasma, serum, bronchoalveolar lavage fluid, or cerebrospinal fluid (CSF) was considered more than 0.5 as per Food and Drug Administration (FDA) revision in 2008.[3] The 1-3 beta D glucan (BDG) was measured using the Fungitell assay that is a microplate-based test.

Case Definition
IFI has been defined as per revised EORTC/MSG 2008 criteria.

Proven IFI: Histopathological/cytopathological proof with evidence of tissue damage or culture positivity from a sterile site.

Probable IFI: Compatible host with the clinical feature or radiological evidence along with mycological evidence from nonsterile sites or elevated biomarkers.

The cutoff value for galactomannan was as follows (as per FDA revision).

1. Single serum or plasma: ≥ 0.5
2. Bronchoalveolar lavage fluid: ≥ 0.5
3. CSF: ≥ 0.5

The cutoff value for serum BDG was considered more than 80 pg/mL.

Possible IFI: The appropriate host factors and with sufficient clinical evidence consistent with IFI but for which there was no mycological support.

Ethical Committee
The study was performed after prior formal approval of the study protocol by the properly constituted institutional ethics committee. Unique Health Identification (UHID) number of patients was used for identification. The names and personal identification were not revealed. The entire data was confined exclusively to the primary investigators' group members.

Statistical Analysis
All continuous variables were represented by mean $\pm$ standard deviation. Categorical variables were expressed as a percentage. Comparison of categorical variables was done by either the chi-squared test or Fisher's exact test. Comparison of continuous variables was done by independent sample t-test. Data entry was done in Microsoft Excel 2007. Data analysis was carried out by IBM SPSS Statistics for Windows version 25.0. All "p" values less than 0.05 were considered statistically significant.

Results

A total of 126 patients underwent HSCT between 2014 and 2018. Of these 56 (44.4%) patients had auto-HSCT, 64 (50.8%) had allo-HSCT, and 6 (4.8%) had haplo-identical HSCT.

Out of the total 126 cases, 83 were male (63%) and 43(34%) female. Regarding ethnicity, 113 (83.9%) patients were Asians and 13 (10.3%) Africans. The hematological conditions that required HSCT were acute myeloid leukemia (AML) ($n = 23$; 18.25%), acute lymphoblastic leukemia ($n = 16$; 12.69%), chronic myeloid leukemia ($n = 4$; 3.17%), Hodgkin
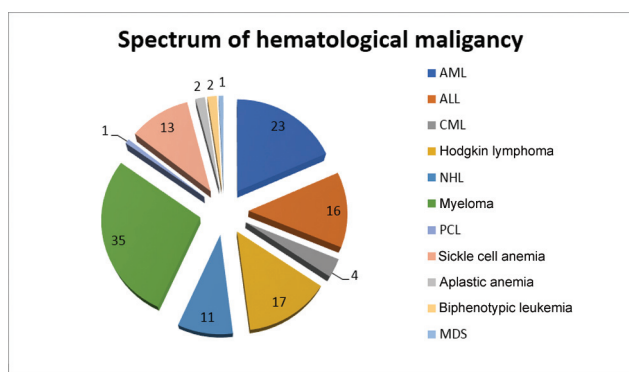
Fig. 1 The spectrum of hematological malignancies in the hematopoietic stem cell transplant recepient. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; PCL, plasma cell leukemia.

lymphoma ($n = 17$; 13.4%), non-Hodgkin lymphoma ($n = 11$; 8.73%), myeloma ($n = 35$; 27.7%), plasma cell leukemia ($n = 1$; 0.79%), sickle cell disease ($n = 13$; 10.31%), aplastic anemia ($n = 2$; 1.58%), biphenotypic leukemia ($n = 2$; 1.58%), idiopathic myelofibrosis ($n = 1$; 0.79%), and myelodysplastic syndrome (MDS, $n = 1$; 0.79%; ►Fig. 1).

Majority of the patients ($n = 111$; 88%) received myeloablative conditioning and 15(12%) non-myeloablative conditioning. Total body irradiation was given to 24 (19%) patients.

