ORIGINAL ARTICLE

DOI: 10.4274/nkmj.galenos.2024.25152
Nam Kem Med J 2024;12(4):310-317

A Single-Center Retrospective Evaluation of The Incidence and Survival of Invasive Fungal Infection in Allogeneic Stem Cell Transplant Patients

Allojeneik Kök Hücre Nakli Yapılan Hastalarda İnvazif Fungal Enfeksiyon Sıklığının, Risk Faktörlerinin ve Sağkalıma Etkisinin Retrospektif Değerlendirilmesi

Emre ODABAŞ[1], Ajda GÜNEŞ[2], Nur SOYER[2], Mahmut TOBU[2], Fahri ŞAHİN[2], Güray SAYDAM[2], BİLGİN ARDA[3], Filiz VURAL[2]

[1]İskenderun State Hospital, Clinic of Gastroenterology, Hatay, Turkey
[2]Ege University Medical Faculty Hospital, Department of Internal Medicine, Division of Hematology, İzmir, Turkey
[3]Ege University Medical Faculty Hospital, Department of Infectious Diseases and Clinical Microbiology, İzmir, Türkiye

ABSTRACT

Aim: The incidence of invasive fungal infection (IFI) is high in patients undergoing allogeneic hematopoietic stem cell transplantation. Despite new antifungal agents, IFI is still an important cause of mortality. Our study aimed to determine the risk factors of IFI and its effect on mortality.

Materials and Methods: One hundred and fifty-four patients who underwent allogeneic transplantation were included in the study. Demographic characteristics, underlying disease, transplantation characteristics, and IFI status of all patients were evaluated retrospectively. The study group was divided into two: 75 patients with definite, high probability and possible IFI (group 1) and 79 patients without IFI (group 2) according to the criteria of the international committee.

Results: Of 154 patients, 92 were male (59.7%) and 62 were female (40.3%) with a mean age of 41.87±14.04 years (range: 18-67 years). The most common transplant indication was acute myeloid leukemia in 58 patients (37.7%). In the analyzes performed on two groups, more IFI were observed in those who had acute graft-versus-host disease after transplantation (p= 0.035) and in those with CMV reactivation (p=0.002). The mean neutropenia duration was 30.89±20.40 in group 1 and 19.98±11.01 in group 2 (p=0.001). Underlying diseases, preparation regimen, donor compatibility, consanguineous marriage and IFI history were not found to be significant in terms of the development of IFI. The mortality rate due to IFI was found to be 24%. The mean duration of neutropenia was found to be longer in patients who died (p=0.02).

Conclusion: In our study, the frequency of IFI, risk factors and mortality rates were found to be similar to the literature. It would be appropriate for each center to evaluate the frequency of IFI and the risk factors that increase it and decide which treatment strategy is more beneficial for their patients.

Keywords: Allogeneic transplantation, invasive fungal infections, risk factors, mortality markers

ÖZ

Amaç: Allojeneik hematopoetik kök hücre nakli yapılan hastalarda invaziv fungal enfeksiyon (İFE) görülme sıklığı yüksektir. Yeni antifungal ajanlara rağmen İFE bu hastalarda halen önemli bir mortalite sebebidir. Çalışmamızda İFE gelişimini kolaylaştıran risk faktörlerinin ve mortaliteye etkisinin belirlenmesi amaçlanmıştır.

Gereç ve Yöntem: Allojeneik nakil yapılan 154 hasta çalışmaya dahil edildi. Tüm hastaların demografik özellikleri, altta yatan hastalığı, nakil özellikleri, İFE durumu retrospektif olarak değerlendirildi. Çalışma grubu uluslararası komitenin kriterleri kullanarak kesin, yüksek olası ve olası İFE olan 75 hasta (grup 1) ve İFE olmayan 79 hasta (grup 2) olarak ikiye ayrıldı.

