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Epidemiology and analysis of invasive fungal infections in patients with hematological malignancies: a single-center real-life experience

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Background/aim: Invasive fungal infection (IFI) causes morbidity and mortality among patients with hematological malignancies. We evaluated the incidence and treatment characteristics of IFIs between October 2012 and December 2013.

Materials and methods: Patients who received chemotherapy or stem cell transplantation were retrospectively evaluated. Fungal infections were classified according to EORTC criteria.

Results: Prophylaxis and antifungal therapy were given in 30.5% and 23.6% of 522 chemotherapy courses, respectively. The incidence of proven/probable IFI was 6.7%. The incidence of IFI among patients who received prophylaxis was significantly higher than among those who did not receive it (11.3% vs. 4.6%, P = 0.005). There was no significant difference between patients who received mold-active and no mold-active prophylaxis (P = 0.098). The most common single agent therapy and causative pathogen was liposomal amphotericin B (57.1%) and *Aspergillus* (n = 5), respectively. IFI-attributable mortality rate was 14.2% in 6 weeks.

Conclusion: The IFI incidence and mortality rate were similar to that reported in the literature. The IFI rate was higher in the group using prophylaxis, as this is a high-risk group. Although the IFI rate was not significantly different between groups using prophylaxis, patients should be followed closely for the effective use of posaconazole prophylaxis.

Key words: Invasive fungal infection, treatment, prophylaxis, hematological malignancies, epidemiology

1. Introduction

Invasive fungal infection (IFI) causes morbidity and mortality among patients with hematological malignancies who receive chemotherapy or hematopoietic stem cell transplantation (HSCT). The incidence of IFI has increased worldwide over the last two decades (1–3). Prolonged neutropenia, HSCT, and underlying disease, particularly acute leukemia, have been identified as risk factors for IFI (4–6). In recent years, epidemiological studies have revealed that the incidence of candidiasis has been decreasing, whereas the incidence of aspergillosis has been increasing (2,3,6,7). Using novel agents, the development of diagnostic methods and early administration of antifungal therapy has improved the management of IFIs (8).

Many studies have investigated the incidence and treatment outcomes of IFIs in selected hematological malignancies or treatment modalities (8–10). The first purpose of this study was to evaluate the incidence of IFIs in patients receiving chemotherapy for hematological malignancies. The second purpose of the study was to determine the epidemiology, antifungal prophylaxis, and antifungal prescriptions of IFIs and the treatment outcomes of proven and probable IFIs in our cohort at a Turkish university hospital.

2. Materials and methods

Our hematology unit contains 7 conventional single rooms, 6 single rooms with HEPA filtration and positive pressure isolation, and 30 conventional double rooms. We conducted this monocentric and retrospective study to describe our fungal infection and antifungal treatment status. All hospitalized patients with hematological malignancies who received chemotherapy or HSCT between 1 October 2012 and 31 December 2013 were included this study. Patient diagnosis, treatment phase, clinical signs, imaging and microbiological results, prophylaxis, antifungal treatment, treatment outcomes, and reasons for changing the therapy were recorded.

IFIs were classified according to EORTC criteria as possible, probable, and proven (11). Basically, these

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criteria demand clinical features in combination with host factors for a possible diagnosis. Probable IFI requires the presence of host factors, clinical features, and certain microbiological criteria (e.g., serum galactomannan), whereas a proven diagnosis demands histopathological findings or positive culture from a primary sterile site in combination with host factors and clinical features. In the case of proven or probable IFI, microbiological evidence was produced by bronchoscopy, blood culturing, and histology after biopsy. For patients meeting the criteria of proven IFI, data on fungal species, organs involved, method of fungal identification, treatment results, and 6-week survival were recorded.

Galactomannan (GM) testing was performed twice a week during hospitalization. GM test results with an optical density index (ODI) of ≥0.5 are considered positive at our center. These results were obtained over a period of 7 days.

Complete response was defined as the resolution of all signs of IFI, and partial response was defined as clinical and radiological improvement or resolution of all attributable symptoms and signs of fungal disease. Radiological stabilization can be equated with a partial response. Stable response was defined as minor or no improvement in signs of disease and radiological stabilization, whereas progressive disease was defined as worsening clinical symptoms or signs of disease and new sites of disease or radiological worsening of preexisting lesions (12).

As this was an observational study, diagnosis and treatment practices were determined by treating physicians according to routine hospital practice. Empirical antifungal therapy was administered to patients with persistent neutropenic fever, whereas preemptive antifungal therapy was administered to those whose clinical or radiological findings were suggestive of IFIs.

