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Original Article

Evaluation of antifungal treatment strategies in febrile neutropenic episodes of high-risk hematologic malignancies: A single center retrospective study

Aycan Acet[1], **Vildan Ozkocaman**[2], **Fahir Ozkalemkas**[3]

[1] Department of Internal Medicine, Kütahya Health Sciences University, Faculty of Medicine, Kütahya, Türkiye

[2] Department of Internal Medicine, Division of Hematology, Uludağ University Faculty of Medicine, Bursa, Türkiye

ABSTRACT

Background Febrile neutropenic patients are at high risk for developing invasive fungal infection (IFI). Currently, two treatment strategies, empiric and preemptive, are used in febrile neutropenic patients with IFI. This study aimed to evaluate empirical and preemptive treatment strategies in patients with high-risk hematologic malignancies.

Methods We retrospectively analyzed 402 febrile neutropenic attacks in 281 patients with hematological malignancies hospitalized in a university hospital hematology clinic. Between June 2006 and January 2009, 154 febrile neutropenic episodes of 104 patients who met the study eligibility criteria were included. Patients who received antibiotic and antifungal treatment for febrile neutropenia were retrospectively recorded. Patients treated with empiric and preemptive approaches were identified and compared with statistical methods.

Results Antifungal treatment was initiated as empiric treatment in 62 (40%), preemptive therapy in 55 (36%) (subgroups; 45 [29%] possible-IFI and 10 [7%] probable-IFI), and 37 (24%) for secondary prophylaxis. In terms of length of hospitalization and all-cause mortality, no statistically significant results were found when patients receiving empiric and preemptive treatment were compared. ($p>0.05$).

Conclusion In patients with high-risk hematologic malignancies, even if empiric treatment is initiated, a dynamic approach that can be summarized as persistently trying to obtain evidence by using ancillary diagnostic tools and early termination of therapy in unnecessary cases seems appropriate.

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Address for Correspondence:
Aycan ACET, Department of Internal Medicine, Kütahya Health Sciences University, Kütahya, Türkiye
E-mail: aycanacet80@icloud.com

INTRODUCTION

In recent decades, the frequency of invasive fungal infection (IFI) has increased in patients with hematologic malignancy.[1] While empirical treatment approaches based on fever were at the forefront in the past, in recent years, the high cost of empirical treatment, the side effect profile of amphotericin B, which increases morbidity and cost, and the development of computed tomography and serologic methods for detecting fungal cell wall antigens in body fluids have led to the discussion of preemptive treatment approaches to start antifungal treatment with more evidence. Patients with high-risk hematologic malignancies with fever refractory to broad-spectrum antibacterial therapy and new infiltration with unexplained causes on radiologic imaging are candidates for fungal infections. One of the most critical problems faced by clinicians is the decision to initiate antifungal drugs in a neutropenic patient with prolonged fever, which is costly and may have high side effects. The high risk of invasive pulmonary aspergillosis (IPA), especially in patients with hematologic malignancies or those undergoing stem cell transplantation, emphasizes the importance of decision-making in this situation. However, delay in diagnosis is the most important problem in invasive aspergillosis.[2] Aspergillosis rarely grows in blood cultures; its growth is generally considered contamination. The sensitivity of cultures obtained from respiratory tract secretions is low. Growth occurs in only 8-34% of sputum samples and 45-62% of bronchoalveolar lavage (BAL) samples of patients with invasive aspergillosis. Histopathology is required for diagnosis but marked pancytopenia, respiratory distress, and bleeding risk are inhibiting factors for diagnosis.[3] Empirical antifungal treatment is a common approach. Only 20-25% of those receiving empirical antifungal treatment in the USA and Europe are IFIs. Another known fact is that while the frequency of aspergillosis is around 2-10% with empirical treatment, this rate approaches 30% in patients without empirical treatment and with prolonged neutropenia.[4,5] To move away from the empirical approach, providing evidence of fungal infection through tissue diagnosis or culture results is essential.