Address for Correspondence: Emre ODABAŞ MD, İskenderun State Hospital, Clinic of Gastroenterology, Hatay, Turkey
E-mail: emre331odabas@hotmail.com **ORCID ID:** orcid.org/0000-0002-9982-0257
Received: 12.08.2024 **Accepted**: 05.10.2024

Bulgular: Yüz elli dört hastanın 92'si erkek (%59,7), 62'si kadın (%40,3) ve ortalama yaşı 41,87±14,04 (yaş aralığı: 18-67) idi. En sık nakil endikasyonu 58 hasta (%37,7) ile akut myeloid lösemi tanısıydı. İki grup üzerinden yapılan analizlerde nakil sonrası akut graft versus host hastalığı geçirenlerde (p=0,035) ve CMV reaktivasyonu görülenlerde (p=0,002) daha fazla İFE görüldü. Ayrıca grup 1'in nötropeni süresi ortalama 30,89±20,40 iken, grup 2'nin ortalama 19,98±11,01 idi (p=0,001). Hastalık tanısı, hazırlama rejimi, donör uyumu, akrabalık durumu ve İFE öyküsü ile İFE gelişimi açısından anlamlı farklılık bulunmadı. İFE nedeniyle mortalite oranı %24 saptandı. Exitus olan hastaların ortalama nötropeni süresi daha uzun bulundu (p=0,02).

Sonuç: Çalışmamızda literatürle benzer oranlarda İFE sıklığı, risk faktörleri ve mortalite oranı saptandı. Her merkezin İFE sıklığını, artıran risk faktörlerini değerlendirmesi ve hastaları için hangi tedavi stratejisinin daha yararlı olduğuna karar vermesi uygun bir seçenek olacaktır.

Anahtar Kelimeler: Allojeneik nakil, invaziv fungal enfeksiyonlar, risk faktörleri, mortalite belirteçleri

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a process that involves the infusion of stem cells from the patient (autologous HSCT) or from a human leukocyte antigen (HLA) compatible donor (allogeneic HSCT) following high-dose chemotherapy. It is a treatment method used in the treatment of many hematological, immunological and neoplastic diseases[1]. After allogeneic HSCT, immunosuppressive agents such as calcineurin inhibitors are taken for a long period of time for the prophylaxis or treatment of graft-versus-host reaction (GVHD)[2]. For this reason, patients who undergo HSCT are at high risk for serious life-threatening infections[3,4].

The incidence of invasive fungal infections (IFI) is high in patients undergoing allogeneic HSCT, and despite the recent use of new antifungal agents, IFI is an important cause of mortality in these patients. Factors such as the development of aplasia or GVHD after transplantation and the intensive use of immunosuppressive treatments also increase the risk of IFI[5,6]. In 2008, the European Organization for Research and Treatment of Invasive Fungal Infections Cooperative Group/ National Institute of Allergy and Infectious Diseases Mycosis Study Group (EORTC/MSG) Consensus group developed criteria for the classification of potential cases according to the probability of IFI, and these were revised in 2020[7,8]. As the frequency of antifungal prophylaxis increases, the importance of determining the patient group at risk for IFI increases[5,6]. Risk factors include the type of disease requiring allogeneic HSCT, type of preparatory regimen, history of previous IFI, presence of HLA compatibility, type and duration of prophylactic antifungal treatment, development and severity of acute or chronic GVHD after allogeneic transplantation, intensive treatment due to GVHD development, and cytomegalovirus (CMV) reaction[5,6,9-13].

Over the past 20 years, the epidemiology of IFI has changed with the prophylactic use of fluconazole against Candida albicans, and mold infections have become more common[14-17].

Changes in transplantation practices, including unrelated or haploidentical donor preferences, conditioning regimens, and strategies for diagnosing and treating IFI, likely influence the epidemiology and outcomes of IFI[16-19]. Although the frequency and response rates of IFI in allogeneic HSCT vary in the literature, the average frequency has been reported to be 10% to 26% and the mortality rate has been reported to be 40% to 90%, depending on the presence of risk factors[6,18,20,21,22].

The aim of this single-center and retrospective study was to evaluate the frequency, risk factors, clinical picture, treatment and survival of IFI in patients undergoing allogeneic stem cell transplantation.

MATERIALS AND METHODS

Patient Selection

All patients hospitalized in the adult hematology clinic of Ege University between 2011 and 2017, who underwent allogeneic stem cell transplantation regardless of indication, who were over 18 years of age and whose data were completely available, were included in the study. Exclusion criteria included transplantation for non-hematological malignancies or solid tumors. Patients who underwent multiple allogeneic HSCT during the study period were evaluated separately at the time of the second or third transplantation. Data were collected independently for each transplantation.

Study Design

A total of 154 patients who met our study criteria were included. All patients' data were retrospectively scanned from their medical files and the hospital's digital data system. Collected variables included the subject's demographic characteristics, underlying disease, transplant characteristics, IFI type, ad outcome.

Underlying disease and transplant characteristics included diagnosis of hematologic malignancy (according to the French-American-British criteria) or type and status of other underlying disease, donor type, HLA compatibility, regimen type (myeloablative, non-myeloablative), age at transplantation, and presence of previous IFI.