Fluconazole (78; 61.9%), posaconazole (20; 15.87%), voriconazole (4; 3.17%), liposomal amphotericin B (1; 0.79%), and micafungin (23; 18.25%) were the antifungal agents used as prophylaxis. There was no statistically significant difference in the rate of fungal infections between groups who received any particular antifungal agent as prophylaxis. However, the number of patients with fungal infections in the study population was very low (10/126) and hence any comparison of the rate of IFI in different groups will not be meaningful. We experienced the same limitation while analyzing other risk factors as well (►Table 1).

The overall rate of IFI (possible cases included) was auto-HSCT ($n = 5$; 7.81%), and allo-HSCT ($n = 5$; 8.92%). Among auto-HSCT, the rate of IFI was as follows: proven = 0, probable $n = 1$(1.5%), and possible $n = 4$ (6.25%). Among allo-HSCT, proven = 0, probable $n = 2$ (3.57%), and possible $n = 3$(5.35%). No patients in haplo-HSCT had IFI. If we exclude possible cases, the IFI rates were as follows: auto-HSCT ($n = 1$; 1.56%), allo-HSCT ($n = 2$; 3.57%; ►Fig. 2).

The 1-year survival rate among the IFI cases was 8/10 (80%). Serum galactomannan was positive in 3/3 probable IFI cases with mean value of 0.8. Serum BDG was measured in 5/7 cases of possible IFI and all of them were less than 80 pg/mL. It was found that 2/10 (20%) patients with coexisting cytomegalovirus (CMV) infection developed IFI compared to 5/116(4.3%) without coexisting CMV. This difference was not statistically significant ($p = 0.096$). There was no statistically significant difference in the occurrence of IFI with anti-CMV therapy compared to non-IFI cases.

Atelectasis, nodules, and ground-glass opacities were more common in the computed tomography chest of IFI cases versus non-IFI cases. Pleural effusion was less common in IFI compared to non-IFI (►Table 2). The interval from date of bone marrow transplant (BMT) to diagnosis of IFI was 23.2 ± 26.5 days. We could not compare the difference in the interval between allo- and auto-HSCT patients as the number of patients with fungal infections in the study population was very low. For the same reason, we could not compare the effectiveness of various antifungal agents as therapeutic agents in the HSCT setting.

Discussion

Older studies such as the 2001 study by Baddley et al reported invasive mold infection in 15 of 94 (16%) BMT patients of which 87% were proven and 13% were probable categories. Only half of the patients (51%) in the Baddley et al's study received antifungal prophylaxis. The overall mortality was 55%, with 87% of these deaths related to invasive mold infections.[4] In 2003, Hagen et al reported 24 proven/probable/possible cases of IFI, out of 31 cases of nonmyeloablative allogeneic transplants. Of those 24 cases, 7 were proven, 11 were probable, and 6 were possible IFI. Invasive aspergillosis was more common (11/14). Infections with *Candida glabrata*, *Cladosporium*, and mucor were also seen. The mortality related to fungal infection in the Hagen study was 23% with an overall mortality of 33%.[5]

Harrison et al performed a retrospective cohort study of allogeneic HSCT cases, in Vienna from 2009 to 2011. The 1-year incidence for IFI was 10.3% (25/242). Invasive aspergillosis was the predominant IFI ($n = 18$), followed by invasive candidiasis ($n = 7$) and pneumocystis pneumonia ($n = 3$). The median time from HSCT to the diagnosis of IFI was 8 days for invasive candidiasis, 36 days for invasive aspergillosis, and 319 days for pneumocystis pneumonia. In this cohort, 12% of patients had evidence of IFI before HSCT.[6]

In our study, the mean interval from HSCT to IFI was 23.2 ± 26.5 days. However, the mean interval in our study is based on a very small number of probable and possible IFI cases. Though some studies had included cases who had IFI prior to HSCT,[7] in our study, we excluded patients with prior episodes of IFI, as with this criterion we can identify the true prevalence of post HSCT IFI.

