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Risk factors for febrile neutropenic attacks in patients who were given chemotherapy treatment for hematological malignancies

Hematolojik malignite nedeniyle kemoterapi verilen hastalarda febril nötropenik atak gelişimi için risk faktörleri

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Abstract

Aim Febrile neutropenic attacks are an important problem during and after chemotherapy. We retrospectively reviewed the records of patients who were administered chemotherapy treatment to identify the risk factors for febrile neutropenic attacks.

Materials and Methods: A total of 261 inpatient periods that included 154 patients (92 male and 62 female) between 2004 and 2006 were analyzed retrospectively. The median age was 49.5 (range, 17-80) years. Patients' clinical and demographic data were collected. We analyzed the relationship between febrile neutropenic attacks and clinical variables (diagnosis, age, sex, chemotherapy regimen, stem cell transplantation, the length of the neutropenic period, the presence of central venous catheter, and granulocyte colony stimulating factor [G-CSF] use) by a stepwise logistic regression model.

Results: Febrile neutropenic attacks were detected in 201 (77%) inpatient periods. A diagnosis of acute leukemia (OR: 3.36, 95% CI: 1.16-9.78, p=0.02), stem cell transplantation (OR: 8.77, 95% CI: 2.41-31.821, p=0.001), G-CSF use (OR: 8.46, 95% CI: 3.28-22.04, p=0.000) and length of the neutropenic period ≥ 10 days (OR: 4.01, 95% CI: 0.83-19.24, p=0.001) were risk factors for febrile neutropenic attacks.

Conclusion: Acute leukemia, stem cell transplantation, length of the neutropenic period ≥ 10 days and treatment with G-CSF were the most important risk factors for febrile neutropenic attacks. The result that G-CSF was a risk factor for febrile neutropenia was attributed to the fever-inducing effect of this drug. The use of G-CSF should be questioned in neutropenic patients with fever, especially in those without signs and symptoms of infection.

Keywords: Chemotherapy, febrile neutropenic attacks, hematological malignancy, risk factors.

Öz

Amaç: *Febril nötropenik ataklar kemoterapi sırasında ve sonrasında önemli bir problemdir. Biz febril nötropenik atak için risk faktörlerini saptamak için kemoterapi alan hastaların kayıtlarını geriye dönük olarak inceledik.*

Gereç ve Yöntem: *Toplam 154 (92 erkek ve 62 kadın) hastanın 2004-2006 yılları arasındaki 261 yatış periyodu geriye dönük olarak analiz edildi. Ortanca yaş 49.5 (17- 80) idi. Hastaların klinik ve demografik verileri toplandı. Febril nötropenik atak ve klinik değişkenler (tanı, yaş, cinsiyet, kemoterapi rejimi, kök hücre transplantasyonu, nötropeni süresi, santral venöz kateter varlığı ve G-CSF kullanımı) arasındaki ilişki logistic regresyon modeli kullanılarak analiz edildi.*

Bulgular: *Febril nötropenik atak 201(% 77) yatış periyodunda saptandı. Akut lösemi tanısı (OR: 3.36, % 95 CI, 1.16-9.78, p: 0.02), kök hücre nakli (OR:8.77, %95 CI,2.41-31.82, p:0.001), G-CSF kullanımı (OR: 8.46, 95% CI, 3.28-22.04, p: 0.000) ve nötropenik periyodun ≥ 10 gün olması (OR: 4.01, % 95 CI, 0.83- 19.24, p: 0.001) febril nötropenik atak için risk faktörü olarak saptandı.*

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Sonuç: *Akut lösemi, kök hücre nakli, nötropenik periyodun 10 günden uzun olması ve G-CSF kullanımı febril nötropenik atak için risk faktörü olarak saptanmıştır. G-CSF'nin febril nötropeni için risk faktörü olması ilacın ateş yapıcı etkisine bağlanmıştır. Özellikle infeksiyon semptom ve bulgusu olmayan febril nötropenik hastalarda G-CSF kullanımı sorgulanmalıdır.*

Anahtar Sözcükler: *Kemoterapi, febril nötropenik atak, hematolojik malignite, risk faktörleri.*

Introduction

Febrile neutropenic attacks (FNA) during and after chemotherapy treatment are important problems in patients with malignancies. These attacks can cause longer inpatient periods, can require more medication and can be life threatening.