Features observed during follow-up of patients who underwent allogeneic transplantation were also recorded. Immunological risk factors (duration of neutropenia, duration of intensive care, presence of acute GVHD, GVHD treatment, CMV response)

and features related to IFI (primary and secondary prophylactic antifungal use status, type of antifungal used in prophylaxis, time of onset and duration) were recorded.

EORTC/MSG criteria were used to evaluate the presence of IFI, and blood galactomannan antigen positivity, high-resolution computed tomography findings, pathological evidence, and culture evidence were recorded. The patient group was divided into two. The first group consisted of 75 patients with definite, highly probable, and possible IFI using EORTC/MSG criteria. The definitions for IFI are summarized in Figure 1. Among these patients, there were patients who were started on antifungal treatment due to fever of unknown origin and were included in the probable IFI group. The other group consisted of 79 patients without IFI. All analyses were performed on these two groups. In patients who received IFI treatment, the type of IFI, the day of transplantation on which it developed, empirical treatment status, the type of antifungal drug used in treatment and any changes, the response to IFI after treatment, and the cause of death, if any, were recorded.

The study was carried out after obtaining the necessary permissions from the Clinical Research Ethics Committee of the Ege University Faculty of Medicine (decision no: 17-2/7, date: 13.03.2017).

Statistical Analysis

SPSS computer package program was used for statistical analyses. Data were given as number, percentage, mean and standard deviation. Frequency tables were used when evaluating study data. chi-square test and/or Fisher's exact test were used in statistical analyses. Wilcoxon W or Mann-Whitney U test was used for comparison of independent means. Significance level was taken as $p<0.05$.

RESULTS

General Patient Characteristics

A total of 154 patients who underwent allogeneic HSCT were included in the study. The mean age of the patients was 41.87±14.04 years (age range: 18-67), consisting of 92 males (59.7%) and 62 females (40.3%). The duration of hospitalization of the patients ranged from 25 to 195 days (median value: 47 days).

The most common allogeneic HSCT indication was acute myeloid leukemia diagnosis in 58 patients (37.7%). The graft source in all patients was granulocyte colony stimulation factor stimulated peripheral blood. Demographic data and transplantation-related characteristics of the patients (HLA compatibility, donor type, regimen type) are given in Table 1.

