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Research Article

In the management of febrile neutropenia; evaluation of the factors affecting the lenght of hospital stay

Febril nötropeni yönetiminde yatış süresine etki eden faktörlerin değerlendirilmesi

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Abstract

Aim: Febrile neutropenia (FEN) is one of the most serious and commonly seen complications of patients receiving chemotherapy for a diagnosis of hematological malignancy. FEN is an emergency condition with mortality rates reaching 40% because of an increase in antimicrobial-resistant pathogens in particular. In a situation with such high mortality rates, parameters that can predict prognosis play an important role in the approach to the patient. The aim of this study was to investigate the parameters that could affect prognosis in the follow-up of FEN.

Material and Methods: The study included 58 patients hospitalised in the Hematology Clinic with a diagnosis of FEN. The patients were evaluated in respect of the recorded demographic characteristics, blood group, MASCC score, hemogram, procalcitonin, C-reactive protein (CRP), Interleukin-6 (IL-6), D-dimer, fibrinogen, pre-albumin, albumin, HbA1c, anthropometric measurements and length of stay in hospital.

Results: According to the statistical analysis results, patients with a length of hospital stay of ≥14 days were determined to have a significant decrease in the MASCC score and thrombocyte count and the procalcitonin, Il-6, D-dimer values and the number of antibiotics used were higher. No significant difference was determined between the groups in respect of the other parameters.

Conclusion: In the management of febrile neutropenia, the most important points are the establishment of indications for hospitalisation, rapid and early recognition of a worsening status and intervention made in the right place at the right time. Parameters with prognostic benefit will help the clinician in decision-making.

Keywords: febrile neutropenia, hematological malignancy, length of hospital stay, IL-6, procalcitonin

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Öz

Amaç: Febril nötropeni (FEN); kemoterapi alan hematolojik malignite tanılı hastalarda en yaygın karşılaşılan ve en ciddi komplikasyonlardandır. .FEN ; özellikle antimikrobiyal dirençli patojenlerin artışı nedeniyle mortalitesi %40 lara varan acil bir durumdur. Mortalitesi bu kadar yüksek olan bir durumda prognozu öngören parametrelerin olması ; hastaya yaklaşımda önemli rol oynayabilir. Çalışmamızda FEN takibinde prognozu etkileyebilecek parametreler araştırılmıştır.

Gereç ve Yöntemler: FEN tanısı ile hematoloji kliniğine yatmış olan 58 hasta çalışmaya dahil edilmiştir. Hastaların demografik özellikleri, kan grubu, MASCC skoru, hemogram, procalsitonin, CRP(C-reaktif protein), IL-6(interlökin-6), D-Dimer, Fibrinojen, prealbumin , albümin, HbA1c, antropometrik ölçümler ve yatış süresi kayıt edilmiştir.

Bulgular: Yapılan istatistiksel analiz sonucuna göre yatış süresi 14 gün ve üstünde olan grupta MASCC skoru , trombosit sayısı , anlamlı düşük saptanmış iken prokalsitonin, IL-6, D-dimer , kullanılan antibiyotik sayısı yüksek saptanmıştır. Diğer parameterlerde iki grup arasında anlamlı farklılık saptanmamıştır.

Sonuçlar: Febril nötropeni yönetiminde; hastaya yatış endikasyonu konulması, kötüye gidişin hızlı ve erken farkedilmesi, müdahalelerin yerinde ve zamanında yapılması en önemli noktalardandır. Bunlara karar verilmesinde prognostik yararı olan parameterelerin olması klinisyene yarar sağlayacaktır.

Anahtar Kelimeler: febril nötropeni; hematolojik malignite; yatış süresi; IL-6; prokalsitonin

Introduction

Febrile neutropenia (FEN) is one of the most serious and commonly seen complications of patients receiving chemotherapy for a diagnosis of hematological malignancy. Neutropenic fever is defined as a single measurement of >38.3°C or fever ≥38°C lasting for 1 hour with absolute neutrophil count <500µl, or expected to fall to <500 within 48 hours. Neutrophil values of <100µl are defined as deep neutropenia and this creates a higher risk of bacteremia (1). FEN is an emergency condition with mortality rates reaching 40% because of an increase in antimicrobial-resistant pathogens in particular, and there are documented microbial infections in only 30%.

Therefore, a rapid first evaluation with full blood count for the degree of neutropenia, then performing the necessary tests for infection focus screening (blood culture, urine culture, the necessary tests for the potential infection region) will allow a rapid transition to empirical treatment (2, 3). In a condition with such high mortality rates, parameters that can predict prognosis and response to treatment can play an important role in the approach to the patient, the early initiation of empirical treatment, and a change in treatment. The aim of this study was to investigate the parameters that could affect prognosis in patients with hematological malignancy who were receiving chemotherapy and were hospitalised because of FEN.