In many studies, a diagnosis of acute leukemia was reported to be a risk factor for FNA (1-3). In addition, many other risk factors (such as age, the chemotherapy protocol, prophylactic antifungal treatment, gastrointestinal system sterilization, the neutrophil count during the attack, and thrombocytopenia) were identified as risk factors in many studies (1-7).

The Multinational Association for Supportive Care in Cancer score can be used for low-risk patients with solid tumors, but its usage is limited for hematologic malignancies (8-9). Here, using practical clinical parameters, we attempt to identify the risk factors for febrile neutropenic attacks in patients who were administered chemotherapy treatment.

Materials and Methods

Patients

A total of 261 inpatient periods that included 154 patients (92 male and 62 female) between 2004 and 2006 were analyzed retrospectively. The median age was 49.5 years (range, 17-80) years. The median duration between the diagnosis and the FNA was 6 months (range, 1-108 months). Patients were diagnosed with acute leukemia (68 patients), multiple myeloma (40 patients), or lymphoma (46 patients, Table 1).

Table-1. The Clinical Features and Characteristics of the Patients.

Age (years, median, range)	49.5 (17-80)
Sex (Male / Female)	92 / 62
Diagnosis	154
Multiple myeloma	40
Acute leukemia	68
ALL	20
AML	48
Lymphoma	46
NHL	30
HL	16
Stem cell transplantation (261 inpatient periods)	77
Autologous	67
Allogeneic	10
Length of the neutropenic period (days, median, range)	10 (1–96)
Neutrophil count (/mm^3, median, range)	68 (0–15400)

Five myeloablative (busulphan and cyclophosphamide) and one nonmyeloablative allogeneic conditioning regimens were administered in 6 of 113 inpatient periods of acute leukemia patients. Autologous conditioning regimen (busulphan and cyclophosphamide) was used in seventeen of them. Remission induction, consolidation or salvage chemotherapies were administered in 90 of 113 inpatient periods of acute leukemia patients. One non-myeloablative allogeneic conditioning regimen and 23 myeloablative autologous conditioning regimens (melphalan) were administered in 24 of 65 inpatient periods of myeloma patients. Induction chemotherapy (VAD [vincristine, adriamycin, dexamethasone] or bortezomib and dexamethasone) or mobilization chemotherapies (cyclophosphamide) were administered to 41 of 65 inpatients periods of myeloma patients. Two myeloablative (busulphan and cyclophosphamide) and one non-myeloablative allogeneic conditioning regimen were administered in 3 of 83 inpatient periods of lymphoma patients. Twenty-seven of them were treated with autologous conditioning regimen (BEAM [BCNU, etoposide, cytosine arabinoside, melphalan]). First line chemotherapy (CHOP for non-Hodgkin lymphoma patients and ABVD for Hodgkin lymphoma patients) or salvage chemotherapies (ESHAP or ICE) were administered in 16 of 83 inpatient periods of lymphoma patients.

The clinical features and characteristics of the patients (age, sex, diagnosis, stem cell transplantation, the length of the neutropenic period, use of granulocyte colony stimulating factor (G-CSF), the presence or absence of central venous catheter, neutrophil count, cause of death, chemotherapy regimen, antibiotic and/or antifungal treatments, culture results, and interventional procedures) were documented from the records of the hematology clinic.

Fluconazole and acyclovir were used as prophylaxis during the course of autologous and allogeneic transplantation treatment.

Settings

Our unit contained 3 rooms equipped with positive pressure isolation and HEPA filtration. Other rooms which contained 2 or 3 beds were conventional. The rooms with HEPA filtration were used for allogeneic transplantation.

Definitions

Fever was defined as a single oral temperature of 38.3°C or a temperature of 38.0°C for 1 hour.

Neutropenia was defined as a neutrophil count of <500 cells/mm^3. FNA was defined as any febrile period during the neutropenic period.

Physical examination was performed on all patients to help determine the cause of the fever. Before antibiotic treatment, blood cultures were obtained from a peripheral vein and from the central venous catheter if available. Urine samples and urine cultures were also obtained from all patients. The empirical antibiotic treatment was changed according to the culture and antibiogram results.