The 2013 RISK study from Korea by Choi et al in 521 allo-HSCT cases showed proven/probable rate of 31.6% (15.5% of these were proven and 84.5% were probable cases based on EORTC/MSG 2008). Invasive aspergillosis was most common (87.3%) followed by candidiasis (9.9%). Most patients (80%) in that study received antifungal prophylaxis. Most of the mold infections were seen in the late phase after HSCT, especially in those who did not receive mold active antifungal prophylaxis.[3]

In the year 2015 Shi et al documented 92 episodes (22.5%) of proven//probable IFI in 408 patients of allogenic HSCT as per EORTC/MSG 2002 criteria. Out of the 92 episodes, 4 were proven and 88 were probable IFI. Invasive candidiasis was seen in 50 cases and invasive mold infection in 42 with *Aspergillus* species in 76% of these cases. Invasive candidiasis was observed in the relatively early phase, whereas invasive

Table 1 Comparison of baseline characteristics of IFI versus non-IFI

Variables	Categories	IFI ($n = 10$)	Non-IFI ($n = 116$)	Probability value
Sex	Male	6 (60%)	77 (66.4%)	0.463
	Female	4 (40%)	39 (33.6%)	
Ethnicity	Asian	9 (90%)	104 (89.7%)	0.725
	African	1 (10%)	12 (10.3%)	
Diagnosis	AML/ALL	5 (50%)	36 (31%)	0.845
	CML/CLL	Nil	4 (3.4%)	
	NHL/HL	3 (30%)	25 (21.6%)	
	Myeloma/PCL	2(20%)	34 (29.3%)	
	Sickle cell disease	Nil	13 (11.2%)	
	Aplastic anemia	Nil	2 (1.7%)	
	IMF	Nil	1 (0.9%)	
	MDS	Nil	1 (0.9%)	
Graft type	Allogenic	5 (50%)	51 (44%)	0.743
	Autologous	5 (50%)	59 (50.9%)	
	Haplo-Allogenic	Nil	6 (5.2%)	
HLA matching	Matched	5 (100%)	57 (100%)	Constant
	Mismatched	Nil	Nil	
Donor (ALLO)	Related	5 (100%)	51 (89.5%)	0.445
	Unrelated	Nil	6 (10.5%)	
GVHD	Acute	5 (50%)	57 (49.1%)	0.958
	Chronic	Nil	Nil	
	None	5 (50%)	59 (50.9%)	
Steroids	Given	5 (50%)	53 (45.7%)	0.793
	Not given	5 (50%)	63 (54.3%)	
Conditioning	Myeloablative	8 (80%)	103 (88.8%)	0.339
	Nonmyeloablative	2 (20%)	13 (11.2%)	
Immunosuppressants	Given	4 (40%)	55 (47.4%)	0.455
	Not given	6 (60%)	61 (52.6%)	
GCSF	Given	10 (100%)	103 (88.8%)	0.322
	Not given	0(0%)	13(11.2%)	

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphoblastic leukemia; CML, chronic myeloid leukemia; GCSF, granulocyte colony-stimulating factor; GVHD, graft versus host disease; HL, Hodgkin lymphoma; IFI, invasive fungal infection; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; PCL, plasma cell leukemia.

molds infections were found in the late phase. Overall, 60% of the IFI had late presentation more than 100 days after transplant.[8]

Data from Indian BMT setting on IFI is limited. In the prebiomarker era, Chandy et al in 2001 published their experience in allogeneic BMT patients from 1986 to 1999 in an Indian setting that showed biopsy or culture-proven fungal sepsis (some at autopsy) in 36 patients (*Aspergillus* 21, *Candida* 9, *Zygomycetes* 1, and Mucor 1). With the advent of improved IFI diagnosis as well as newer antifungal prophylaxis, the epidemiology is expected to change over time.[9]

IFI remains a concern in hematological malignancy and HSCT patients. Very recently in a multicenter observational

study in India done by George et al from 2014 to 2016 with a population of 200 patients with AML undergoing chemotherapy showed that the overall incidence of IFI was 26.5%. Incidence of proven/probable IFI was 8.5%.[10] This study provides a perspective to the current IFI epidemiology in India in the era of antifungal prophylaxis, though the data is not exclusive to HSCT patients.