MATERIAL AND METHODS

Patient selection and study design

We retrospectively analyzed 402 febrile neutropenic episodes of 281 patients with hematologic malignancies who received inpatient treatment during the 2.5-year period between June 2006 and January 2009 in the department of hematology, Uludağ University Faculty of Medicine. Among these, 154 FEN of 104 patients who received antifungal drugs were analyzed.

Patients aged 18 years or older, patients who received chemotherapy for hematologic malignancy and had a febrile neutropenic episodes, patients diagnosed with IFI (possible, probable, proven) according to the guidelines and/or patients who received systemic (oral or parenteral) antifungal therapy for treatment were included in the study. Only patients with a diagnosis of mucosal (oropharyngeal, vaginal) candidiasis and patients younger than 18 years of age were excluded. Patient files were reviewed and age, sex, comorbidity, underlying hematologic malignant disease, duration of hospitalization, number and duration of febrile neutropenic episodes, antifungal treatment strategies, reasons for use, side effects, reasons for change, duration and doses of antifungal drugs used, Blood, catheter, BAL, sputum cultures, blood and BAL galactomannan (GM) antigen, infections that developed under treatment, radiology and laboratory findings, data about the operation if an operation was performed, and data about the patient and disease status at the end of the febrile neutropenic episode were recorded.

The use of computerized tomography and bronchoalveolar lavage in FEN episodes

Computed tomography (CT) was performed if fever did not respond to broad-spectrum antibacterial treatment within 96 hours and signs of lower respiratory tract infection or new infiltrates were detected on chest radiography. Bronchoscopy and BAL were performed in patients with CT findings compatible with IFI (nodules, halo sign, air-crescent sign, cavitation); BAL fluid was examined microbiologically and serologically. Serum samples were collected twice a week, and GM antigen testing was performed; BAL GM antigen testing was also performed.

Invasive fungal infection criteria and antifungal treatment strategies

Invasive fungal infection was defined according to EORTC/MSG criteria[6], and patients were classified as possible, probable and proven. Antifungal treatment strategies were empiric and preemptive; initial treatment was usually amphotericin B deoxycholate, and other antifungals were switched to in case of

severe side effects, intolerance or non-response.

Statistical analysis

Statistical analysis of the obtained data was performed with the SPSS 13.0 computer program. In the study, temporal variables were presented as minimum, maximum and median values and categorical variables were presented as frequency (%) when necessary. Pearson chi-square test was used to compare the empiric and preemptive groups. In the study, $p<0.05$ was considered statistically significant.

RESULTS

Of the 104 patients who met the inclusion criteria, 65 (63%) were male and 39 (37%) were female. Of the patients, 60 (57.6%) were acute myeloid leukemia (AML), 21 (20.1%) acute lymphoid leukemia (ALL), 7 (6.73%) non-Hodgkin's lymphoma (NHL), and 2 (1.92%) Hodgkin's lymphoma, 2 were biphenotypic leukemia, 2 (1.94%) myelodysplastic syndrome, 3 (2.88%) multiple myeloma (MM), 4 (3.84%) aplastic anemia and 3 (2.88%) chronic lymphocytic leukemia. Regarding primary hematologic disease, 52 episodes of febrile neutropenia (34%) were newly diagnosed. Forty-three (28%) of the episodes were in complete response to treatment, 41 (27%) were recurrent disease, 10 (6%) were resistant disease, and 8 (5%) were in other groups. Twenty-seven (26%) of the patients had a concomitant chronic disease. The hospitalization duration range was 8-151 (median: 37.5) days. All patients had neutropenic fever. The total duration of antifungal use was 2-77 (median: 18) days. The number of patients who died at the end of all episodes was 40. Patient and episode characteristics are summarized in Table 1. When the group of patients receiving treatment for secondary prophylaxis was excluded from all episodes of febrile neutropenia, 62 (53%) of the remaining 117 episodes of febrile neutropenia were empiric, and 55 (47%) were preemptive antifungal treatment. The distribution of antifungal treatment according to febrile neutropenia episodes is shown in Table 2. In the empirical treatment group, CT findings included ground-glass opacities in 28 (56%), nodular infiltrates in 9 (18%), consolidation in 11 (22%), a mass appearance in 1 (2%), and six attacks. Pleural fluid appearance was detected in 6 (12%) patients, while the findings were normal in 8 (16%). Characteristic findings for IPA included a halo sign in 14 (28%) and cavitation and air-crescent sign in 2 (4%) attacks.