An antibiotic against gram-positive microorganisms was added to the initial treatment if the fever persisted for more than 72 hours. An antifungal regimen was added to the treatment if no microorganism was identified and the fever persisted for more than 48 to 72 hours. For the diagnosis of a possible fungal infection, computed tomography of the sinuses and high resolution computed tomography of lung was performed. Biopsies of the possibly infected tissues were performed.

Sterility testing and microbial sampling

For microbiologic cultures, 2 to 3 mL of each sample was inoculated in blood culture bottles of a commercially available bacterial detection system (BacT/ALERT 3D automated system, bioMérieux, Durham, NC, USA). The blood culture bottles were transported to the Ege University Medical Faculty Microbiology Laboratory. Bottles were incubated in the BacT/ALERT 3D system for a minimum of 7 days or until considered positive. Positive cultures were subcultured in 5% sheep blood agar, chocolate agar, eosin methylene blue agar, and Sabouraud dextrose agar. Mid-stream urine samples from the patients were transported to the Microbiology Laboratory. They were quantitatively inoculated in 5% sheep blood agar and eosin methylene blue agar. All isolated microorganisms were identified using conventional biochemical procedures and an automated bacterial identification system (VITEK 2, bioMérieux, Marcy-l'Etoile, France). In addition, antimicrobial susceptibility testing was performed for each isolate according to the Clinical and Laboratory Standards Institute guidelines.

Statistical analysis

For the univariate analysis, each potential risk factor was assessed using χ^2-test or, when appropriate, Fisher's exact test. We analyzed the relation between FNA and clinical variables (diagnosis, age, sex, chemotherapy regimen, stem cell transplantation, the length of the neutropenic period, the presence of central venous catheter, and G-CSF use) by the stepwise logistic regression model. P values less than 0.05 were considered significant. The data were analyzed using computer software (SPSS 16.0, SPPS, Inc., Chicago, IL).

Results

The median neutrophil count was 68/mm^3 (range, 0-15,400), and the median length of the neutropenic period was 10 days (range, 1-96 days) (Table 1). A total of 201 (77%) FNA were documented in 261 inpatient periods. We documented 80.1% of the FNA in 151 inpatient periods with central venous catheters, and 83.2% of the FNA were reported in 190 instances of G-CSF use. There were 151 inpatient periods with central venous catheters. 77 of them were double lumen dialysis catheter (32 juguler, 34 femoral and 11 subclavian dialysis catheters were used), and 74 were port catheter. Twenty-seven (13.4%) patients died in 201 FNA periods. The cause of death was related to infection in 21 (10.4%) and disease in 6 (3%) of those patients.

Wide-spectrum antibiotics against gram-negative bacteria were administered to all patients during the FNA. Antibiotics against gram-positive bacteria were administered in 52.2% of the cases. In cases in which the fever could not be controlled (44.8%), antifungal treatment was added to the initial antibiotic treatment. Antibiotic or antifungal modification was not performed in 138 (68.7%) periods. It was necessary to change the antibiotic agent, antifungal agent, or both in 31 (15.4%), 13 (6.5%) and 19 (9.5%) attacks, respectively. Proven fungal infection was reported in 9 (4.4%) febrile attacks.

Cultures were positive in 73 (36.3%) of 201 febrile periods. A total of 42 (47.8%), 37 (42 %) and 9 (10.2%) culture results revealed gram-positive bacteria, gram-negative bacteria and fungal organisms, respectively. The most commonly isolated gram-negative organisms were *E. coli* and *K. pneumonia*, and the most commonly isolated gram-positive organisms were *Staphylococcus* spp. Seventy-three febrile attacks were documented microbiologically and 11 (5.5%) were documented clinically and radiologically; 117 (58.2%) febrile attacks were accepted as fever of unknown origin (FUO).

Positive results were obtained from blood (49.3%), central venous catheter (15%), urine (9.5 %) and sputum (4.1%). The other cultures from which positive results were obtained (9.5%) were necrotic tissue, central venous catheter exit site, and abscess. A total of 12.3% of FNA produced positive results from more than one culture site.