However, the data of IFI in HSCT from Asian countries is available. Hsu et al conducted a 2-year multicenter prospective observational study in Asia that revealed IFI in 412 subjects (28.2% possible, 38.3% probable, and 33.5% proven IFIs). The study included different hematological malignancies including HSCT patients. Among all IFI cases,16.8% had
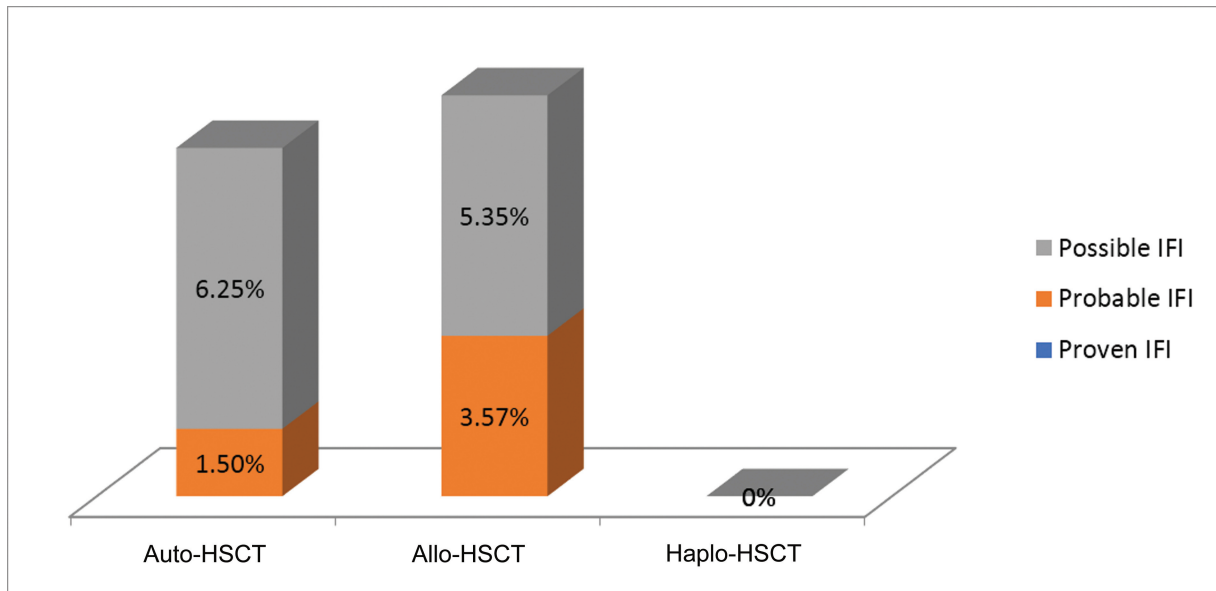
Fig. 2 The type of hematopoietic stem cell transplant (HSCT) in the recepient. IFI, invasive fungal infection.

Table 2 Comparison of CT findings, antifungal prophylaxis, and treatment

CT finding		IFI	No-IFI	*p*-Value
Atelectasis	Yes	5 (50%)	7 (6%)	0.00
	No	5 (50%)	109 (94%)	
Nodule	Yes	7 (70%)	3 (2.6%)	0.00
	No	3 (30%)	113 (97.4%)	
Halo sign	Yes	1 (10%)	0(0%)	0.079
	No	9 (90%)	116 (100%)	
Air crescent sign	Yes	Nil	Nil	Constant
	No	10 (100%)	116 (100%)	
Reverse halo	Yes	Nil	Nil	Constant
	No	10 (100%)	116 (100%)	
GGO	Yes	7 (70%)	7 (6%)	0.00
	No	3 (30%)	109 (94.0%)	
Cavity	Yes	1 (10%)	0 (0%)	0.079
	No	9 (90%)	116 (100%)	
Consolidation	Yes	4 (40%)	5 (4.3%)	0.002
	No	6 (60%)	111 (95.7%)	
Pleural effusion	Yes	3 (30%)	4 (3.4%)	0.011
	No	7 (70%)	112 (96.6%)	
Previous fungal infection	Yes	0 (0%)	5 (4.3%)	0.657
	No	10 (100%)	111 (95.7%)	
Prophylaxis	Fluconazole	4 (40%)	74 (63.7%)	0.178
	Posaconazole	2 (20%)	18 (15.51%)	0.659
	Voriconazole	1 (10%)	3 (2.6%)	0.284
	Liposomal amphotericin B	1 (10%)	NIL	0.079
	Micafungin	2 (20%)	21 (18.1%)	1

(*Continued*)

Table 2 (Continued)