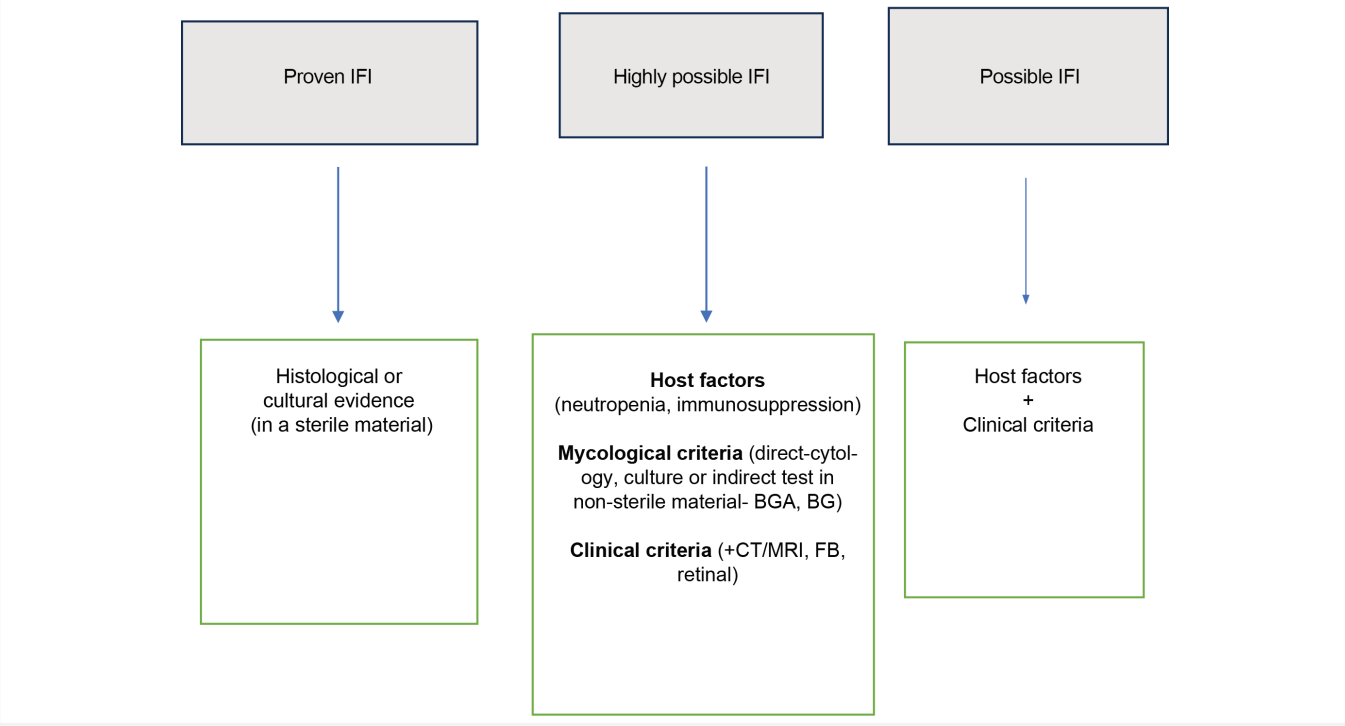

Figure 1. The main criteria of proven, highly possible and possible fungal infections

IFI: Invasive fungal infection, BGA: Galactannan antigen in the blood, BG: 1,3-β-d-glukan, CT: Computed tomography, FB: Flexible bronchoscopy, MRI: Magnetic resonance imaging

Thirty-four of the patients included in the study had acute GVHD. Twenty-nine of these 34 patients were treated with methylprednisolone. Five patients were given multiple treatments and photophoresis was applied after methylprednisolone. After transplantation, CMV-DNA elevation was observed in 46 of 154 patients. While antifungal treatment received due to IFI before transplantation was continued in five patients, 149 patients were given prophylactic antifungal treatment, 20 of which were for secondary prophylaxis (Table 2).

In 75 patients, according to EORTC/MSG criteria, 9 patients were diagnosed with proven IFI, 19 patients with high probability, and 47 patients with possible IFI (Group 1). No IFI findings developed in 79 patients and were included in the group that did not develop IFI (Group 2) (Table 2). In 7 of the 9 patients in the proven IFI group, the source of infection pathogen was isolated. The IFI characteristics of these 9 patients (patients' culture, pathology, CGA positivity, and CT findings and growth status) are summarized in Table 3.

Of the 75 patients who developed IFI, 26 out of 32 patients whose infection focus could be determined had IFI focus in the lungs, while 5 patients had other organ involvement. Nine of the patients who developed IFI received targeted therapy, 37 received preemptive therapy, and 29 received empirical therapy. The most preferred agent in first-line therapy was liposomal amphotericin-B (L-AmB) 43 (57.3%), followed by caspofungin with 32%. Voriconazole was not preferred in empirical therapy. L-AmB and caspofungin were preferred at approximately the same rates in empirical therapy. Antifungal

Table 1. Demographic characteristics of patients

Patient characteristics	Number (%) n=154 (100)
Age, year	
Mean ± SD	41.87±14.04
Median (min-max)	44 (18-67)
Male/Female (%)	92/62 (59.7/40.3)
Diagnoses (%)	
Acute myeloid leukemia	58 (37.7)
Acute lymphocytic leukemia	24 (15.6)
Myelodysplastic syndrome	19 (12.3)
Lymphomas	19 (12.3)
Myeloma	14 (9.1)
Aplastic anemia	8 (5.2)
Chronic leukemia	7 (4.5)
Myelofibrosis	5 (3.2)
Donor type	
Relative	136 (88.3)
HLA compatibility (A, B, DRB1, C and DQ pairs)	
10/10 (full)	126 (81.8)
9/10 (good)	18 (11.7)
5-8/10 (partial match, haploidentical transplantation)	10 (6.5)
Regime type	
Myeloablative	88 (57.1)
Duration of hospitalization (day)	
Mean ± SD	58.44±29.07
Median (min-max)	47 (25-195)
Acute GVHD	34 (22.1)
CMV response, present	46
Duration of hospitalization (day)	
Mean ± SD	25.29±17.12
Median (min-max)	20 (5-87)

SD: Standard deviation, HLA: Human leukocyte antigen, GVHD: Graft Versus Host Disease, CMV: Cytomegalovirus, SD: Standard deviation

Table 2. Fungal infection history and current status of patients with allogeneic HSCT