Table 1. Characteristics of 154 febrile neutropenia episodes in 104 patients

Gender (male/female) (n)	65/39
Age (years)	41 (18-79)
Hematological disease (n)	
Acute myeloid leukemia	60
Acute lymphocytic leukemia	21
Non-Hodgkin lymphoma	7
Hodgkin lymphoma	2
Biphenotypic leukemia	2
Myelodysplastic syndrome	2
Multiple myeloma	3
Aplastic anemia	4
Chronic lymphocytic leukemia	3
Hematological disease status n (%)	
New Diagnosis	52 (34%)
Complete response	43 (28%)
Relapse	41 (27%)
Refractory	10 (6%)
Other	8 (5%)
Total duration of antifungal use (days)	18 (2-77)
Total hospitalization duration (days)	37.5 (8-151)
Discharged/died (n)	114/40

The data were given as median (min: max).

Table 2. Distribution of antifungal treatment according to febrile neutropenia episodes

Antifungal treatment	Episodes n (%)
Empiric	62 (40%)
Preemptive (total)	55 (36%)
Possible-IFI	45 (29%)
Probable-IFI	10 (7%)
Secondary prophylaxis	37 (24%)

In the preemptive treatment group, CT findings

Table 3. Chest computerized tomography findings of patient attacks

Reason for antifungal use	Empirical	Preemptive	Secondary prophylaxis	Total
Attack/patient (n)	49/46	52/49	25/19	126/114
Findings n (%)				
Ground-glass opacity	28 (56%)	43 (78%)	11 (52%)	82 (65%)
Nodular infiltrates	9 (18%)	23 (42%)	2 (9%)	34 (27%)
Consolidation	11 (22%)	25 (45%)	5 (24%)	41 (33%)
Cavitation/air-crescent sign	2 (4%)	9 (16%)	2 (9%)	13 (11%)
Halo sign	14 (28%)	21 (38%)	3 (14%)	38 (30%)
Mass	1 (2%)	-	-	1 (1%)
Pleural effusion	6 (12%)	4 (7%)	2 (9%)	12 (9%)
Normal	8 (16%)	-	3 (14%)	11 (8%)

consisted of ground-glass opacities in 43 (78%) attacks, nodular infiltrates in 23 (42%), consolidation in 25 (45%), and pleural fluid appearance in 4 (7%) attacks. Specific findings for IPA included a halo sign detected in 21 (38%) and cavitation and air-crescent sign in 9 (16%) attacks.

In the group receiving secondary prophylaxis, CT findings showed ground-glass opacities in 11 (52%) attacks, nodular infiltrates in 2 (9%), consolidation in 5 (24%), and pleural fluid appearance in 2 (9%) attacks. Normal findings were observed in 3 attacks (14%). Specific findings for IPA included a halo sign in 3 (14%) attacks, along with cavitation and air-crescent sign in 2 (9%).

Considering all febrile neutropenic episode attacks, CT findings revealed ground-glass opacities in 82 (65%), nodular infiltrates in 34 (27%), consolidation in 41 (33%), and pleural fluid in 12 (9%) attacks. Normal findings were noted in 11 (8%) patients. The specific findings for IPA included a halo sign in 38 attacks (30%) and an air-crescent sign and cavity in 13 attacks (11%). The CT findings related to patient attacks are summarized in Table 3.