Material and Methods

The study included 58 patients hospitalised in the Hematology Clinic of Dışkapı Yıldırım Beyazıt Training and Research Hospital between July 2021 and August 2022. The patients were receiving chemotherapy for a diagnosis of hematological malignancy and were then hospitalised with a diagnosis of FEN. The patients were evaluated in respect of the recorded demographic characteristics, blood group, MASCC score, hemogram, procalcitonin, C-reactive protein (CRP), Interleukin-6 (IL-6), D-dimer, fibrinogen, pre-albumin, albumin, HbA1c, anthropometric measurements, and length of stay in hospital.

Statistical Analysis

The data obtained were analyzed using SPSS vn 28.0 software. Descriptive statistics were stated as mean ±standard deviation, median, minimum and maximum values, number (n) and percentage (%). Conformity of the data to normal distribution was assessed with the Kolmogorov-Smirnov test. In the analysis of independent quantitative data, the Mann Whitney U-test was used. Qualitative data were analyzed using the Chi-square test, or the Fischer test if Chi-square conditions were not met.

Ethical approval and informed consent

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Etlik City Hospital, Ankara, Turkey (03.05.2023-AESH-EK1-2023-143).

Results

Evaluation was made of 58 patients, comprising 40 (69%) males and 18 (31%) females with a mean age of 55.8 ± 16.5 years. The demographic characteristics and descriptive statistics of the patients are shown in Table 1.

Table 1. Descriptive statistics of the data and distribution of demographic parameters of the patients

		Mean±SD/n-%		
Age (years)		55.8	±	16.5
Gender	Female	18		31.0%
	Male	40		69.0%
Fever		40		69.0%
Cough		21		36.2%
Abdominal pain		5		8.6%
Anal pain		7		12.1%
Difficulty swallowing		5		8.6%
Toothache		3		5.2%
Cellulite		4		6.9%
Duration of fever		3.1	±	2.1
MASCC		18.1	±	4.3
WBC		732.2	±	579.2
HGB		8.0	±	2.0
PLT		55190	±	79287
PDW		11.5	±	2.9
PCT		0.1	±	0.1
MPV		10.5	±	1.2
Glucose		120.3	±	36.6
Procalcitonin		10.6	±	25.6
CRP		171.6	±	102.2
IL-6		170.9	±	283.0
D-Dimer		6.5	±	24.2
Fibrinogen		438.1	±	184.6
Pre-albumin		0.1	±	0.1
Albumin		3.5	±	3.6
HbA1C		6.2	±	1.0
Malnutrition Risk	(-)	31		53.4%
	(+)	27		46.6%
Number of antibiotics		2.6	±	1.5

MASCC: Multinational Association for Supportive Care in Cancer, WBC:White Blood Count, HBG:Hemoglobin , PLT:Platelet
PDW: Platelet Distribution Width, PCT:Plateletcrit, MPV: Mean Platelet Volume, CRP: C-Reactive Protien, IL-6:Interleukin-6

The factors affecting length of hospital stay were examined. According to the statistical analysis results, patients with a length of hospital stay of ≥14 days were determined to have a significant decrease in the MASCC score and thrombocyte count and the procalcitonin, IL-6, D-dimer values, and the number of antibiotics used were higher. No significant difference was determined between the groups in respect of the other parameters (Table 2).

Discussion

Febrile neutropenia (FEN), which has a high mortality rate, is one of the most frequently encountered complications in patients receiving chemotherapy. In a 1966 study by Bodey et al., increased mortality was determined in patients diagnosed with acute myeloid leukemia who had neutrophil values <500 (4). Approximately 40%-50% of the hospital costs of cancer patients have been reported to be due to FEN (5).

The Multinational Association for Supportive Care in Cancer (MASCC) score was developed in 2000 and is recommended to be used for the risk classification of patients. The MASCC score is used mostly for outpatients, with a value of ≥21 evaluated as low risk and a value <21as high risk. With this evaluation, it is predicted that low-risk patients can be treated with oral antibiotics as outpatients (6). Although there is no routine use of this score for hospitalised patients, some studies have recommended that it can be used for hospitalised patients (7, 8). In the current study, a relationship was determined between the MASCC score and the length of stay in hospital, and the score was determined to be statistically significantly low in patients with a hospital stay of ≥14 days.

The thrombocyte count, which is affected by the production and destruction of platelets, may decrease with an imbalance between these two states. One of these factors is infection and fever. Thrombocytopenia has been found to be associated with increased mortality in intensive care patients (9). The results of the current study also showed that thrombocytopenia was associated with a longer length of stay in hospital. As a longer length of hospital stay indirectly shows the severity of the patient, these data obtained were consistent with the literature.