All patients n=154 (%)	
Those with history of IFI	65 (42.2)
Antifungal prophylaxis status	**n=154 (%)**
Primary prophylactic antifungal use, yes	129 (83.8)
Secondary prophylactic antifungal use, yes	20 (13)
Those getting active fungal infection therapy during allogeneic HSCT	5 (3.2)
Prophylactic antifungal type	**n=149 (%)**
Fluconazole	88 (59.1)
Posaconazole	44 (29.5)
Voriconazole	17 (11.4)
Fungal infection (according to EORTC/MSG criteria)	**n=154 (%)**
Proven	9 (5.9)
Highly possible	19 (12.3)
Possible	47 (30.5)
Impossible	79 (51.3)
Those with BGA positivity	26 (16.9)
Those with findings on CT	34 (22.1)
Fungal agent growth in culture, yes	7 (4.5)
Pathological finding	4 (2.6)
Those with invasive fungal infection n=75(%)	
Fungal infection type	**n=75(%)**
Pneumonia	26 (34.6)
Others	5 (9.4)
Non-focused	42 (56)
Treatment type (initial treatment)	**n=75 (%)**
L-AmB	43 (57.3)
Kaspofungin	24 (32.0)
Voriconazole	8 (10.7)
Those getting dual antifungal treatment	10 (13.3)

HSCT: Hemopoietic stem cell transplantation, IFI: Invasive fungal infection, EORTC/MSG: European Organization for Research and Treatment of Cancer/ Mycoses Study Group, BGA: Blood galactomannan antigen, CT: Computed tomography, L-AmB: Liposomal amphotericin-B

change was required in 30 patients (40%). The reason for antifungal change in the majority of patients was the lack of fever response. Of the patients who underwent antifungal drug change, 8 (26.6%) were exitus. Of the 10 patients who received dual antifungal therapy, 6 (60%) were exitus. 56 patients (76%) were evaluated as responding to IFI treatment. 18 patients were accepted as exitus due to IFI and related reasons.

Patients who developed and did not develop IFI were divided into Group 1 and Group 2, and possible risk factors and mortality analyses related to IFI development were performed on these two groups. Possible risk factors for IFI and significance rates for IFI development are shown in Table 4. IFI was significantly more common in those who had acute GVHD after transplantation (p=0.035) and in those who had CMV reactivation (p=0.002). In addition, the mean neutropenia duration in Group 1 (IFI development) was 30.89±20.40 (median value: 23.00), while in Group 2 (no IFI), it was 19.98±11.01 (median value: 17.00) (p=0.001).

Table 3. Factors and findings in proven IFI patients

Proven IFI patients	Growth in culture and its location	Pathology	BGA positivity	CT finding
1	Blood culture Candida crusei	No	No	No
2	No	Maxillary sinus Aspergillus spp.	No	Yes
3	Nasal tissue culture Aspergillus flavus	Nasal biopsy Mucormicosis	Yes	Yes
4	Blood culture Trichosporon spp.	No	Yes	Yes
5	DTA Aspergillus spp.	No	No	Yes
6	Maxillary sinus Pseudallescheriae boydii	Yes	Yes	Yes
7	No	Maksiller sinus Aspergillus spp.	No	Yes
8	Tissue biopsy Aspergillus spp.	yok	No	Yes
9	Blood culture Candida kefyr Saccharomyces cerevisiae	yok	yok	var

IFI: Invasive fungal infection, BGA: Blood galactomannan antigen, CT: Computed tomography, DTA: Deep tracheal aspiration

No significant difference was found between the two groups in terms of disease diagnosis, preparation regimen, donor compatibility, consanguinity status, previous IFI history and IFI development.

12% (n=20) of all patients died. While mortality due to IFI was 24% (n=18) in 75 patients with IFI, mortality was 3% (n=2) in 79 patients without IFI (p=0.001). The mean neutropenia duration of these 18 patients was 34.78±20.06 (median value: 35.00) days, while the duration of neutropenia in the 134 surviving patients was 23.76±16.20 (median value: 19.00) days and was found to be statistically significant (p=0.02).