Table 4 presented the characteristics of patients with hematologic malignancies who underwent BAL. Among the 38 patients, the most common diagnosis was AML (68.4%), followed by ALL (23.6%), with fewer cases of NHL (2.6%), MM (2.6%), and aplastic anaemia (2.6%). All patients had neutropenia and fever during hospitalization, with a median hospitalization duration of 39 days (range: 22–101). BAL GM antigen was positive in 47% of patients, while serum GM positivity was observed in 26%. Non-specific chest CT findings were the most common (63.1%), with the halo sign (23.6%) and air-crescent sign or cavity (13.1%) detected in fewer cases.

A total of 62 febrile neutropenia episodes of patients who received antifungal treatment with an

Table 4. Characteristics of patients undergoing bronchoscopy-guided bronchoalveolar lavage

Reason for antifungal administration	Empirical	HP-IPA	LP-IPA	Secondary prophylaxis	Total
Attack/patient (n)	8/8	12/12	11/11	7/7	38/38
Gender (male/female)	5/3	12/0	9/2	4/2	25/6
Age (years)	44.5 (24-57)	52.5 (29-70)	38 (24-63)	38 (24-57)	48 (24-70)
Diagnosis (n)					
AML	7	8	6	5	26 (68.4%)
ALL	1	3	3	2	9 (23.6%)
NHL	-	1	-	-	1 (2.6%)
MM	-	-	1	-	1 (2.6%)
AA	-	-	1	-	1 (2.6%)
Hematological disease status (n)					
New Diagnosis	5	8	6	3	22 (57.8%)
Remission	2	4	4	1	11 (28.9%)
Relapse	1	-	1	2	4 (10.5%)
Resistance	-	-	-	1	1 (2.6%)
Hospitalization duration (days)	42.5 (23-89)	38 (27-82)	39 (26-82)	39 (22-101)	39 (22-101)
Patient factors					
Neutropenia	8	12	11	7	38 (100%)
Fever	8	12	11	7	38 (100%)
Steroid usage	-	-	-	-	-
Duration of antifungal therapy (days)	20.5 (9-50)	15 (5-26)	19 (5-47)	29 (11-48)	18 (5-50)
CT findings					
Halo sign	1	6	2	-	9 (23.6%)
Air-crescent sign/cavity	1	3	-	1	5(13.1%)
Non-specific	6	3	9	6	24 (63.1%)
BAL GM					
Positive	2	5	9	2	18 (47%)
Negative	6	7	2	5	20 (53%)
Serum GM					
Positive	2	1	6	1	10 (26%)
Negative	6	11	5	6	28 (74%)
Number of serum GM evaluated (per attack)	12 (9-25)	11 (8-23)	15 (7-23)	11 (6-29)	11 (6-29)
Discharged/died (n)	7/1	9/3	9/2	7/0	32/6

The data were n, n (%), or median (min: max).

HP-IPA: highly probable invasive pulmonary aspergillosis, LP-IPA: low probable invasive pulmonary aspergillosis, AML: acute myeloid leukemia, ALL: acute lymphoblastic leukemia, NHL: non-Hodgkin lymphoma, AA: aplastic anemia, CT: computerized tomography, BAL GM: bronchoalveolar lavage galactomannan antigen, GM: galactomannan antigen.

