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

Abdul Ghafur¹ Bikram Das¹ T. Raja² Jose Easow² Radhika Kartikeyan¹ Benjamin M. Easow¹ S. G. Ramanan²

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

South Asian J Cancer

Abstract

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

How to cite this article: Ghafur A, Das B, Raja T, et al. Invasive Fungal Infection in Hematopoietic Stem Cell Transplant Recipient from an Indian Oncology Setting. South Asian J Cancer 2023;00(00):00–00


© 2023. MedIntel Services Pvt Ltd. All rights reserved. This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (https://creativecommons.org/licenses/by-nc-nd/4.0/) Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India
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. Mold infection is more common than yeast infection in some studies. 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. 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 ± 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
analyzing other risk factors as well (meaningful. We experienced the same limitation while comparison of the rate of IFI in different groups will not be
the study population was very low (10/126) and hence any
However, the number of patients with fungal infections in
and micafungin (23; 18.25%) were the antifungal agents used
iconazole (4; 3.17%), liposomal amphotericin B (1; 0.79%),
Atelectasis, nodules, and ground-glass opacities were
more common in the computed tomography chest of IFI
age. Total body irradiation was given to 24 (19%) patients.
Harrison et al performed a retrospective cohort study of
allo-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.
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, 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

Fig. 1 The spectrum of hematological malignancies in the hematopoietic stem cell transplant recipient. 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%)
idio-
pathic myelofibrosis (n = 1; 0.79%), and myelodysplastic
syndrome (MDS, n = 1; 0.79%; – Fig. 1).
Majority of the patients (n = 111; 88%) received myelo-
ablative conditioning and 15 (12%) non-myeloablative condi-
tioning. Total body irradiation was given to 24 (19%) patients.
Fluconazole (78; 61.9%), posaconazole (20; 15.87%), vor-
iconazole (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 differ-
ence 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, proba-
able = 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.

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

Spectrum of hematological malignancy

Fig. 2

IFI in HSCT Recipient from an Indian Oncology Setting Ghafur et al.
molds infections were found in the late phase. Overall, 60% of the IFI had late presentation more than 100 days after transplant.  

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

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

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

**Abbreviations:** ALL, acute lymphoblastic leukemia; AML, acute myeloid 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.
**Fig. 2** The type of hematopoietic stem cell transplant (HSCT) in the recipient. IFI, invasive fungal infection.

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

<table>
<thead>
<tr>
<th>CT finding</th>
<th>IFI</th>
<th>No-IFI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atelectasis</td>
<td>Yes</td>
<td>5 (50%)</td>
<td>7 (6%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>5 (50%)</td>
<td>109 (94%)</td>
</tr>
<tr>
<td>Nodule</td>
<td>Yes</td>
<td>7 (70%)</td>
<td>3 (2.6%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>3 (30%)</td>
<td>113 (97.4%)</td>
</tr>
<tr>
<td>Halo sign</td>
<td>Yes</td>
<td>1 (10%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>9 (90%)</td>
<td>116 (100%)</td>
</tr>
<tr>
<td>Air crescent sign</td>
<td>Yes</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>10 (100%)</td>
<td>116 (100%)</td>
</tr>
<tr>
<td>Reverse halo</td>
<td>Yes</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>10 (100%)</td>
<td>116 (100%)</td>
</tr>
<tr>
<td>GGO</td>
<td>Yes</td>
<td>7 (70%)</td>
<td>7 (6%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>3 (30%)</td>
<td>109 (94.0%)</td>
</tr>
<tr>
<td>Cavity</td>
<td>Yes</td>
<td>1 (10%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>9 (90%)</td>
<td>116 (100%)</td>
</tr>
<tr>
<td>Consolidation</td>
<td>Yes</td>
<td>4 (40%)</td>
<td>5 (4.3%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>6 (60%)</td>
<td>111 (95.7%)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>Yes</td>
<td>3 (30%)</td>
<td>4 (3.4%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>7 (70%)</td>
<td>112 (96.6%)</td>
</tr>
<tr>
<td>Previous fungal infection</td>
<td>Yes</td>
<td>0 (0%)</td>
<td>5 (4.3%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>10 (100%)</td>
<td>111 (95.7%)</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Fluconazole</td>
<td>4 (40%)</td>
<td>74 (63.7%)</td>
</tr>
<tr>
<td></td>
<td>Posaconazole</td>
<td>2 (20%)</td>
<td>18 (15.51%)</td>
</tr>
<tr>
<td></td>
<td>Voriconazole</td>
<td>1 (10%)</td>
<td>3 (2.6%)</td>
</tr>
<tr>
<td></td>
<td>Liposomal amphotericin B</td>
<td>1 (10%)</td>
<td>NIL</td>
</tr>
<tr>
<td></td>
<td>Micafungin</td>
<td>2 (20%)</td>
<td>21 (18.1%)</td>
</tr>
</tbody>
</table>

(Continued)
prophylaxis in HSCT is a dynamic topic, with the guidelines and among 116 patients without IFI 58 patients (50%) had not have IFI. So, among 10 patients of IFI, 5 (50%) had GVHD these, 5 patients had IFI, and the remaining 58 patients did 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. 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. 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. 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

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

Abbreviations: CMV, cytomegalovirus; CT, computed tomography; GGO, ground-glass opacity; IFI, invasive fungal infection.
posaconazole may be the best prophylactic option for patients with AML or MDS.\textsuperscript{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, amphoterica 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.

Funding

The study was carried out with the research grant from Cipla Pharmaceuticals, as an investigator-initiated study. The design or data collection of the study and the content of the paper are in no way influenced by the grant provider.

Conflicts 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


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


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


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