Table 4. Factors affecting IFI development

	Group1 (those with IFI) n=75	Group 2 (those without IFI) n=79	p-value
Presence of acute GVHD			**0.035**
Yes	22	12	
CMV infection			**0.002**
Yes	31	15	
Duration of Neutropenia (day) Median (min-max)			**0.001**
	23.0 (8-87)	17.0 (5-71)	
Disease diagnosis			**0.67**
AML	27	31	
ALL	13	11	
MDS	11	8	
Lymphoma	11	8	
MM	4	10	
AA	4	4	
Chronic leukemia	4	**3**	
Myelofibrosis	1	**4**	
HLA compatibility (A, B, DRB1, C and DQ pairs)			**0.72**
10/10 (full)	61	65	
9/10 (good)	10	8	
5-8/10 (partial)	4	6	
Donor type			**0.26**
Relative	64	72	
Non-relative	11	7	
Preparation regime			**0.09**
Myeloablative	48	40	
Non-myeloablative	39	27	
History of previous IFI			**0.44**
Var	34	31	

IFI: Invasive fungal infection, GVHD: Graft versus host disease, CMV: Cytomegalovirus, AML: Acute myeloid leukemia, ALL: Acute lymphocytic leukemia, MDS: Myelodysplastic syndrome, MM: Multiple myeloma, AA: Aplastic anemia, HLA: Human leucocyte antigen

The prophylactic antifungal duration of these 18 patients was 23.00±17.58 (median value: 23.00). The prophylactic antifungal duration of the surviving 134 of these 152 patients was 31.07±14.52 (median value: 30.00). This was found to be statistically significant (p=0.017).

DISCUSSION

In our study evaluating the frequency, treatment and outcome of IFI developing after allogeneic HSCT, we found that the presence of acute GVHD, use of high-dose corticosteroids (CS) for GVHD, CMV infection and prolonged neutropenia were risk factors for the development of IFI. In addition, the duration of neutropenia was found to be associated with mortality after transplantation.

When we examine the distribution of IFI in our study, we see that the majority of the cases are possible IFI and the fever group of unknown cause. In many studies, only proven and high probability patients were accepted for IFI and the incidence of IFI was seen between 8.8% and 26%[6,13,18,20,23,24,25]. When we looked at the proven and high probability group among IFI patients in our study, the incidence was seen to be 18.2%, similar to other studies.

The gender distribution, mean age and allogeneic HSCT indication preparation regimens in our study were similar to the literature[6,23,24,26]. Similar to the literature, the most commonly used prophylactic antifungal was fluconazole[27] and the most common focus in the group developing IFI was the lungs[25,28]. The most preferred agent in the first-line treatment was L-AmB. In empirical treatment, L-AmB and caspofungin were preferred at approximately the same rates. These treatment options were consistent with the literature[29,30,31].

In our study, the most frequently isolated agent in patients with proven IFI was aspergillus. Mold species and non-albicans candida species were found to be higher. One of the reasons for this may be the decrease in candida species due to routine prophylaxis with fluconazole. The non-c.albicans increase in recent years is also seen in our center[9,15].

In our study, disease diagnosis, HLA compatibility, donor type, and regimen type were not found to be significant in terms of IFI development. While disease diagnosis and preparation regimen type were not found to be significant in terms of IFI development in studies, there are different results in terms of HLA compatibility and donor type and IFI development in studies[6,23,25,32].

A history of previous IFI was not found to be a significant risk factor for the development of IFI, which is inconsistent with the literature[6,23,24]. This may be due to the fact that antifungal treatments were started with a diagnosis of fever of unknown cause and possible IFIs were included in the study.

In an observational study conducted by Shi et al.[6], which examined 408 patients who underwent allogeneic HSCT, a history of IFI, HLA incompatibility, prolonged neutropenia duration, and grade 3 and 4 acute GVHD development were found to be associated with the development of IFI. In another study including 1248 patients who underwent allogeneic HSCT, proven and highly probable IFI developed in 163 patients, and HLA incompatibility, duration of neutropenia, and development of GVHD were found to be risk factors for IFI[10]. In a multicenter study conducted in China, independent risk factors for proven/probable IFI in patients undergoing allogeneic HSCT were identified as diabetes, HLA-matched unrelated donor, prolonged severe neutropenia, and immunosuppressive therapy[23]. In our study, similar to the literature, the presence of acute GVHD, use of high-dose CS for GVHD, and CMV infection were found to be significant risk factors for the development of IFI[6,10,11,20,23,24,28,33]. In addition, prolonged neutropenia was found to be the most important risk factor for the development of IFI in all patient groups.

In our study, it was found that IFI significantly increased transplantation treatment mortality (24% in the IFI group, 2% in the non-IFI group). In the literature, mortality rates related to IFI vary among studies. In a multicenter observational study conducted in China and evaluating 1401 patients who underwent allogeneic HSCT, the mortality rate in patients who developed IFI, similar to our study, was found to be 25%[24]. In many studies, mortality rates ranged from 40% to 90%[21,22]. It was thought that this difference was due to the longer follow-up period in studies with higher mortality rates.