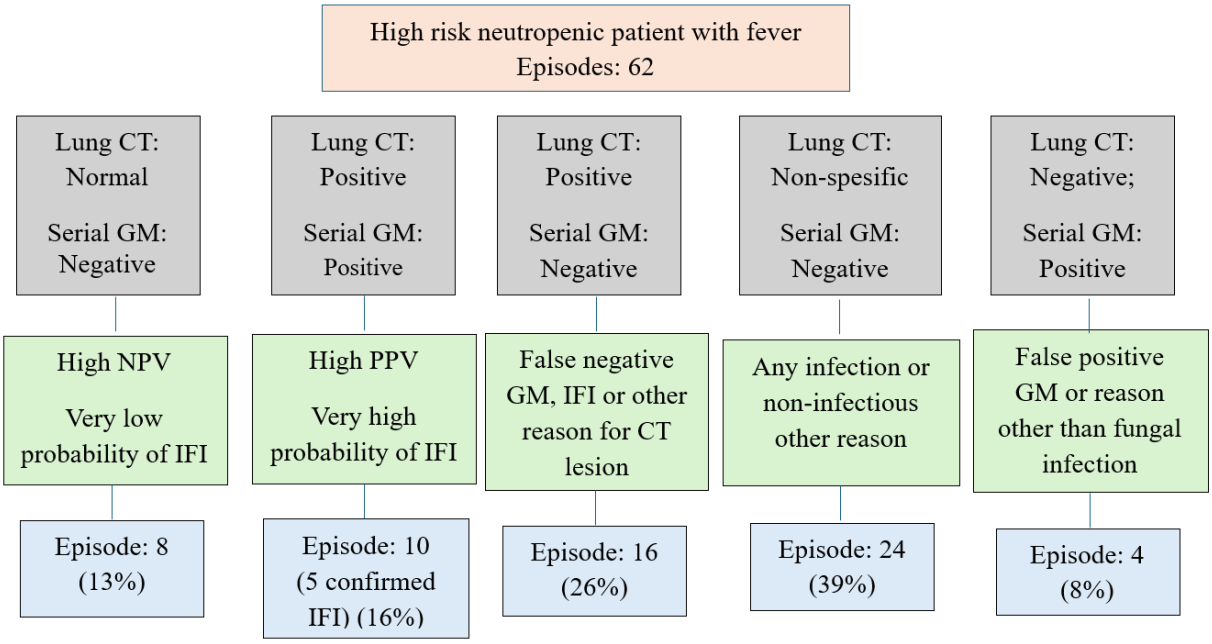

Figure 1. Re-evaluation of febrile neutropenia attacks in patients who received antifungal treatment with empirical approach in line with preemptive approach
NPV: negative predictive value, PPV: positive predictive value, GM: galactomannan, CT: computerized tomography, IFI: invazive fungal infection.

empirical approach were re-evaluated after the end of the febrile neutropenia episode in line with the preemptive approach. Radiologic and laboratory findings suggestive of fungal infection were identified in 10 (16%) of these episodes, and fungal growth was detected in 5 (8%) (Figure 1). Our analysis of 55 febrile neutropenia episodes in the preemptive group found that 26 (47%) febrile neutropenia episodes had findings suggestive of fungal infection with radiologic and laboratory diagnostic methods. Of these episodes, fungal infection was proven in 11 (20%) (Figure 2). The two antifungal treatment groups were similar in terms of the compared characteristics. Since mortality due to IFI was not evaluated in our study, all-cause mortality was calculated by comparing empiric-preemptive antifungal treatment strategies. Regarding all-cause mortality, there was no statistically significant difference between the episodes of patients treated with empirical antifungal therapy and those treated with preemptive therapy ($p>0.05$). Comparative characteristics of these two treatment groups were presented in Table 5.