2.1. Statistical analysis

Quantitative variables were described as the number and percentage while qualitative variables were the median and range. Statistical analysis was performed using the chi-square test, Fisher's exact test, or t-test as appropriate using SPSS 20.4 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Patient characteristics

We evaluated 416 patients receiving 522 chemotherapy courses. The demographics and clinical characteristics of the patients are shown in Table 1. The median age of the 416

Table 1. Demographics and clinical characteristics of patients (n = 416) treated with chemotherapy (n = 522) for hematological malignancies.

Patients characteristics	All patients (n = 416)	All chemotherapy courses (n = 522)
Median age (min–max)	57 (17–89)	57 (17–89)
Male/female (%)	259/157 (62.2/37.8)	320/202 (61.3/38.7)
Diagnoses (%)		
Acute leukemia	93 (22.3)	124 (23.8)
Myelodysplastic syndrome	30 (7.3)	35 (6.7)
Lymphoma	148 (35.6)	186 (35.6)
Myeloma	110 (26.4)	137 (26.2)
Chronic leukemia	32 (7.7)	37 (7.1)
Myelofibrosis with myeloid metaplasia	3 (0.7)	3 (0.6)
Treatment phase (%)		
Remission induction	169 (40.6)	176 (33.7)
Postremission treatment	118 (28.4)	176 (33.7)
Relapse or refractory disease treatment	49 (11.8)	62 (11.9)
Transplantation (allo/auto)	80 (19.2)	108 (20.7)
Previous IFI (n, %)	4 (0.9)	6 (1.1)
Antifungal prophylaxis, yes (%)	122 (29.3)	159 (30.5)
Mold-active	48 (11.5)	60 (11.4)
No mold-active	74 (17.8)	99 (19)

Allo: Allogeneic, auto: autologous, CR: complete remission, PR: partial remission.

patients was 57 years (17–89 years), and 62.2% of patients were male. The underlying diseases in the patients were acute leukemia (22.3%), lymphoma (35.6%), plasma cell disorders (26.4%), and other hematological malignancies (15.7%). The most common chemotherapy phase was remission induction (40.6%). Previous IFI history was obtained from 4 (1%) of the patients.

3.2. IFI prophylaxis

Prophylaxis was used in 159 (30.5%) of 522 chemotherapy courses. In 6 (1.1%) of 522 chemotherapy courses, voriconazole was used for secondary prophylaxis. In 54 (10.3%) and 99 (19%) of 522 chemotherapy courses, posaconazole and fluconazole were given for primary prophylaxis, respectively. The most common reasons for prophylaxis were transplantation (n = 108, 68%) and remission induction chemotherapy (n = 36, 22.6%).

All patients who underwent autologous transplantations (n = 70) received fluconazole prophylaxis. In 23 and 14 of 38 patients who underwent allogeneic transplantations, fluconazole and posaconazole were used for prophylaxis, respectively. One patient received voriconazole prophylaxis.

3.3. Incidence of IFI

Among the 522 chemotherapy courses, 9 (1.7%) were diagnosed as having proven IFI, 26 (5%) as probable IFI, and 29 (5.6%) as possible IFI, while 59 (11.3%) failed to meet the EORTC diagnostic criteria. The incidence of proven/probable IFI was 6.7%. The mean age of the patients diagnosed with proven/probable IFI and not with IFI was 55.49 ± 12.51 and 58.31 ± 15.019 years, respectively (P = 0.27). Their sex, underlying disease, treatment phase, and antifungal prophylaxis are shown in Table 2.

Table 2. Incidence of IFIs in patients treated with chemotherapy (n = 522) for hematological malignancies and antifungal therapies.

Patient characteristics	All courses	Number of IFI cases (n)	Incidence of IFI (%)
All chemotherapy	522	35	6.7
Sex			
Male	320	28	8.8
Female	202	7	3.4
Diagnoses			
Acute leukemia	124	21	16.9
AML	101	17	16.8
ALL	23	4	17.4
Myelodysplastic syndrome	35	2	5.7
Lymphoma	186	5	2.7
Myeloma	137	4	3
Chronic leukemia	37	3	8.1
MMM	3	0	0
Treatment phase			
Remission induction	176	11	6.3
Postremission treatment	176	4	2.3
Relapse or refractory disease treatment	62	10	16.1
HSCT (allo/auto)	108	10	9.3
Antifungal prophylaxis			
Yes	159	18	11.3
Mold-active	60	10	16.6
No mold-active (fluconazole)	99	8	8
No	363	17	4.6

Allo: Allogeneic, auto: autologous, AML: acute myeloid leukemia, ALL: acute lymphoblastic leukemia, MMM: myelofibrosis with myeloid metaplasia, CR: complete remission, PR: partial remission.