Study Limitations

The limitations of our study were evaluated as its being retrospective, single-centered, the fact that patients were followed up only during hospitalization, and the low number of proven IFIs due to the lack of further examination due to the clinical response obtained after the initiation of empirical antifungal treatment.

CONCLUSION

In our study, the presence of acute GVHD, CMV infection and long duration of neutropenia were found to be risk factors for the development of IFI. In addition, the duration of neutropenia was found to be associated with mortality after allogeneic HSCT. In the prevention and treatment of IFIs, which seriously increase transplantation mortality, it would be appropriate for each center to evaluate the frequency of IFIs, take infection control measures, antifungal prophylaxis and identify patients at high risk of IFIs and decide which treatment strategy is more beneficial.

Ethics

Ethics Committee Approval: The study was carried out after obtaining the necessary permissions from the Clinical Research Ethics Committee of the Ege University Faculty of Medicine (decision no: 17-2/7, date: 13.03.2017).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: E.O., N.S., M.T., F.Ş., G.S., B.A., F.V., Design: B.A., F.V., Data Collection or Processing: E.O., Analysis or Interpretation: E.O., A.G., N.S., M.T., F.Ş., G.S., B.A., F.V., Literature Search: E.O., A.G., F.V., Writing: E.O.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Goldman L, Schafer AI. Goldman's Cecil Medicine, 24th ed. Elsevier, 2012;1158-9.
2. Zeiser R, Blazar BR. Acute Graft-versus-host disease - biologic process, prevention, and therapy. N Engl J Med. 2017;377:2167-79.
3. Sahin U, Toprak SK, Atilla PA, Atilla E, Demirer T. An overview of infectious complications after allogeneic hematopoietic stem cell transplantation. J Infect Chemother. 2016;22:505-14.
4. Neofytos D. Antimicrobial prophylaxis and preemptive approaches for the prevention of infections in the stem cell transplant recipient, with analogies to the hematologic malignancy patient. Infect Dis Clin North Am. 2019;33:361-80.
5. Neofytos D, Horn D, Anaissie E, Steinbach W, Olyaei A, Fishman J, et al. Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance registry. Clin Infect Dis. 2009;48:265-73.
6. Shi JM, Pei XY, Luo Y, Tan YM, Tie RX, He JS, et al. Invasive fungal infection in allogeneic hematopoietic stem cell transplant recipients: single center experiences of 12 years. J Zhejiang Univ-Sci B. 2015;16:796-804
7. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis. 2008;46:1813-21.
8. Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, et al. Revision and update of the consensus definitions of invasive fungal disease from the european organization for research and treatment of cancer and the mycoses study group education and research consortium. Clin Infect Dis. 2020;71:1367-76.
9. Kontoyiannis DP, Marr KA, Park BJ, Alexander BD, Anaissie EJ, Walsh TJ, et al. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001-2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. Clin Infect Dis. 2010;50:1091-100.
10. Garcia-Vidal C, Upton A, Kirby KA, Marr KA. Epidemiology of invasive mold infections in allogeneic stem cell transplant recipients: biological risk factors for infection according to time after transplantation. Clin Infect Dis. 2008;47:1041-50.
11. Fukuda T, Boeckh M, Carter RA, Sandmaier BM, Maris MB, Maloney DG, et al. Risks and outcomes of invasive fungal infections in recipients of allogeneic hematopoietic stem cell transplants after nonmyeloablative conditioning. Blood. 2003;102:827-33.
12. Thursky K, Byrnes G, Grigg A, Szer J, Slavin M. Risk factors for post-engraftment invasive aspergillosis in allogeneic stem cell transplantation. Bone Marrow Transplant. 2004;34:115-21.
13. Omer AK, Ziakas PD, Anagnostou T, Coughlin E, Kourkoumpetis T, McAfee SL, et al. Risk factors for invasive fungal disease after allogeneic hematopoietic stem cell transplantation: a single center experience. Biol Blood Marrow Transplant. 2013;19:1190-6.
14. Slavin MA, Osborne B, Adams R, Levenstein MJ, Schoch HG, Feldman AR, et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation--a prospective, randomized, double-blind study. J Infect Dis. 1995;171:1545-52.
15. Marr KA, Seidel K, Slavin MA, Bowden RA, Schoch HG, Flowers ME, et al. Prolonged fluconazole prophylaxis is associated with persistent protection against candidiasis-related death in allogeneic marrow transplant recipients: long-term follow-up of a randomized, placebo-controlled trial. Blood. 2000;96:2055-61.
16. Marr KA, Carter RA, Boeckh M, Martin P, Corey L. Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. Blood. 2002;100:4358-66.
17. Kontoyiannis DP, Wessel VC, Bodey GP, Rolston KV. Zygomycosis in the 1990s in a tertiary-care cancer center. Clin Infect Dis. 2000;30:851-6.
18. Post MJ, Lass-Floerl C, Gastl G, Nachbaur D. Invasive fungal infections in allogeneic and autologous stem cell transplant recipients: a single-center study of 166 transplanted patients. Transpl Infect Dis. 2007;9:189-95.
19. Pagano L, Caira M, Nosari A, Van Lint MT, Candoni A, Offidani M, et al. Fungal infections in recipients of hematopoietic stem cell transplants: results of the SEIFEM B-2004 study--Sorveglianza epidemiologica infezioni fungine nelle emopatie maligne. Clin Infect Dis. 2007;45:1161-70.
20. Koldehoff M, Zakrzewski JL. Modern management of respiratory failure due to pulmonary mycoses following allogeneic hematopoietic stem-cell transplantation. Am J Hematol. 2005;79:158-63.
21. Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. Clin Infect Dis. 2001;32:358-66.
22. Dagenais TR, Keller NP. Pathogenesis of Aspergillus fumigatus in Invasive Aspergillosis. Clin Microbiol Rev. 2009;22:447-65.
23. Liu YC, Chien SH, Fan NW, Hu MH, Gau JP, Liu CJ, et al. Incidence and risk factors of probable and proven invasive fungal infection in adult patients receiving allogeneic hematopoietic stem cell transplantation. J Microbiol Immunol Infect. 2016;49:567-74.
24. Sun Y, Meng F, Han M, Zhang X, Yu L, Huang H, et al. Epidemiology, management, and outcome of invasive fungal disease in patients undergoing hematopoietic stem cell transplantation in China: a multicenter prospective observational study. Biol Blood Marrow Transplant. 2015;21:1117-26.
25. Harrison N, Mitterbauer M, Tobudic S, Kalhs P, Rabitsch W, Greinix H, et al. Incidence and characteristics of invasive fungal diseases in allogeneic hematopoietic stem cell transplant recipients: a retrospective cohort study. BMC Infect Dis. 2015;15:584.
26. Horowitz MM: Uses and Growth of Hematopoietic cell transplantation Thomas' Hematopoietic Cell Transplantation. In: Forman SJ, Negrin RS, Antin JH, Appelbaum FR, (eds). Stem Cell Transplantation 5th ed. 2015.
27. Maertens J, Marchetti O, Herbrecht R, Cornely OA, Flückiger U, Frêre P, et al. Third European Conference on Infections in Leukemia. European Conference on Infections in Leukemia. European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3--2009 update. Bone Marrow Transplant. 2011;46:709-18.
28. Maziarz RT, Brazauskas R, Chen M, McLeod AA, Martino R, Wingard JR, 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;52:270-8.