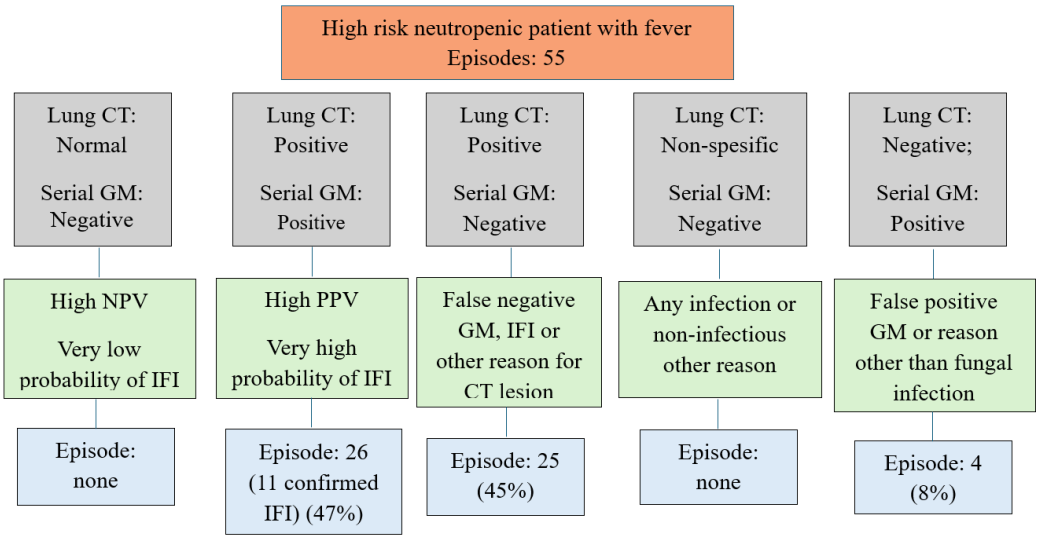

Figure 2. Evaluation of febrile neutropenia attacks in patients given antifungal therapy with a preemptive approach
NPV: negative predictive value, PPV: positive predictive value, GM: galactomannan, CT: computerized tomography, IFI: invazive fungal infection.

Table 5. Comparison of antifungal treatment strategies

Variables	Empiric (%)	Preemptive (%)
Attack/patient (n)	58/62	54/55
Gender (male/female)	39/23 (67%/33%)	36/18 (67%/33%)
Age (years)	39 (19-71)	48 (18-79)*
Diagnosis (n)		
Acute myeloid leukemia	34 (59%)	31 (58%)
Acute lymphocytic leukemia	10 (17%)	12 (22%)
Non-Hodgkin lymphoma	3	4
Hodgkin lymphoma	1	1
Biphenotypic leukemia	2	0
Myelodysplastic syndrome	2	1
Multiple myeloma	2	1
Aplastic anemia	3	2
Chronic lymphocytic leukemia	1	2
Hematological disease status (n)		
New Diagnosis	27 (44%)	23 (42%)
Remission	11 (18%)	10 (18%)
Relapse	14 (22%)	13 (24%)
Resistance	6 (10%)	4 (7%)
Other	4 (6%)	5 (9%)
Total duration of antifungal use (days)	18 (2-69)	14 (2-60)
Total hospitalization duration (days)	39 (14-151)	38 (11-91)
Discharged/died (n)	47/15	34/21

* $p<0.05$

DISCUSSION

Infections in neutropenic patients are an important cause of morbidity and mortality. In this patient group, signs of inflammation are faint due to neutropenia. Therefore, it is often not possible to identify the focus of infection. However, the initiation of antimicrobial therapy is urgent as the patient's condition may deteriorate rapidly, and the patient could die within hours. In this case, the only criterion for starting antimicrobials in neutropenic patients is the patient's fever. In national and international guidelines published on febrile neutropenia, the finding that directs treatment is high fever.[7,8] Accordingly, broad-spectrum antibiotics are started empirically in neutropenic patients with fever. If the patient's fever persists on the 3rd to 5th day of treatment, it is not easy to understand whether the reason for the patient's fever not decreasing is due to a bacterial or fungal cause. Diagnosis of fungal infections in neutropenic patients is difficult. The time spent to make the diagnosis may negatively affect the prognosis. The faster fungal infections developing in neutropenic patients are treated, the better the outcome.[9] Based on these data, guidelines recommend initiating antifungal treatment in case of persistent fever on the 3rd to 5th day of antimicrobial treatment.[7,8] This approach, which accepts the patient's fever as the main criterion, is called empirical treatment. Approximately two-thirds of febrile neutropenic patients receive antifungal treatment with this approach.[10] The aim is to ensure that patients likely to have IFI are treated early in the disease. Early initiation of treatment is thought to change the survival rate favorably.[10] Empirical antifungal treatment can be administered to up to 40-50% of the high-risk neutropenic patient population, although the actual incidence of IFI is believed to be between 10-15%. [12]