Compared to the overall population, the incidence of IFI was higher among patients with acute leukemia (n = 21, 16.9%, P = 0.000), those in relapse/refractory treatment phase (n = 10, 16.1%, P = 0.001), and those receiving antifungal prophylaxis (n = 18, 11.3%, P = 0.005). The risk of developing IFI was greater in males (n = 28, 8.8%, P = 0.019). The antifungal agents used in proven/probable IFIs were liposomal amphotericin B (LAmpB) (n = 20, 57.1%), caspofungin (n = 5, 14.3%), voriconazole (n = 9, 25.7%), and amphotericin B deoxycholate (AmpB) (n = 1, 2.9%). Only 2 patients were treated with a combination of two antifungal agents. One of these patients was treated with LAmpB and caspofungin for probable IFI, and the other was treated with voriconazole and LAmpB for proven IFI.

The incidence of proven/probable IFI was 11.3% in 159 chemotherapy courses using prophylaxis. Proven and probable IFIs were diagnosed in 10 (16.6%) of 60 chemotherapy courses that used mold-active prophylaxis [posaconazole (15%) and voriconazole (1.6%)] and in 8 (8%) of 99 chemotherapy courses that did not use any mold-active prophylaxis. The risk of developing IFI was similar among those receiving mold-active prophylaxis and those not receiving it (P = 0.098). One patient who received secondary prophylaxis with voriconazole was diagnosed with mucormycosis. The median time from neutropenia to the diagnosis of proven/probable IFI was 7 days (range: 1–40), the median treatment duration was 24 days (range: 5–77), and the median neutrophil count was 56/mm^3 (range: 0–10600).

Among the 108 patients who underwent HSCT (38 allogeneic HSCT recipients and 70 autologous HSCT recipients), proven/probable IFIs occurred in 10 patients (overall incidence: 9.2%). IFI-attributable mortality was 0.9% (n = 1). Of 10 patients, 6 received fluconazole prophylaxis and 4 received posaconazole prophylaxis.

3.4. Antifungal therapy

Systemic antifungal agents were used in 123 (23.6%) of 522 chemotherapy courses. The median time from neutropenia to first administration of antifungal agents was 6 days (range: 1–40), the median neutrophil count was 30/mm^3 (range: 0–10600), and the median treatment duration was 15 days (range: 1–77) in patients who received antifungal treatment. Prophylaxis was given to 71 of 123 (57.7%) chemotherapy courses that used systemic antifungal agents. There were 32 (26%) courses using fluconazole, 37 (30%) courses using posaconazole, and 2 (1.7%) courses using voriconazole. Among those using antifungal therapy, the most common underlying disease was acute leukemia (n = 69, 57%), and the most common therapy phases were remission induction (n = 44, 35.8%) and transplantation (n = 38, 30.9%).

The used antifungal agents were LAmpB (n = 68, 55.3%), caspofungin (n = 25, 20.3%), voriconazole (n = 15, 12.2%), and AmpB (n = 15, 12.2%). In 56 (45.5%) of the 123 patients, the first antifungal agent was changed into another. The reasons for changing were lack of efficacy (n = 28, 50%), adverse event (n = 22, 39.3%), and drug–drug interactions (n = 6, 10.7%). The antifungal therapy approach was preemptive in 11 (9%) and empirical in 112 (91%) chemotherapy courses.

3.5. Patient characteristics with proven and probable IFIs

Among proven and probable IFI cases, the most common underlying disease was acute leukemia (n = 21) and the most common therapy phases were remission induction (n = 11) and transplantation (n = 10). Twenty-six patients were diagnosed with probable pulmonary aspergillosis, as determined by computed tomography scan and positive GM assay.

In 9 patients with proven IFI, *Candida* (n = 2), *Mucor* (n = 2), and *Aspergillus* (n = 5) were the causative pathogens. The sites of infection among patients with proven *Aspergillosis* were lung (n = 2), nasal sinus (n = 1), and both lung and nasal sinus (n = 2). Samples were obtained from nasal sinus biopsy and bronchoalveolar lavage fluid. Two patients were diagnosed with candidemia and positive blood cultures. Patients with mucormycosis (n = 2) were identified with nasal sinus biopsies. The demographics and clinical characteristics of patients with proven IFIs are shown in Table 3. The incidence of invasive aspergillosis was 5.9%, the incidence of candidiasis was 0.4%, and the incidence of mucormycosis was 0.4% among the 522 chemotherapy courses.