CT finding		IFI	No-IFI	p-Value
Treatment	Echinocandin	8 (80%)	62 (53.4%)	0.105
	Liposomal amphotericin B	6 (60%)	17 (14.7%)	0.00
	Voriconazole given	4 (40%)	2 (1.7%)	0.00
CMV-positive-treatment	Valganciclovir/Ganciclovir	2 (20%)	5 (4.3%)	0.096
	Not given	8 (80%)	111 (95.7%)	
Rifle	Risk	5 (100%)	16 (64%)	0.463
	Injury	0 (0%)	5 (20%)	
	Failure	0 (0%)	2 (8.0%)	
	End-stage renal disease	0 (0%)	2 (8.0%)	
Overall survival	Alive	8 (80%)	95 (81.9%	0.578
	Death	2 (20%)	21 (18.1%)	
28 Day outcome	Alive	9 (90%)	103 (88.8%)	0.693
	Death	1 (10%)	13 (11.2%)	

Abbreviations: CMV, cytomegalovirus; CT, computed tomography; GGO, ground-glass opacity; IFI, invasive fungal infection.

prior HSCT. Among the HSCT populations, 78.9% were autologous and 4.2% were allogenic. Interestingly 54.6% of allogeneic or cord blood HSCT had GVHD at the time of diagnosis of IFI and 10% of which had acute GVHD. The epidemiology and mortality (30-day mortality 22.1%) of overall IFI reported by Asian centers were similar to the western data. IFI included *Aspergillus* spp. (65.9%) or *Candida* spp. (26.7%).[11]

In our study, the overall rate of IFI (possible cases included) was auto-HSCT ($n = 5$; 7.81%) and allo-HSCT ($n = 5$; 8.92%). Among auto-HSCT, the rate of IFI was as follows: proven $= 0$, probable $n = 1$ (1.5%), and possible $n = 4$ (6.25%). Among allo-HSCT, proven $= 0$, probable $n = 2 (3.57\%)$, and possible $n = 3 (5.35\%)$. If we exclude possible cases, the IFI rates were as follows: auto-HSCT $n = 1$ (1.56%) and allo-HSCT $n = 2 (3.57\%)$. Compared to the Asian study, the IFI incidence in HSCT was lower. This may be due to the good infection control practices in our hospital as well as the use of antifungal prophylaxis. Interestingly, there was no IFI among haplo-HSCT cases. The overall mortality rate of IFI was 2/10 (20%) in our study. The overall survival was better in IFI cases than in other studies. This could be due to the availability of timely targeted therapy. However, larger multicenter studies are needed to comment on the effectiveness of individual antifungal agents as prophylactic or therapeutic agents.

Prolonged neutropenia, prior IFI, GVHD, CMV infections, intensified immunosuppressive therapy (high-dose cortisone and basiliximab or etanercept), and environmental conditions were documented as possible risk factors for IFI in HSCT patients in different studies.[4,7,8,12,13] In our study, out of the 126 patients, 63 (50%) patients had acute GVHD. Of these, 5 patients had IFI, and the remaining 58 patients did not have IFI. So, among 10 patients of IFI, 5 (50%) had GVHD and among 116 patients without IFI 58 patients (50%) had GVHD. Again, the small number of patients with IFI makes the risk factor assessment difficult. The choice of antifungal prophylaxis in HSCT is a dynamic topic, with the guidelines

being updated live. A randomized controlled trial in 2007 by Ullmann et al compared posaconazole with fluconazole in severe GVHD and posaconazole was found to be similar to fluconazole for preventing the overall fungal infections among patients with GVHD. In this study, however, posaconazole was found to be superior in preventing invasive aspergillosis and reducing the rate of deaths related to fungal infections.[14] ECIL (European Conference on Infections in Leukaemia) 2018 guideline makes specific antifungal prophylaxis recommendations for pre-engraftment and post-engraftment phase. In ECIL, a recommendation of A is better than B or C. In the pre-engraftment phase, fluconazole received A level recommendation in settings with low mold infection rate. Itraconazole oral solution, posaconazole solution or tablet, voriconazole, and micafungin received B level recommendation. Liposomal amphotericin B had a C level recommendation. There was no data on caspofungin and anidulafungin. In the post-engraftment phase, posaconazole solution or tablet has A level recommendation, while voriconazole and itraconazole received B, and liposomal amphotericin B and micafungin received C level recommendation.[15] There was a strong recommendation against using fluconazole in the post-engraftment phase. A recent meta-analysis by Wang et al comparing antifungal prophylaxis in hematological disorder and HSCT patients provides much insightful data.[16] Posaconazole treatment was associated with a significant reduction in IFIs (relative risk [RR], 0.57; 95% confidence interval [CI], 0.42–0.79) and invasive aspergillosis (RR, 0.36; 95% CI, 0.15–0.85) compared with placebo. However, posaconazole was associated with a higher incidence of withdrawal because of the adverse effects of the drug. Voriconazole was associated with a significant reduction in invasive candidiasis (RR, 0.15; 95% CI, 0.09–0.26) compared with placebo. They have concluded that in terms of the prevention of IFIs and tolerance, voriconazole may be the best prophylactic option for patients undergoing HSCT, and