Antifungal treatment was given in 154 (38%) of the 402 febrile neutropenic episodes analyzed in our study. When the episodes in which antifungal treatment was given for secondary prophylaxis were excluded from these episodes, this rate decreased to 29%. The episodes in which empirical antifungal treatment was given only for fever constituted 12% of all febrile neutropenic episodes and 40% of all antifungal treatments. In the empiric treatment group, at least one evidence of IFI was obtained in 49% of episodes using diagnostic methods such as CT, BAL, GM measurement, and culture. In contrast, no evidence was obtained in 51%. In summary, in the empiric treatment group, no concrete evidence in favor

of IFI could be obtained in approximately half of the patients. Studies have shown that empirical therapy remains the standard of care in many institutions, with a significant percentage of chemotherapy courses employing this strategy.[13,14]

Recent advances in non-culture diagnostic methods and a better understanding of risk factors will narrow the patient population that may benefit from antifungal treatment. In this way, the concept of early treatment will not be compromised, and drug interactions, drug toxicity, and cost increases due to unnecessary drug administration will be reduced. Cost-effectiveness analyses have highlighted the economic implications of both strategies. Empirical treatment is less expensive than preemptive therapy, with one study reporting costs of $147,482 for empirical treatment compared to $147,910 for preemptive treatment.[15] This cost difference is significant, particularly in healthcare systems where resource allocation is crucial. Additionally, rapid diagnostic tests can further improve the cost-effectiveness of preemptive strategies by reducing unnecessary antifungal exposure and associated side effects.[16]

The time between the onset of IFI and clinical signs and symptoms may provide an opportunity to identify these patients through screening and achieve a better response with early treatment. Fever is not the only criterion in such a preemptive approach.[17] Currently, non-culture microbiologic methods that can be used in daily practice are serum GM measurement, serum beta-D-glucan measurement, and fungal DNA determination by polymerase chain reaction. These methods have deficiencies or superiorities compared to each other.[18] The use of biomarkers such as GM has been explored to guide preemptive therapy, allowing antifungal treatment to be initiated only when specific thresholds are met.[19,20] In preemptive treatment, diagnostic accuracy is improved when combining the diagnostic tools of CT and GM results. Our findings suggest a notable relationship between chest CT findings and BAL GM results. Among patients with positive BAL GM results, 23.6% exhibited specific chest CT findings such as the halo sign, and 13.1% demonstrated the air-crescent sign or cavitation. These characteristic CT findings for IPA were more commonly observed in the preemptive treatment group, aligning with the higher rates of BAL GM positivity. In contrast, serum GM positivity was observed in a smaller proportion of patients (26%), suggesting that serum GM may have lower diagnostic sensitivity than BAL GM. This discrepancy highlights the potential value of BAL GM in correlating with specific radiological findings, such as the halo and air-crescent signs. At the same time, serum GM appears less consistently associated with these features. These results underscore the importance of integrating BAL GM results with chest CT findings to improve diagnostic accuracy in febrile neutropenic episodes of patients with hematologic malignancies.

