Original Article

Evaluation of Risk Factors for Mortality in Febrile Neutropenia

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Abstract

Introduction: We aimed to evaluate the epidemiology of infections and factors associated with mortality in patients with febrile neutropenia (FEN).

Methodology: The adult patients, who developed FEN after chemotherapy due to a hematologic malignancy or a solid tumor in a training and research hospital were evaluated, retrospectively. The demographic data of the patients, underlying malignancy, administered antimicrobial therapy, microbiological findings, and other risk factors associated with mortality were evaluated.

Results: A total of 135 FEN episodes of 115 patients, who comprised of 72 (63%) patients with 89 FEN episodes due to hematologic malignancies (hemato-group) and 43 (37%) patients with 46 FEN episodes due to solid organ cancers (onco-group), were evaluated in the study. The median age was 47 years (range: 17-75 years) and 66 (57%) patients were male. A total of 12 patients (8.8%) died during 135 episodes of FEN including nine cases from hemato-group and three cases from onco-group. Those factors including a presence of pneumonia, advanced age, persistent fever despite an antimicrobial treatment, and need for mechanical ventilation in intensive care unit (ICU) with were determined as risk factors associated with mortality.

Conclusions: Morbidity and mortality are more common in patients with hematological malignancies compared to patients with solid organ cancers due to prolonged neutropenia. In case of persistent fever, an invasive fungal infection (IFI) should be kept in mind in patients with hematologic malignancies and then antifungal treatment should be initiated. Although a persistent fever is also common in patients with solid tumors, the necessity of antifungal therapy is rare due to the short duration of neutropenia.

Key words: Febrile neutropenia; Hematologic malignity; solid tumor; mortality; invasive fungal infection.

Introduction

Febrile Neutropenia (FEN) is an important cause of mortality and morbidity in oncology patients receiving chemotherapy. At least one episode of FEN develops in 80% of those patients after chemotherapy, and 5-10% of those result in mortality despite a broad-spectrum antimicrobial therapy [1]. Therefore, FEN is considered an oncologic emergency and needs a rapid initiation of a broad-spectrum antibacterial therapy [2,3]. The diagnosis of infection in oncology patients is carried out with the ascertainment of causative microorganism in microbiological cultures or other tests, as it depends on clinical findings in some patients. Fever without other findings and test results is defined as febrile neutropenic

fever of unknown origin. Monotherapy with a beta-lactam/beta-lactamase inhibitor, or an antipseudomonal cephalosporin or a carbapenem (imipenem or meropenem) is preferred in the empirical treatment of FEN [4,5]. The patient's symptoms and findings on physical examination, possibly causative microorganisms and antimicrobial resistance patterns of the local setting, previous infections, colonization of the patient with resistant microorganisms should be taken into consideration in the empirical treatment [6].

This study aims to evaluate the epidemiology of infections and mortality related factors in patients with FEN.

Methodology

The adult patients who developed FEN after chemotherapy due to a hematological malignancy or solid tumor in a teaching hospital between 1 January and 31 December 2015, were evaluated retrospectively. The criteria for inclusion in the study were being seventeen years or older, having a FEN episode due to chemotherapy, and receiving inpatient treatment. Patients who were not neutropenic during fever episodes and who were outpatients were excluded from the study.

FEN is defined as a fever $\geq$ 38.3 °C or $\geq$ 38° C during 1 hour and the absolute neutrophil count (ANC) <500 / mm^3 or neutrophil count <1000 / mm^3 and expected to fall below 500 / mm^3 in 48 hours. 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 (EORCT / MSG) criteria were used for the diagnosis of IFI [7].

All patients with FEN episodes were evaluated by the history of the illness and detailed physical examination according to the protocol of our hospital. Two sets of blood cultures (one aerobic, one anaerobic) were taken on the first day, and more than one set of blood cultures were implemented if fever persisted on the second and the third days.