Procalcitonin (PCT), which is a precursor of calcitonin hormone, was first described as a sepsis marker in 1993 (10). It has been shown in many studies that PCT is a marker with high sensitivity for the diagnosis of infection and the follow-up of progression (11, 12). In the current study, PCT was found to be statistically significantly associated with a long stay in hospital.

D-Dimer is a cross-linked fibrin degradation product, which has been shown to be a marker of fibrinylosis and indirectly of thrombotic activity (13). Other than in thrombotic events, D-dimer can also be elevated in conditions of inflammation and severe infection (14). In the current study, D-dimer was found to be elevated proportional to a longer hosptial stay. FEN of varying degrees can be confused with infection. The examination of D-dimer at the time of diagnosis can be of guidance in respect of severe infection, a severe course, and the decision for hospitalisation and rapid intervention.

Table 2. Comparisons of the parameters of the groups with length of hospital stay of more or less than 14 days

		Hospital stay <14 days			Hospital stay ≥14 days			P	
		Mean±SD/n-%			Mean±SD/n-%				
Age (years)		54.7	±	10.6	56.3	±	18.5	0.472	m
Gender	Female	8		47.1%	10		24.4%	0,089	X^2
	Male	9		52.9%	31		75.6%		
Fever		2.5	±	1.7	3.3	±	2.2	0.231	m
Cough		4		23.5%	17		41.5%	0.156	X^2
Abdominal pain		3		17.6%	2		4.9%	0.144	X^2
Anal pain		1		5.9%	6		14.6%	0.182	X^2
Difficulty swallowing		1		5.9%	4		9.8%	0.548	X^2
Toothache		1		5.9%	2		4.9%	0.504	X^2
Cellulite		2		11.8%	2		4.9%	0.504	X^2
MASCC		20.2	±	3.3	17.1	±	4.4	0.007	m
WBC		648	±	466	767	±	622	0.871	m
HGB		8.4	±	1.7	7.9	±	2.1	0.171	m
PLT		94706	±	112159	38805	±	54658	0.038	m
PDW		11.3	±	1.9	11.6	±	3.2	0.765	m
PCT		0.08	±	0.09	0.05	±	0.05	0.203	m
MPV		10.3	±	0.95	10.5	±	1.2	0.510	m
Glucose		118	±	30.4	121	±	39.2	0.952	m
Procalcitonin		7.4	±	24.3	11.9	±	26.3	0.010	m
CRP		160	±	86.2	177	±	109	0.758	m
IL-6		49.0	±	27.9	221	±	324	0.029	m
D-Dimer		2.6	±	3.8	8.1	±	28.6	0.030	m
Fibrinogen		432	±	158	441	±	196	0.905	m
Pre-albumin		0.15	±	0.08	0.12	±	0.08	0.111	m
Albumin		3.2	±	0.65	3.7	±	4.3	0.183	m
HbA1C		5.8	±	0.93	6.4	±	1.02	0.065	m
Malnutrition Risk	(-)	12		70.6%	19		46.3%	0,092	X^2
	(+)	5		29.4%	22		53.7%		
Number of antibiotics		1.8	±	1.3	2.9	±	1.5	0.001	m
Length of hospital stay (days)		11.2	±	2.4	28.4	±	12.7	0.000	m

X^2 Chi-square test / m Mann Whitney U-test
MASCC: Multinational Association for Supportive Care in Cancer, WBC:White Blood Count, HBG:Hemoglobin , PLT:Platelet
PDW: Platelet Distribution Width, PCT:Plateletcrit, MPV: Mean Platelet Volume, CRP: C-Reactive Protien, IL-6:Interleukin-6

IL-6 is a cytokine that has an effect on hematopoietic cell differentiation with T and B lymphocytes. In literature, IL-6 has been shown to be a sensitive biomarker for disease severity and infection, it can be more effective than CRP and some other markers in severe infectious conditions, and it has been emphasized that specificity can be further increased when it is evaluated combined with some other markers (15-17). In the current study, the IL-6 level was found to be statistically significant in patients with a length of hospital stay of ≥14 days.

Conclusion

In patients diagnosed with cancer and especially those with a diagnosis of a hematological malignancy, neutropenia is frequently seen and is an inevitable condition following chemotherapy. FEN must be kept in mind at all times as it is a complication that requires good management. The most important points in the management of FEN are the establishment of indications for hospitalisation, rapid and early recognition of a worsening status, and intervention made in the right place at the right time. Parameters with prognostic benefit used singly or combined will help the clinician in decision-making.

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Conflict of Interests

The authors have no conflict of interests to declare

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