posaconazole may be the best prophylactic option for patients with AML or MDS.[16]

In our study, all the 126 patients were on one or the other antifungal prophylaxis such as fluconazole (78; 61.9%), posaconazole (20; 15.87%), voriconazole (4; 3.17%), liposomal amphotericin B (1; 0.79%), and micafungin (23; 18.25%). There was no incidence of intolerance-related discontinuation of antifungal prophylaxis among our patient population. Interestingly, overall only one-third of patients received antimold prophylaxis (voriconazole, posaconazole, amphotericin B, micafungin), but the overall mold infection was lower than the reported literature. However, it is noteworthy that at the onset of fever, the fluconazole was changed to a mold active agent, as a part of empirical management of febrile neutropenia protocol. Hence, most patients received a mold active agent, though not strictly as a prophylactic agent. This could be one of the main reasons why the overall IFI rate was very low. The good infection control practices could have very well contributed to the low IFI rates. In our study, there was no incidence of candidemia. None of the 5 out of 7 patients of possible IFI cases had serum BDG level above the cutoff of 80 pg/mL. This was based on the manufacturer cutoff that also showed a very good negative predictive value of 94% for IFI in hematological malignancy patients in a study by Azoulay et al in 2016.[17] The absence of a single case of candidemia could be due to the fact that all patients had received antifungal prophylaxis.

Several studies have reported an association between CMV viremia and IFI. Yong et al showed that CMV viremia and recipient CMV serostatus also increased the risk of both early and late-onset IFI. Treatment-related factors, such as ganciclovir-induced neutropenia and host genetic toll-like receptor polymorphisms, might be the likely contributory factors.[12] Marchesi et al had also noticed a strong correlation between CMV and IFI. Eight cases of IFI out of a total of twelve had simultaneous or more often subsequent symptomatic CMV reactivation.[13] In our study, due to the low number of IFI cases, we could not accurately analyze the relationship between CMV and IFI.

Limitations of the Study

We could not perform a diagnostic autopsy for those who died during hospital stay. Hence, the actual number of IFI may be underestimated. The majority of the IFI cases were diagnosed and treated as possible/probable IFI. There was no proven IFI in this group of patients because invasive investigations were usually deferred due to various reasons, especially in the neutropenic phase. Our data reflects the real-life scenario where majority of the IFI cases in HSCT setting are diagnosed as probable or possible. However, this caveat in no way underestimates the prevalence of IFI, as invasive investigation helps in reclassifying a probable or possible case into a proven one. We used EORTC/MSG 2008 cutoff value for the galactomannan. This value has been recently updated to a higher cutoff, increasing the specificity. Using the older cutoff has not affected the sensitivity. This study is not powered enough to comment on the risk factors

of IFI or compare the effectiveness of different antifungal prophylaxis/treatment options, as the total number of IFI cases was very low.

Conclusion

The overall rate of IFI in HSCT patients in our setting was low. Larger multicenter studies are needed to assess the current epidemiology and risk factors of IFI in HSCT patients in India, in the era of improved diagnostic techniques and newer antimicrobial prophylactic agents.

Ethical Committee and Institutional Review Board Approval

The study was performed after prior formal approval of the study protocol by the properly constituted institutional ethics committee. UHID number of patients was used for identification. The names and personal identification were not revealed. The entire data was confined exclusively to the primary investigators' group members.

Conflict of Interest

Presenting author has received lecture fees, advisory fees, travel or research grant, from Cipla, Glenmark, Pfizer, Sanofi, Astellas, Mylan, Natco, Biomerioux, Bharath Serum, GSK.
Other authors none to disclose.

