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Evaluation of malnutrition in patients with febrile neutropenia

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ABSTRACT

OBJECTIVE: Febrile neutropenia is a critical condition in patients with malignancy, requiring oral and/or parenteral antibiotic treatment; and a significant cause of mortality and morbidity. It is well known that nutritional status is excessively impaired in these patients due to underlying disease itself along with the chemotherapeutics used. In this study we investigated nutritional status and general characteristics of patients admitted to our internal medicine clinic with febrile neutropenia.

METHODS: Thirty patients who were followed up in the internal medicine service were included in the study. For the analysis of the data of the patients, height, weight, body mass index (BMI), weight loss in the last three months, albümin and total iron binding capacity values were recorded. Hand grip strength, mid-upper arm and mid-calf circumference measurements were obtained for the assessment of muscle strength; Mini Nutritional Assessment (MNA) and Nutrition Risk Screening 2002 (NRS 2002) scores were calculated at admission and discharge to evaluate nutritional status. Multinational Association of Supportive Care in Cancer (MASCC) score was used to identify risk and manage treatment.

RESULTS: We included thirty patients (mean age 58.27±16.52 years, 53% females). Of 30, six patients had lung cancer, four patients had myelodysplastic syndrome, three patients had stomach cancer, two patients had gastrointestinal system lymphoma, two patients had colon cancer, two patients had breast cancer, two patients had Non-Hodgkin's lymphoma.

CONCLUSION: Majority of the patients, admitted to our internal medicine clinic, with febrile neutropenia were found to be malnourished; regardless of their risk classifications. Nutritional assessment scores of the majority were in the low-risk group. In conclusion, patients hospitalized with febrile neutropenia had poor nutritional status.

Keywords: Febrile neutropenia; malnutrition; MASCC score; nutritional tests.

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Febrile neutropenia (FN) is the development of fever ≥38.3 C° in a patient with neutropenia, without any other influential environmental factors [1].

The National Febrile Neutropenia Association Study Group in Turkiye set up a guideline and indicated fever as the measurement of body temperature either oral or axillary ≥38.3 C° once or 38–38.2 C° for an hour. For the same purpose, neutropenia is defined as neutrophil count less than 500/mm^3, or between 500 and 1000/mm^3 and is expected to drop below 500/mm^3 [2].

Febrile neutropenia is still one of the major complications of chemotherapy and a leading cause of morbidity in cancer patients in spite of the developments in prophylaxis treatment. Various approaches, dose reduction and delays in courses of treatment, have been tested for prevention. Mortality is around 5% in solid tumors and over 11% in hematologic malignancies [3].

The source of infection is blood in 34%, upper and lower respiratory tract in 23% and 13%, respectively, soft tissue including skin and intravascular devices in 18%,

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and gastrointestinal tract in 7%; whereas not indicated in 56% of patients with neutropenic fever [4].

Alteration in skin integrity due to injection, venipuncture, or intravascular catheterization causes skin and soft tissue infections. Major causing microorganisms are coagulase-negative staphylococci, Gram-positive cocci mainly *Staphylococcus* aureus and Gram-negative enteric bacilli (e.g., *Escherichia coli* and *Klebsiella* species). Given the humid environment in axillary region, Gram-negative bacilli such as *Pseudomonas aeruginosa* may cause hidradenitis apart from skin flora bacteria. Intravascular catheterization is an important source of infection usually caused by coagulase negative staphylococci, *Propionibacterium* and *Corynebacterium* species, viridans streptococci found in normal skin flora; and other pathogens including *S. Aureus*, Gram-negative bacilli, and *Candida species*. Vancomycin resistant *Leuconostoc*, *Pediococcus* and *Lactobacillus* species are rare causes of infection in FN [5].

Recent epidemiological studies with solid tumors determined an increase incidence of Gram-negative bacteria infections. Gram negative bacteria, most common causes being *E. Coli*, *Pseudomonas* and *Klebsiella* species, are mainly of intra-abdominal origin and seen as polymicrobial infections involving anaerobic bacteria [6, 7].

Fungi may end up with life threatening infections in cancer patients with neutropenia. Frequently, they cause secondary infections. Prolonged and severe neutropenia along with prior antibiotic use are important risk factors for fungal infections; others include long hospital stay, glucocorticoid use, and proximity to construction areas. *Candida* and *Aspergillus* species are the most common fungi detected [4].

Risk assessment for possible complications must be done in all neutropenic patients with fever. For this purpose, "Multinational Association for Supportive Care in Cancer (MASCC)" criteria is the most commonly used assessment tool: maximum score is 26 and ≥21 is categorized as low risk [8].

Malnutrition is a major socioeconomic problem in today's health care environment, with an estimated prevalence of 30–50%. The prevalence may be even higher in long-term care facilities, reportedly as high as 85%. Furthermore, malnutrition has been associated with increased healthcare-related costs, including longer hospital stays and increased rates of major and minor complications [9].