If the patient had a central venous catheter, one set of blood cultures were taken from each lumen of the catheter, as well posteroanterior (PA) chest X-ray, urinalysis, urine culture, and other specimen cultures were taken related to clinical findings. If the expected duration of neutropenia was more than 7 days, prophylaxis with fluconazole and valacyclovir and were administered until the patient recovered from neutropenia. Posaconazole was used for antifungal prophylaxis during the induction treatment of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and allogeneic stem cell transplantation with graft versus host disease. Trimethoprim/ sulfamethoxazole was used if there was an indication for the prophylaxis against *Pneumocystis jirovecii* pneumonia.

Escalation or de-escalation strategies were performed according to the guideline of the European Conference on Infections in leukemia- 4 (ECIL-4) in the initiation of the empirical antibiotic therapy [5].

If the patient was hemodynamically stable, the escalation strategy was preferred and an antipseudomonal beta-lactam/beta-lactamase inhibitor was administered. For those patients who were in septic shock, respiratory failure, or multi-organ failure and infected or colonized with a resistant microorganism, the de-escalation strategy was carried out with a carbapenem (imipenem or meropenem) in the initial therapy.

If a patient had one of those conditions, including catheter or soft tissue infection, hypotension, colonization with methicillin-resistant *Staphylococcus aureus* (MRSA), or penicillin-resistant *S. pneumoniae*, or if there was a positive culture with a Gram-positive microorganism, a glycopeptide antibiotic (vancomycin or teicoplanin) was added to the treatment.

All of the patients were re-evaluated at the 72-hours of FEN episode, the antimicrobial treatment was rearranged in line with the culture results. If the cultures were negative and the fever persisted, a thoracic computed tomography (CT) was performed, the spectrum of the antimicrobial therapy was escalated, and the patient was evaluated for antifungal therapy. If the patient had taken antibiotics for at least three days and been afebrile for the last 48 hours, the cultures were negative and there was no sign of infection in physical examination, antibiotic treatment was discontinued.

Data of the patients like age, gender, underlying disease, disease status, comorbidity, and clinical findings were recorded from the hospital automation system and thepatient files. The relevance of the first antimicrobial therapy, the need for treatment change, antifungal therapy (if it was given), the duration of neutropenia, duration of antimicrobial treatment, duration of hospitalization, and outcome of the treatment were recorded. White blood cell and neutrophil count, C-Reactive protein (CRP), glucose, creatinine, alanine aminotransferase (ALT), aspartate amino transferase (AST) values were recorded from laboratory findings.

Statistics

Patient data were evaluated using SPSS for Windows version 21.0. The chi-square test was used for the analysis of variables showing normal distribution, and the Student-t-test was used for the analysis of numerical variables. Fischer's exact test was used for categorical variables that were not normally distributed and the Mann-Whitney U test was used for numerical variables. Bivariate logistic regression analysis was conducted to obtain unadjusted odds ratios and revealed as (Odds Ratio (OR); 95% Confidence interval; *p* value) in the comparison between the hemato-group and the onco-group. The statistical significance level was determined as $p < 0.05$ in our study.

Results

A total of 135 FEN episodes of 115 patients, who comprised of 72 (63%) patients with 89 FEN episodes due to hematologic malignancies and 43 (37%) patients with 46 FEN episodes due to solid organ cancers, were evaluated in the study. The median age was 47 years (range: 17-75 years) and 66 (57%) patients were male. The number of male patients was 43 (59%) with hematological malignancy and 23 patients (53%) with solid organ cancer. A stem cell transplantation was recorded in 30 patients (15 autologous and 15 allogeneic), whereas diabetes mellitus (DM) in two patients, chronic obstructive pulmonary disease (COPD) in two patients, and chronic kidney disease (CKD) in two patients were recorded. The demographic data and underlying diseases of the patients are shown in Table 1.

The mean age of the hemato-group was 45.1 ± 16.28 years and the mean age of onco-group was 46.88 ± 16.03 years. Infections were diagnosed clinically in 31 (22.9%) of the FEN episodes (24 in hemato group, 7 in onco-group), microbiologically in 49 (36.2%) FEN episodes with positive culture results (39 in hemato-group, 10 in onco-group), and as a fever of unknown origin in 55 (40.7%) FEN episodes (27 in hemato-group, 28 in onco-group). The most common recorded infection was bloodstream infection (26%), followed by pneumonia (19%) and soft tissue infection (11%).