However, some points should be noted in the evaluation of laboratory results. False-positive results in GM testing, a critical diagnostic tool for invasive aspergillosis, can significantly complicate clinical decision-making. Various factors contribute to these false positives, particularly the influence of certain antibiotics, nutritional supplements, and underlying health conditions. One of the primary causes of false-positive GM tests is the administration of beta-lactam antibiotics, such as piperacillin-tazobactam and amoxicillin-clavulanate. These antibiotics can lead to cross-reactivity due to their structural similarities with GM, a polysaccharide found in the cell walls of certain fungi, including Aspergillus species.[21] Studies have shown that patients receiving these antibiotics often exhibit elevated GM levels, which can mislead clinicians into suspecting invasive aspergillosis when it is not present.[22]

In our study, the rate of febrile neutropenia episodes with high positive predictive value and very high probability of IFI was 16% in the empiric group and 47% in the preemptive group. In the empiric group, the rate of febrile neutropenia episodes with high negative predictive value and very low probability of IFI was 13%. In contrast, there was no such episode in the preemptive group. Since the factors that make non-culture microbiologic methods false negative or false positive are not fully known and since the number of patients with tissue diagnosis is very low and postmortem biopsy cannot be performed, it is difficult to comment on episodes with suspicious probability of IFI. Although the percentage of all-cause mortality was higher in the preemptive group than in the empiric group, there was no statistically significant difference between them.

Preemptive therapy can lead to lower overall antifungal exposure and reduced healthcare costs without increasing mortality rates compared to empirical therapy.[23,24] The efficacy of preemptive therapy is contingent upon the accuracy of diagnostic

tests and the timely identification of at-risk patients. Limitations in the sensitivity of tests such as the GM assay can delay treatment initiation, potentially allowing IFIs to progress.[19,20] The reliance on imaging studies, such as CT scans, introduces additional complexity, as these tests may not always provide definitive results.[19] Despite these challenges, some studies have reported that preemptive therapy can be as effective as empirical therapy in preventing IFIs, particularly in high-risk populations.[24,25]

A systematic review highlighted that patients receiving preemptive therapy had significantly lower antifungal exposure and clinical expenses without an increase in mortality rates.[23] Therefore, the answer to whether empirical or preemptive treatment is superior cannot be given with certainty.[26]

In our study, in 55 (36%) of the episodes in which antifungal drugs were used, antifungal treatment was initiated based on at least one CT, GM, and culture results. There were 40 episodes (26%) in which the initial treatment was empiric or secondary prophylaxis, and later evidence in favor of fungal infection was obtained by culture and non-culture diagnostic methods. Regardless of the initial treatment, 62% of all antifungal treatment episodes had varying degrees of evidence of fungal infection.

In a meta-analysis of 6 randomized controlled trials comparing patients with hematologic malignancies who received empirical antifungal therapy with those who did not, it was reported that empirical treatment did not significantly reduce mortality but significantly reduced the development of IFI.[27] In Europe and the USA, 20-25% of those receiving empirical antifungal treatment have IFI.[28]

The retrospective nature of our data, the fact that the data included patients for whom decisions were made on a case-by-case basis (not randomized, hence the high probability of unequal risk profiles). The fact that deaths directly related to fungal infection were not fully distinguished among the causes of death in the mortality rate calculation makes it difficult to finalize the conclusions reached in our study.

CONCLUSIONS

In conclusion, for an empirical and preemptive treatment approach in febrile neutropenic patients with hematologic malignancies who have fever resistant to antibacterial therapy, it may be an appropriate option for each center to evaluate the risk profile and frequency of IFIs of their patients and decide which treatment strategy is suitable for their patients. A ‘ dynamic ‘ approach seems appropriate even if empirical treatment is initiated in high-risk patients. It can be summarized as urgent and persistent efforts to obtain evidence using auxiliary diagnostic tools and early termination of therapy in unnecessary cases. On the other hand, well-designed randomized prospective studies are needed to arrive at a definitive judgment on empirical and preemptive approaches.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Statement

The protocol of the study was approved by the Medical Ethics Committee of Uludag University Faculty of Medicine (Decision number: 2009-3/39).

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Authors’ Contribution

Study Conception: FÖ, VÖ; Study Design: FÖ, VÖ; Literature Review: AA; Critical Review: AA; Manuscript preparing: AA.

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