Highlight key points

- According to NRS 2002, 59% of patients were found to be malnourished; based on MNA assessment, 56% had malnutrition, 37% were at risk of malnutrition, and 7% had normal nutritional status.
- There was a significant increase in leukocyte, neutrophil, and lymphocyte counts between admission and discharge ($p<0.05$).
- The source of infection could not be identified in 30% of the patients; among the identified sources, the most common was lower respiratory tract infection (26.7%).
- Following initial treatment, fever subsided within the first 24 hours in 64% of patients; 77% were classified as low-risk febrile neutropenia according to the MASCC score.
- No significant correlation was found between MASCC score and hand grip strength, nutritional assessment scores, or neutrophil-related parameters.

Protein malnutrition (PM) is the most common type of malnutrition and leads to various physiological consequences depending on its duration and intensity. PM primarily affects hematopoietic tissues due to continuous turnover. PM causes changes in the lymphohematopoietic organs (bone marrow (BM), spleen and thymus), anemia, leukopenia and changes in the immune system, increasing susceptibility to infections [10]. Malnutrition increases the risk of febrile neutropenia in children with malignancies by decreasing cytokine response and hormonal changes [11]. The presence of malnutrition increases treatment-related toxicities in cancer patients receiving chemotherapy. it is estimated that deaths in 10–20% of patients are due to adverse events related to malnutrition, not the tumor itself. therefore, it is recommended to assess malnutrition and ensure adequate nutrition before starting treatment [12].

Our aim in this study was to evaluate the nutritional status of patients admitted to our internal medicine clinic with febrile neutropenia.

MATERIALS AND METHODS

In our single center study, we included patients admitted to our internal medicine clinic with febrile neutropenia after receiving cancer treatment. Patients were included regardless of their malignancy types, treatments, receiving chemotherapy and/or radiotherapy, course of treatment and disease activity status. For the purpose of not to interfering with nutritional assessments, patients with

physical disabilities or failure of oral feeding were excluded. Height, weight, body mass index (BMI), weight loss in the last three months, albumin and total iron binding capacity (TIBC) levels were recorded. Anthropometric measurements could not be taken for 3 patients because they died or were sent to intensive care.

A hand grip test was performed to evaluate for sarcopenia. The hand grip test was performed using a hand dynamometer with the dominant hand [13]. A weight <16 kg (kilogram) for women and <27 kg for men was considered as possible sarcopenia [14].

Mini Nutrition Assessment (MNA), Nutritional Risk Screening 2002 (NRS 2002) scores were calculated at the time of admission and at discharge in order to evaluate nutritional status. Patients with an NRS-2002 total score ≥3 were defined as malnourished. According to MNA evaluation, patients were classified as well-nourished with a score above 24 points, at risk of malnutrition between 17–23 points, and severely malnourished with a score below 17 points.

Mid-upper arm measurement was performed at the midpoint between the tip of the shoulder and the tip of the elbow; mid-calf measurement was performed at the widest part of the gastrocnemius muscle.

We recorded general clinical characteristics; primary malignancy site and metastatic disease if present, source of infection, obtained cultures and grown microorganisms, received antibiotics, duration of the treatment, afebrile time point and following laboratory tests; lymphocyte, neutrophile, hemoglobin levels during admission and at discharge. Multinational Association of Supportive Care in Cancer (MASCC) score was used to identify risk and manage treatment.

Ethical Standards

The study was conducted in accordance with the Declaration of Helsinki. The institutional clinical research ethics committee approved this study protocol on May 6, 2016 (approval number: 6905).

Statistical Analysis

For statistical analysis, descriptive analysis was used for continuous variables (mean, median, mode, standard deviation, minimum, maximum). Normal distribution was tested with Shapiro-Wilks's test. Student's T-test was used for dependent and not normally distributed two group comparison and ANOVA was used to comparise more than two groups. Two dependent and normally distributed continuous variables were compared with Wilcoxon Signed Rank Test, and Friedman test was used to compare of more than two variables. McNemar test was used for paired nominal variables. Statistical significance was set at $p<0.05$. MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013) was used for the analyses.

Table 1. Sociodemographic data (n=30)

Gender (%)	
Woman	53.3
Male	46.7
Age (Mean±SD)	58.27±16.52
Marriage status (%)	
Married	80
Single	6.66
Widowed/divorced	13.33
Education status (%)	
Illiterate	13.33
Primary school	46.66
Middle school	23.33
High school	10
University	6.66

SD: Standard deviation.

RESULTS

We included 30 patients (mean age 58.27±16.52 years, 53% females) (Table 1). Mean body temperature measured at admission was 38.5±0.4 and mean absolute neutrophil count was 219.3±222.3. Out of 30 patients, 6 (20%) had lung cancer, 4 (13.4%) had myelodysplastic syndrome and 3 (10%) had gastric cancer. 8 patients had metastases and 22 patients had no metastases.

There was statistical significance in leukocyte, neutrophil, and lymphocyte levels of patients between measurements during admission and at discharge ($p<0.05$ for all) (Table 2). However, there was no significant change in MNA and NRS 2002 scores. Based on NRS 2002, 59% of our patients had malnutrition. When we assessed patients with MNA test; 56% had malnutrition, 37% had malnutrition risk, and %7 had normal nutritional status.