FEN episodes developed once in 84 (62%) patients, as second or more FEN episodes developed in 51

Table 1. Demographic characteristics and underlying diseases of the patients.

Patients (n)	115
Median age (minimum-maximum)	47 (17-75)
Male gender, n (%)	66 (57%)
Type of malignity	n (%)
Hematologic Malignancy, n (%)	72 (63)
Acute myeloid leukemia	29
Non-Hodgkin's lymphoma	16
Acute lymphocytic leukemia	9
Multiple myeloma	8
Hodgkin's disease	6
Others	4
Solid tumors, n (%)	43 (37)
Breast cancer	11
Lung cancer	8
Bone/ soft tissue tumor	7
Head/Neck tumor	5
Testicular cancer	3
Others	3
Comorbidities	n (%)
Diabetes mellitus	2 (1.7)
Chronic Obstructive Pulmonary Disease	2 (1.7)
Chronic Kidney Disease	2 (1.7)

Table 2. Microbiological Findings.

Microorganisms isolated from blood cultures	n (%)
E.coli (ESBL+)	18 (10)
Coagulase-negative staphylococci (methicillin-resistant)	6 (5)
Klebsiella pneumoniae (ESBL+)	6 (2)
Candida spp.	2
Aeromonas spp.	1
Pseudomonas aeruginosa	1
Streptococcus spp.	1
Phaeoacremoniumparasiticum	1
Microorganisms isolated in other cultures (urine, sputum, abscess, tissue)	**n**
E.coli (ESBL +)	6 (1)
Enterococcus spp.	3
Coagulase-negative staphylococci (methicillin-resistant)	1 (1)
Klebsiella pneumoniae (ESBL +)	2 (2)
Aspergillus spp.	1
Acremonium spp.	1

ESBL: Extended-spectrum beta-lactamases.

(37%). The escalation strategy was performed in 103 FEN episodes. A piperacillin-tazobactam therapy was initiated in 58 episodes, cefoperazone-sulbactam therapy was recorded in 45 episodes. A carbapenem therapy was administrated in 32 patients in line with the de-escalation strategy. A glycopeptide antibiotic was added to the initial treatment in 29 episodes.

Microbiological cultures yielded Gram-negative bacteria (n: 33; 68%), Gram-positive bacteria (n: 10; 20%), and fungi (n: 5; 10%). A polymicrobial infection was diagnosed in one (2%) episode. In the bloodstream infections, 26 (69%) Gram-negative bacteria isolates, seven (22%) Gram-positive isolates, and 3 (8%) fungi isolates were cultured (Table 2).

A Multinational Association for Supportive Care in Cancer (MASCC) score less than 21 (*p*: 0.023), subclavian catheter use (*p*: 0.0005), a switch in the antimicrobial therapy (*p*: 0.028), pneumonia (19 vs 6), a bloodstream infection (19 vs 3; *p*: 0005), a central venous catheter-associated infection (2 vs 0; *p*: 0005), a soft tissue infection (15 vs 4; *p*: 0005), an urinary tract infection (6 vs 2; *p*: 0005), a gastrointestinal tract infection (6 vs 2; *p*: 0005), the frequency of clinically and microbiologically proven infections (*p*: 0.0005) and the blood culture positivity (30 vs 6; *p*: 0.0005) was significantly higher in the hemato-group than the onco-group.

There was no statistically significant difference between the hemato-group and the onco-group in terms of the use of granulocyte colony-stimulating factor, the frequency of surgical intervention, having diarrhea, endocarditis, and comorbidities (*p* > 0.05).

Table 3. Infections and malignancies of survivors and non-survivors during FEN episodes.