References

1 Mikulska M, Raiola AM, Bruno B, et al. Risk factors for invasive aspergillosis and related mortality in recipients of allogeneic SCT from alternative donors: an analysis of 306 patients. Bone Marrow Transplant 2009;44(06):361–370

2 Pagano L, Caira M, Candoni A, et al. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. Haematologica 2006;91(08):1068–1075

3 Choi J-K, Cho SY, Yoon SS, et al. Epidemiology and risk factors for invasive fungal diseases among allogeneic hematopoietic stem cell transplant recipients in Korea: results of "RISK" study. Biol Blood Marrow Transplant 2017;23(10):1773–1779

4 Baddley JW, Stroud TP, Salzman D, Pappas PG. Invasive mold infections in allogeneic bone marrow transplant recipients. Clin Infect Dis 2001;32(09):1319–1324

5 Hagen EA, Stern H, Porter D, et al. High rate of invasive fungal infections following nonmyeloablative allogeneic transplantation. Clin Infect Dis 2003;36(01):9–15

6 Harrison N, Mitterbauer M, Tobudic S, et al. Incidence and characteristics of invasive fungal diseases in allogeneic hematopoietic stem cell transplant recipients: a retrospective cohort study. BMC Infect Dis 2015;1–9

7 Maziarz RT, Brazauskas R, Chen M, et al. Pre-existing invasive fungal infection is not a contraindication for allogeneic HSCT for patients with hematologic malignancies: a CIBMTR study. Bone Marrow Transplant 2017;52(02):270–278

8 Shi JM, Pei XY, Luo Y, et al. Invasive fungal infection in allogeneic hematopoietic stem cell transplant recipients: single center experiences of 12 years. J Zhejiang Univ Sci B 2015;16(09): 796–804

9 Chandy M, Srivastava A, Dennison D, Mathews V, George B. Allogeneic bone marrow transplantation in the developing world: experience from a center in India. Bone Marrow Transplant 2001; 27(08):785–790

10 George B, Menon H, Bhurani D, et al. A Prospective Observational Multi-institutional Study on Invasive Fungal Infections Following Chemotherapy for Acute Myeloid Leukemia (MISFIC Study): A Real World Scenario from India. Indian J Hematol Blood Transfus 2020;36(01):97–103

11 Hsu LY, Lee DG, Yeh SP, et al. Epidemiology of invasive fungal diseases among patients with haematological disorders in the Asia-Pacific: a prospective observational study. Clin Microbiol Infect 2015;21(06):594.e7–594.e11

12 Yong MK, Slavin MA, Kontoyiannis DP. Invasive fungal disease and cytomegalovirus infection: is there an association? Curr Opin Infect Dis 2018;31(06):481–489

13 Marchesi F, Pimpinelli F, Di Domenico EG, et al. Association between CMV and invasive fungal infections after autologous stem cell transplant in lymphoproliferative malignancies: opportunistic partnership or cause-effect relationship? Int J Mol Sci 2019;20(06):1373

14 Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med 2007;356(04):335–347

15 Maertens JA, Girmenia C, Brüggemann RJ, et al; European Conference on Infections in Leukaemia (ECIL), a joint venture of the European Group for Blood and Marrow Transplantation (EBMT), the European Organization for Research and Treatment of Cancer (EORTC), the Immunocompromised Host Society (ICHS) and; European Conference on Infections in Leukaemia (ECIL), a joint venture of the European Group for Blood and Marrow Transplantation (EBMT), the European Organization for Research and Treatment of Cancer (EORTC), the Immunocompromised Host Society (ICHS) and the European LeukemiaNet (ELN). European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia. J Antimicrob Chemother 2018;73(12):3221–3230

16 Wang J, Zhou M, Xu JY, Zhou RF, Chen B, Wan Y. Comparison of antifungal prophylaxis drugs in patients with hematological disease or undergoing hematopoietic stem cell transplantation: a systematic review and network meta-analysis. JAMA Netw Open 2020;3(10): e2017652

17 Azoulay E, Guigue N, Darmon M, et al. (1, 3)-β-D-glucan assay for diagnosing invasive fungal infections in critically ill patients with hematological malignancies. Oncotarget 2016;7(16):21484–21495