3.6. Mortality

Five (14.2%) of 35 patients with proven (3 patients) and probable (2 patients) IFIs died within 6 weeks as a result of progressive IFI. Two of the 5 deaths in patients with proven/probable IFI were newly diagnosed patients who had received induction chemotherapy; one was in relapsed disease; one was in partial remission; and one was in complete remission.

4. Discussion

IFI is a prominent cause of morbidity and mortality in patients with hematological malignancies and HSCT recipients. In this retrospective study, we report the outcomes of real-life experience in patients with hematological malignancies followed and treated at our clinic.

First, the results indicated that the incidence of probable/proven IFI (6.7%) and 6-week IFI-attributable mortality (14.2%) were compatible with other studies. In the SEIFEM-2004 study, the incidence of IFI was reported as 4.6%, and IFI-attributable mortality rate was 39%, which is slightly higher than ours (6). Another study reported the incidence of probable/proven IFI as 8.5% (13). In a French study, the incidence of IFI was found to be 2.1%, and no

Table 3. Demographics and clinical characteristics of patients (n = 9) with proven IFI treated with chemotherapy (n = 522) for hematological malignancies.

Age, sex	Diagnosis	Prophylaxis	Treatment phase	Antifungal therapy	Outcome	Species
68, M	CLL	No	Consolidation	LAmpB/ Caspo	Death/PD	*Candida* spp.
51, M	MM	Posa	Transplant	LAmpB/ Vori	CR	*Aspergillus fumigatus*
52, M	AML	Vori	Reinduction	LAmpB	CR	*Mucor*
56, F	AML	Flu	Transplant	LAmpB+ Vorico	CR	*Aspergillus* spp.
66, M	NHL	Flu	Transplant	LAmpB/ Caspo	PR	*Candida* spp.
43, F	AML	Posa	Transplant	LAmpB	Death/PD	*Aspergillus fumigatus*
63, M	CLL	No	Consolidation	LAmpB/ Vori	CR	*Aspergillus* spp.
46, M	ALL	Posa	Transplant	Caspo/LAmpB	PR	*Mucor*
68, M	MDS	No	Remission induction	LAmpB/ Vori	Death/PD	*Aspergillus flavus*

LAmpB: Liposomal amphotericin B, vori: voriconazole, caspo: caspofungin, posa: posaconazole, flu: fluconazole, PD: progressive disease, CR: complete remission, PR: partial remission.

death was attributed to it (7). According to the available postmortem data, the prevalence of IFIs at autopsy was determined as 6.6% in 1993–1996 and 10.4% in 2001–2005 (14). In a Japanese study, incidence of IFI was 1.3%, but IFI-attributable mortality was 36.8% (15). In the CAESAR study, incidence of IFI was 2.1% per chemotherapy course and mortality rate was 11.7% in the proven/probable IFI (16). These outcomes indicate that mortality rates remain high, although the incidence of IFI has declined in the past decade due to improved preventive strategies.

The rate of systemic antifungal usage was 23.6% in our study. Compared to the literature, systemic antifungal usage was higher than in other studies (13.4%–17%) (7,13,16). This may be mainly related to diagnostic explication differences and local clinical conditions. It is slightly probable that the prepossession of the radiologist might lead to interpreting the diagnosis as IFI, or our GM assays might occasionally conflict due to technical problems or patient-related conditions such as widespread use of penicillin-based antibiotherapy. The distribution of underlying diseases and treatment phases was similar to that of other studies; acute leukemia was the most common diagnosis (57%) and remission induction and transplantation were the most common treatment phases (35.8% and 30.9%, respectively) (7,13). In our study, the most commonly used antifungal agent was LAmpB (55.3%), and the most common reason for changing was lack of efficacy (50%). These findings are similar to other studies in the literature (16). According to this evaluation, the frequency and cost of antifungal treatment during the induction phase of patients with acute leukemia and in the process of HSCT is still conspicuously high and poses a serious problem.

Aspergillus spp. was the most common causative agent in probable/proven IFI, supporting the previously reported data (17). The incidence of aspergillosis was 5.9%, which was slightly higher than that declared in other studies (0.8%–2.6%) (6,7,15). The environmental conditions of our clinic might have led to increased IFI rates, as long-term refurbishment studies might have exacerbated mold-related fungal infections. Additionally, host factors, such as personal hygiene and isolation rules, should be considered. The lung was the most common involvement site in other data, as well. The incidence of candidiasis was 0.4%, which was consistent with other studies (0.2%–10%) (3,6,7,15).