	Survivors (n=123)	Non-survivors (n=12)	Total (n=135)	P
Mean Age (± SD)	42.67 ± 15,86	53.16 ± 15,14	43.6 ± 16,0	**0.030**
Male gender, (n, %)	68 (55.8)	7 (58.3)	75 (55.6)	> 0.05
Type of malignancy				
Hematologic Malignity (n, %)	80 (65)	9 (75)	89 (65.9)	> 0.05
Solid tumor (n, %)	43 (34.9)	3 (25)	46 (34)	
Hematopoietic stem cell transplantation (n, %)	31 (25.2)	2 (16.7)	33 (24.4)	> 0.05
Number of FEN episode				
First (n, %)	77 (62.6)	7 (58.3)	84 (62.2)	> 0.05
≥2nd (n, %)	46 (37.4)	5 (41.7)	51 (37.8)	> 0.05
Mucositis (n, %)	31 (25.2)	4 (33.3)	35 (25.9)	> 0.05
Pneumonia (n, %)	19 (15.4)	7 (58.3)	26 (19.3)	0.02
Hospital acquired infection (n, %)	73 (59.3)	7 (58.3)	80(59.3)	> 0.05
Diarrhea (n, %)	19 (15.4)	2 (16.7)	21 (15.6)	> 0.05
Soft tissue infection (n, %)	17 (13.8)	0	17 (12.6)	> 0.05
Blur of Consciousness (n, %)	6 (4.9)	0	6 (4.4)	> 0.05
Modification of Antimicrobial therapy (n, %)	50 (40.7)	10 (83.3)	60 (44.4)	0.005
Days under fever, (IQR)	3 (2-5)	9 (3-14.5)	3 (2-5)	**0.05**
Comorbidity (n, %)	8 (6.5)	1(8.3)	9 (6.7)	> 0.05
Duration of neutropenia before fever (days)(n, %)	1 (0-4)	1.5 (0-4)	1 (0-4)	> 0.05
Duration of neutropenia (days) (n, %)	7 (2-15)	15.5 (5.25-21.5)	8 (2-6)	**0.05**
Profound neutropenia (n, %)	70 (56.9)	10 (83.3)	80 (59.3)	0.067
Hypoxia	2 (1.6)	1 (8.3)	3 (2.2)	> 0.05
Follow-up in the intensive care unit	3 (2.4)	10 (83.3)	13 (9.6)	**0.000**
Mechanical ventilation (n, %)	2 (1.6)	9 (75)	11 (8.1)	**0.000**
Invasive Fungal Infection (n, %)	6 (4.9)	6 (50)	12 (8.9)	**0.000**
CMV Infection (n, %)	6 (4.9)	0	6 (4.4)	> 0.05

Table 4. Laboratory Findings of survivors and non-survivors.

	Survivors (n=123)	Non-survivors (n=12)	Total (n=135)	p
WBC at the beginning(IQR)	410 (160-850)	215 (52.5-690)	390 (150-780)	> 0.05
Neutrophil count at the beginning (IQR)	80 (30-230)	50 (12.5-97.5)	80 (30-230)	> 0.05
Hemoglobin at the beginning (IQR)	8.8 (8-10.4)	9.1 (8.4-9.9)	8.9 (8-10.3)	> 0.05
Platelet at the beginning (IQR)	40 (19-101)	17 (9.2-86.7)	38 (18-101)	**0.05**
CRP at the beginning (IQR)	110 (28-213)	283 (132-320)	116 (48.9-224.7)	**0.02**
Glucose at the beginning (IQR)	102 (93-121)	102.5 (87.7-147.7)	102 (93-122)	> 0.05
Creatinine at the beginning (IQR)	0.65 (0.58-0.8)	0.74 (0.49-1.32)	0.69 (0.57-0.82)	> 0.05
ALT at the beginning (IQR)	21 (13-37.5)	20.5 (9.5-62.5)	15 (12-25)	> 0.05
AST at the beginning (IQR)	15 (12-24)	20.5 (10.75-35.5)	21 (13-38.5)	> 0.05
WBC (third day) (IQR)	630 (245-3895)	290 (40-500)	525 (222.5-3625)	**0.012**
Neutrophil count (third day) (IQR)	210 (50-2480)	30 (10-120)	180 (32.5-1907)	**0.006**
CRP (third day) (IQR)	63.8 (31.2-158)	196.8 (78-308)	72 (35.4-179.2)	**0.007**
WBC (seventh day) (IQR)	2870 (565-7435)	380 (67.5-4000)	2600 (460-7400)	0.07
Neutrophil count (seventh day) (IQR)	2000 (62.5-4550)	40 (27.7-820)	920 (40-4355)	**0.038**