By univariate analysis, diagnosis (p=0.001), type of the chemotherapy protocol (p=0.000), neutropenic period more than 10 days (p=0.000) and treatment with G-CSF (p=0.000) were documented as risk factors for febrile neutropenic attack.

By multivariate stepwise analysis, diagnosis of acute leukemia (OR: 3.36, 95% CI: 1.16-9.78, p=0.02), stem cell transplantation (OR: 8.77, 95% CI: 2.41-31.821, p=0.001), treatment with G-CSF (OR: 8.46, 95% CI:

3.28-22.04, p=0.000) and the length of the neutropenic period ≥10 days (OR: 4.01, 95% CI: 0.83-19.24, p=0.001) were risk factors for FNA (Table-2).

Table-2. Risk Factors for Febrile Neutropenic Attacks.

	OR	95% CI	P value
Being diagnosed as leukemia	11.72	1.42- 96.39	0.02
Stem cell transplantation	6.75	1.30- 35.01	0.02
G-CSF using	8.46	3.28- 22.04	0.000
The length of the neutropenic period ≥ 10 days	4.01	0.83- 19.24	0.001

Discussion

We documented 77% FNA in 261 inpatients periods of 154 patients who were administered chemotherapy treatment for hematological malignancies. While the incidence of FNA has been reported to be 13% in patients with solid tumors, a prospective study reported a rate of 27.1% for FNA in patients with newly diagnosed hematologic malignancies (10-12). In our study, the high incidence of FNA could be due to the inclusion of stem cell transplanted patients and patients with relapsed and refractory diseases. We included the patients with stem cell transplantation to our study because all patients stay in conventional rooms except 10 patients who were treated with allogeneic transplantation.

The incidence of FNA (35-92%) has been reported to be much higher in autologous stem cell transplanted patients (3, 13-15). We documented an incident rate of 95% of neutropenic febrile attacks in stem cell transplanted patients. All of the allogeneic stem cell transplanted patients and autologous stem cell transplanted patients with acute myeloid leukemia had FNA. However, for autologous stem cell transplanted patients with lymphoma and multiple myeloma, the ratio was 96.3% and 87%, respectively.

The median length of the neutropenic period has been found to be much higher for hematologic malignancies than for solid tumors, at 10.3 days vs. 4.4 days, respectively (1, 10). Here, we found that the median neutrophil count was 68/mm^3, and the median length of the neutropenic period was 10 days. These results were consistent with those found in the literature.

In the present study, while the presence of central venous catheter was not a risk factor for FNA, it has been documented as a risk factor for bacteremia in low-risk patients in another study (16). This result could be due to the fact that most of the patients have a central venous catheter during chemotherapy treatment at our clinic.

We documented the incidence of gram-positive and gram-negative bacteria as 42% and 47.8%, respectively. This was consistent with the literature (36.1-48.8% for gram-positive bacteria and 51.2-58.4% for gram-negative bacteria) (6, 17, 18). The most commonly isolated gram-negative microorganisms in our study were *E. coli* and *K. pneumonia* (34.1%). Sacar et al. found that the percentage of gram-negative microorganisms was 36.1%, which is comparable to our study (17). We also found that the most commonly isolated gram-positive microorganisms were *Staphylococcus* spp. (35.1%), which is similar to results from other studies (30.5-33.7%) in the literature (17, 19).

We found that the incidence of fungal infections confirmed by culture results was 10.2%. Another study found that the incidence of fungal infections confirmed by culture results was 5.6% (17). In our study, the incidence of proven antifungal infection was 4.4%, and the incidence of antifungal treatment was 44.8%. The incidence of antifungal treatment was very high compared to similar studies in the literature. Hoenigl et al. found that the incidence of fungal infection and the use of antifungal treatment were 3.4% and 17%, respectively (20). Another prospective study revealed that the incidence of fungal infection was 3.5% (18). Although the incidence of proven fungal infection was similar, we found that the incidence of empirical antifungal treatment was higher at our clinic. The incidence of mortality (8.4% vs. 6.7-15.6%) was similar to that reported in the literature (17, 18).