Remarkable morbidity and mortality rates related to IFIs emphasize the importance of prophylactic antifungal treatment regimens for high-risk patients (18). Focusing on the patient group that received antifungal therapy (n = 123), we noticed that the prophylaxis rate was 57.7%. These data were slightly higher than those reported in the literature, where the prophylaxis rate has been reported as 41.7%–44% (7,13,19). The main reason for the high rate of prophylaxis might be related to patient characteristics. Among the 123 chemotherapy courses in which AF prophylaxis was used, 38 (30.9%) were autologous or allogeneic HSCT.

Although the proven/probable IFI rate was two-fold higher in the group using mold-active prophylaxis (16.6% vs. 8%), this difference was not statistically significant. In a study from Spain, proven/probable IFI rates were 47% and 47.3% in patients who received mold-active prophylaxis and no mold-active prophylaxis, respectively (20). In another study from France, the probable IFI rate was 11.4%

in patients who received posaconazole prophylaxis. The authors concluded that the posaconazole oral suspension administration did not decrease the incidence of IFI. They also concluded that these findings were associated with interruptions of prophylactic treatment due to mucositis, concomitant use of PPIs, poor absorbers, and diarrhea (21). All causes mentioned above might be associated with two-fold higher IFI rate in our study.

In this study, the prevalence of proven/probable IFI among patients who received antifungal prophylaxis was significantly higher than among patients who did not receive prophylaxis (11.3% vs. 4.6%). The higher prevalence of IFIs among patients who received antifungal prophylaxis might be attributed to patient characteristics, interruptions of prophylactic treatment, unpredictable bioavailability of AF agents used for prophylaxis, and breakthrough IFI (bIFI). It should be noted that the patients who received prophylaxis were in a high-risk group. In this study, the most common causes of prophylaxis were transplantation and remission induction chemotherapy. The rate of high-risk patients for IFI who received prophylaxis, except autologous transplantation, was 46.5%. As mentioned above, interruptions of prophylactic treatment due to mucositis might be associated with a high IFI rate. Another explanation for high IFI incidence may be the unpredictable or sometimes poor bioavailability of antifungal agents (especially posaconazole) used for prophylaxis. In the literature, observational studies on bIFI have reported incidences of probable/proven bIFI ranging from 3% to 13% (22–28). The rate of bIFI observed in the group receiving prophylaxis is compatible with the literature.

The frequencies of posaconazole, fluconazole, and voriconazole usage were found to be 15%, 8%, and 1.6%, respectively. In an observational prospective French study, antifungal prophylaxis was found to be used in 56% of the proven IFIs, and the distribution of prophylactic agents in proven cases was 59.3% fluconazole, 18.5% ampB, 6.2% voriconazole, and 6.2% posaconazole (19). In a prospective epidemiologic study from Austria, the proven/probable IFI rate was 8.5% in patients who received antifungal therapy and there was a different distribution of prophylactic agents: 63.5% of prescriptions were posaconazole, 25% were itraconazole, and 11.5% were fluconazole. The authors suggested that the low rate of IFI correlated with the extensive use of posaconazole (13). Thus, different approaches in prophylaxis may alter the outcomes and provide information about effective preventive strategies. Moreover, ECIL-4 guidelines emphasize the importance of local epidemiology in designing an appropriate institutional prophylaxis strategy (29).

In our study, an empirical approach was used in 91% of chemotherapy courses in which antifungal therapy was given. Although there were encouraging data supporting preemptive treatment, subsequent clinical trials indicated that the empirical approach is still the standard of care for neutropenic patients with hematological malignancies, especially in the high-risk group (8,30–32). LAmpB was the most commonly used antifungal therapy in our study (57.1%). Turkish expert opinion (TEO) articles reported that conventional AmpB is still included in the recommendations of the Turkish Healthcare Implementation Notification for first-line antifungal treatment, although it is not recommended in the guidelines. In TEO, the authors concluded that, especially in high-risk patients, an empirical approach and modification of treatment when required according to the diagnostic outcomes would be more reliable and valid for Turkey (33).

In conclusion, the incidences of IFIs and IFI-attributable mortality were compatible with the literature. The proven/probable IFI rate was higher in those groups using prophylaxis. However, it should be kept in mind that the patients who received prophylaxis are a high-risk group. Although the proven/probable IFI rate was not significantly different between groups using mold-active and no-mold active prophylaxis, patients should be followed closely for the effective use of posaconazole prophylaxis. Improving environmental conditions and using new formulations of posaconazole could improve higher proven/probable IFI rates. Empirical antifungal therapy is still an important approach to reducing mortality rate.

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