IQR: Interquartile range; WBC: White Blood Cell; CRP: C- Reactive Protein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

A total of 12 patients (8.8%) died during 135 episodes of FEN including nine cases from the hemato-group and three from the onco-group. The presence of pneumonia, advanced age, persistent fever despite antimicrobial treatment, need for ICU and mechanical ventilation were identified as risk factors associated with mortality (Table 3; *p* <0.05). The presence of pneumonia (Odds Ratio (OR) 7.66, *p*: 0,002 Confidence Interval (CI) 95%) 2.20- 26.68), a follow-up in ICU (OR: 4.26, *p*: 0.0001 CI: 1.57- 11.5) and the support with a mechanical ventilation (OR: 5.36, *p*: 0.0001 CI: 1.53- 18.80) were independent risk factors for the mortality in multivariate analysis.

The total duration of neutropenia was 7 (2-15 days) days in survivors, and 15.5 (5.25-21.5) in non-survivors, and it was statistically significant (*p* = 0.05). IFI was diagnosed in 12 patients, according to EORTC/MSG criteria (4 possible, 3 probables and 5 proven) and six of these patients (50%) died. Two of the non-survivors had a possible IFI, two of them had a probable IFI, and two had a proven IFI (*p* = 0.0001). Fungemia was recorded in two patients with proven IFI. Six patients had cytomegalovirus (CMV) infection and all of them were survivors.

In the laboratory findings, platelet values of non-survivors on the first day of FEN were found to be significantly lower than those of the survivors (*p* = 0.05). CRP values in the first and third days were higher in non-survivors (*p* = 0.02). The number of white blood cell and neutrophil on day 3 and neutrophil counts on day 7 were lower in non-survivors than those of survivors, significantly (*p* <0.05; Table 4).

Discussion

The duration of neutropenia after chemotherapy is longer in patients with hematologic malignancy than patients with solid tumors. Therefore, the frequent development of infection, a longer duration of hospitalization, higher mortality rates, and higher cost of treatment are seen in patients with hematological malignities [7]. In our study, the higher frequency of infection, higher mortality rates, a longer stay in the intensive care unit, and more frequent IFI were found in patients with hematologic malignancy as well [7]. FEN is an infectious emergency with a high mortality rate (up to 75%), therefore broad-spectrum antimicrobial therapy should be initiated as soon as possible [8]. Neutropenic patients may have an only fever without any other signs of infection. This condition, defined as neutropenic fever of unknown origin, was detected in 40% of our patients. The fever of unknown origin, which was detected in 28 (65%) of patients with solid

tumors, indicated that fever may develop due to non-infectious causes during the neutropenic course without any infection [8]. However, in case of persistent fever during 5-7 days of neutropenia despite antimicrobial therapy, empirical antifungal therapy should be initiated in patients receiving chemotherapy for the treatment of the hematological malignancy [4].

As seen in our study, patients receiving remission – induction chemotherapy for the acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) or high-dose immunosuppressive therapy for the graft versus host disease (GVHD) after hematopoietic stem cell transplantation (HSCT) should receive anti-mold prophylaxis, because of increased risk of IFI [4]. The malignancy, risk of drug-drug interaction, local resistance status of healthcare setting, and the prevalence of invasive fungal infection should also be considered in the choice of antifungal drug for the antifungal prophylaxis [9]. MASSC risk index score is the most widely used for risk the assessment of FEN. MASSC scores were found significantly lower in the hemato-group. The scores of our cases were consistent with the results [10]. Therefore, each patient should be evaluated with the MASSC risk index score, type of malignancy, duration of neutropenia, underlying diseases, the degree of immunosuppression in the choice of antimicrobials. The antimicrobial prophylaxis and treatment and follow-up process should be planned and evaluated separately for each patient [7,9].