29. Walsh TJ, Teppler H, Donowitz GR, Maertens JA, Baden LR, Dmoszynska A, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. N Engl J Med. 2004;351:1391-402.
30. Morrissey CO, Gilroy NM, Macesic N, Walker P, Ananda-Rajah M, May M, et al. Consensus guidelines for the use of empiric and diagnostic-driven antifungal treatment strategies in haematological malignancy, 2014. Intern Med J. 2014;44:1298-314.
31. Hebart H, Klingspor L, Klingebiel T, Loeffler J, Tollemar J, Ljungman P, et al. A prospective randomized controlled trial comparing PCR-based and empirical treatment with liposomal amphotericin B in patients after allo-SCT. Bone Marrow Transplant. 2009;43:553-61.
32. Girmenia C, Raiola AM, Piciocchi A, Algarotti A, Stanzani M, Cudillo L, et al. Incidence and outcome of invasive fungal diseases after allogeneic stem cell transplantation: a prospective study of the Gruppo Italiano Trapianto Midollo Osseo (GITMO). Biol Blood Marrow Transplant. 2014;20:872-80.
33. Hovi L, Saarinen-Pihkala UM, Vettenranta K, Saxen H. Invasive fungal infections in pediatric bone marrow transplant recipients: single center experience of 10 years. Bone Marrow Transplant. 2000;26:999-1004.