We found that acute leukemia (OR: 3.36, 95% CI: 1.16-9.78, p=0.02), stem cell transplantation (OR: 8.77, 95% CI: 2.41-31.821, p=0.001), treatment with G-CSF (OR: 8.46, 95% CI: 3.28-22.04, p=0.000) and the length of the neutropenic period ≥ 10 days (OR: 4.01, 95% CI: 0.83-19.24) were the major risk factors for FNA (Table 2) in this study. In the literature, acute leukemia (OR: 1.89 for AML and 2.04 for ALL) has been documented as a risk factor for FNA in both autologous transplantation and patients who were treated for hematological malignancies (1, 3). This may be due to the longer length of the neutropenic period and the lower nadir neutrophil counts in acute leukemia patients than in multiple myeloma and lymphoma patients. We also did not use G-CSF treatment in acute leukemia patients, and this strategy may contribute to longer neutropenic periods and lower neutrophil counts.

Stem cell transplantation increased the risk of FNA by 8-fold (Table-2). High-dose chemotherapy and mucositis related to chemotherapy increase the risk of febrile neutropenic attacks in patients treated with stem cell transplantation (3, 13-15).

In the literature, it was reported that prophylactic use of In the literature, it was reported that prophylactic use of G-CSF decreases the length of neutropenic period and decreases the risk of infectious complications (21).

Interestingly, we found that G-CSF use was a risk factor for febrile attacks in neutropenic patients. In a recent study with early-stage breast cancer patients, the prophylactic use of filgrastim decreased the febrile neutropenic attacks; however, there was still a group of patients in whom the incidence was increased despite of prophylactic G-CSF treatment. In that study it was thought that this increase was associated with three variables; age, chemotherapy regimen, and primary G-CSF type (filgastrim). Patients receiving primary prophylaxis with G-CSF with pegfilgrastim had a febrile neutropenia incidence of 8% compared with 28% in patients receiving filgrastim (OR: 4.3; p=0.003), a difference that remained highly significant in multivariate analysis (p=0.006) (22). In addition, some studies reported that treatment with G-CSF could cause febrile periods in both cancer patients and healthy volunteers as a side effect (23-26). Since treatment with G-CSF was found to be a risk factor by both univariate analysis and multivariate stepwise analysis we should keep in mind that G-CSF could be responsible for febrile attacks in neutropenic patients without any infectious signs and symptoms. This effect could be due to its side effect, not associated with an infectious event.

It was reported in the literature that a neutropenic period longer than 10 days was a risk factor for febrile neutropenic attacks (1, 27, 28). Our results were consistent with the literature.

Some guidelines provide a general approach to the management of patients with cancer who have neutropenia and present with fever, and it gives special attention to antimicrobial management (29, 30). In the IDSA guidelines, febrile neutropenia incidence over 80% has been reported in patients with hematologic malignancies. Prolonged neutropenia (>7 days) is considered a risk factor. Frequencies of gram-positive and gram-negative bacteremia are approximately 57% and 34%, respectively. Gram-positive organisms have become more common because of increased use of indwelling plastic venous catheters, which can allow for colonization by and entry of gram-positive skin flora. Coagulase-negative staphylococci are the most common blood isolates in most centers; *Enterobacteriaciae* (eg, *Enterobacter* species, *Escherichia coli* and *Klebsiella* species) and nonfermenting gram-negative rods (eg, *Pseudomonas aeruginosa* and *Stenotrophomonas* species) are isolated less often (29). In the ESMO guidelines, the overall mortality rate from febrile neutropenia has been reported as high as 11% in some hematological malignancies (30). Our results were similar to these guidelines.

Our study has limitations common in other retrospective studies. First, there was no randomization, so this could cause selection bias. In addition, there was not a balanced distribution of other possible risk factors between the groups. The sample size was small and there was a heterogeneous group of patients with different malignancies. Only 10 patients were treated with allogeneic stem cell transplantation. We couldn't analyze these patients separately because of the small number of this patient group.

Conclusion

FNAs were detected in 77% of the inpatient periods of patients who were administered chemotherapy treatment for hematological malignancies. Acute leukemia, stem cell transplantation, the length of the neutropenic period ≥ 10 days and treatment with G-CSF were the most important risk factors for febrile neutropenic attacks. The use of G-CSF should be questioned in neutropenic patients with fever, especially in those without signs and symptoms of infection.

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