Bloodstream infection rates, which were reported to be between11-38% in other studies, were 26% in our study [11,12]. The most common infections were reported to be respiratory tract infections, followed by the bloodstream and urinary tract infections in FEN patients [13]. Bloodstream infections were the most common infections, followed by lower respiratory tract and soft tissue infections in our study.

The rates of Gram-negative bacteria have increased in recent years in patients with FEN [14,15]. In our study, Gram-negative bacteria that produce extended-spectrum beta-lactamase (ESBL) in the bloodstream infections in our study were more common causative agents in blood and other cultures. ESBL producing *Enterobacteriaceae spp*. was prominent in the bloodstream infections. A mucosal injury of the gut due to chemotherapy causes the Gram-negative bacteremia arising from the intestinal flora [16]. Bacteremia and bloodstream infections were more common in hemato-group than onco-group, as the chemotherapy-induced mucosal damage was more common and the duration of neutropenia was longer in that group [2].

An antipseudomonal beta lactam-beta lactamase inhibitor antibiotic which is active also against ESBL positive *Enterobacteriaceae spp*. can be the first choice for the empirical therapy of FEN. If the patient has a history of resistant bacterial infection or colonization, a history of hospitalization in the ICU, the spectrum of antimicrobial may be broader [4]. Gedik *et al.* reported that most of the isolated Gram-negative bacteria did not produce ESBL in the infections of febrile neutropenic patients with hematologic cancer. Cefoperazone - sulbactam and piperacillin-tazobactam combinations were found to be effective in 75% of ESBL-producing Gram-negative bacteriemia and the rest of patients were treated with carbapenems [17]. Mortality rates were reported to be 5% of Gram-positive infections, 18% of Gram-negative infections, and 13% of polymicrobial infections in epidemiological studies, respectively. Infections with ESBL-positive Gram-negative bacilli, carbapenem-resistant *Pseudomonas spp*, and *Klebsiella spp*, and vancomycin-resistant enterococci are the main causes of high mortality rates. Early and appropriate antimicrobial therapy with broad-spectrum antibiotics appears to reduce mortality [18-20]. Mortality was reported to be 50% in patients with hematologic malignancy with carbapenem-resistant Gram-negative bacteremia [17]. The presence of pneumonia, persistent fever and necessity of antibiotic replacement or intensive care or mechanical ventilation were significantly higher in non-survivor patients, diagnosed with pneumonia, and followed up in ICU. Mechanical ventilation was found to be an independent risk factor for the mortality in our study. Günalp *et al.* reported that pulmonary infiltration and platelet count < 50,000 cells / mm^3 were independent risk factors for mortality [21]. The frequency of IFI is high in patients receiving chemotherapy. It was reported that mortality rates were between 30–80% in patients with invasive aspergillosis [22]. Therefore, fungal infections should be considered in case of prolonged fever in patients with FEN. Empirical antifungal treatment should be initiated and then radiological and microbiological examinations should be performed in patients with prolonged fever despite broad-spectrum antibiotic treatment. Empirical antifungal therapy was initiated to 26 patients including 12 patients that had clinical and laboratory findings of IFI with persistent fever in our study.

Limitations of the Study

The study was designed as a retrospective cohort study and data of patients were used to evaluate the factors related to the survival of patients. The study did not include any data, such as the response to chemotherapy, stage of the disease, relapse, and refractory illness. Two third of our patients had hematologic malignancies. Since the patient group included both hematologic and solid malignancies, a homogeneous group evaluation was could not be performed.

Conclusions

In conclusion, morbidity and mortality are higher in patients with hematological malignancies than patients with solid organ cancers due to a longer duration of neutropenia. The chemotherapy response of the patients against malignancy determines the prognosis of patients. In case of persistent fever, IFI should be kept in mind in patients with hematologic malignancies and antifungal treatment should be initiated. Although a persistent fever is common in patients with solid tumors, the necessity of antifungal therapy is rare due to the short duration of neutropenia.

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Conflict of interests: No conflict of interests is declared.