Table 2. Blood tests and nutritional assessment in patients admitted with febrile neutropenia

	Mean	SD	p
Hemoglobin – A (n=30)	8.38	2.07	0.06*
Hemoglobin – D (n=30)	9.17	1.15	
Leukocyte – A (n=30)	1810	2881	<0.01**
Leukocyte – D (n=30)	7060	8019	
Neutrophil – A (n=30)	219.3	222.28	<0.01**
Neutrophil – D (n=30)	3698.7	4622	
Lymphocyte – A (n=30)	942	1673	<0.01**
Lymphocyte – D (n=30)	2447	4489	
NRS 2002 – A (n=27)	2.81	1.47	0.180*
NRS 2002 – D (n=26)	2.88	1.68	
MNA – A (n=27)	16.2	5.1	0.160*
MNA – D (n=26)	16.98	5.32	

SD: Standard deviation; A: Admission values; D: Discharge values; NRS 2002: Nutritional Risk Screening; MNA: Mini nutrition assessment; *: Paired samples t Test; **: Wilcoxon Test.

Table 3. Blood culture analysis in patients admitted with febrile neutropenia

Bacteria (n=24)	%
Corynebacterium mucifaciens (n=1)	4.2
Escherichia coli (n=1)	4.2
Klebsiella pneumoniae (n=1)	4.2
Staphhylococcus epidermidis (n=1)	4.2
Stenotrophomonas maltophilia (n=1)	4.2
No growth (n=19)	79.1

Table 4. Antibiotic regimens in patients admitted with febrile neutropenia

Antibiotic (n=30)	%
Not used (n=1)	3.3
Imipenem, daptomycin (n=1)	3.3
Piperacillin Tazobactam, daptomycin (n=1)	3.3
Imipenem (n=1)	3.3
Imipenem, teicoplanin (n=1)	3.3
Meropenem (n=3)	10
Meropenem, vancomycin (n=1)	3.3
Meropenem, metronidazole (n=1)	3.3
Piperacillin tazobactam (n=18)	60
Piperacillin tazobactam, metronidazole (n=1)	3.3
Unknown* (n=1)	3.3

*: Patient was sent to another hospital.

Table 5. Anthropometric measurements of patients admitted with febrile neutropenia (n=27)

	Mean	SD
Height*	164.8	8.3
Weight**	64.15	9.5
Body Mass Index (kg/m2)	23.88	5.06
Weight Loss in Last 3 Months**	3.89	2.37
Mid-upper Arm*	26.96	4.66
Mid-calf Circumference*)	42.15	8.57
Hand Grip Strength**	17.59	8

SD: Standard deviation; *: Centimeter; **: Kilogram.

The source of infection could not be determined in 9 (30%) patients. The source of infection was lower respiratory tract infection in 8 (26.7%) patients, upper respiratory tract infection in 4 (13.3%) patients and urinary tract infection in 3 (10%) patients. Of 30, blood cultures were obtained in 24 patients; and blood culture analysis are shown in Table 3. Urine cultures were checked in 20 patient, 17 patients had no growth. *Enterobacter Aerogenes*, *Escherichia coli* and *Stenotrophomonas maltophilia* were grown in 1 patient. Table 4 demonstrates the antibiotic regimens used. Five patients (19%) had pyuria in urinalysis, eight patients (29%) had pulmonary infiltrates on chest X-ray, and one patient (4%) was found to have a metastatic lesion.

On follow-up, fever was reduced in the first 24 hours after initial treatment in 18 patients (64%) and during second day in 10 patients (36%). Of 30, 23 patients (77%) had low risk and seven patients (23%) had high risk febrile neutropenia based on MASCC scoring. Mean albumin level was 3.0±0.5 and CRP was 14.8±10.4.

Table 5 demonstrates mean height, weight, body mass index (BMI), weight loss in the last three months; mid-upper arm, mid-calf circumference, and hand grip strength measurements.

Table 6. MASCC score and nutritional assessment correlation in patients admitted with febrile neutropenia

	MASCC score
Neutrophil - A	0.01
Neutrophil - D	0.157
NRS 2002 - A	-0.199
NRS 2002 - D	-0.197
MNA - A	0.182
MNA - D	0.295
Neutrophil/lymphocyte	0.133
Hand grip strength	0.08

A: Admission; D: Discharge; NRS: Nutritional Risk Screening; MNA: Mini nutrition assessment; MASCC: Multinational association of supportive care in cancer.

There was no statistically significant correlation between MASCC score and hand grip strength measurement; NRS 2002 and MNA scores; neutrophil count, neutrophil to lymphocyte ratio both during admission and discharge (Table 6).

DISCUSSION

Majority of the febrile neutropenia patients in our study had malnutrition, but there was no relation between malnutrition and MASSC scores.

Antineoplastic therapy in cancer patients mostly effects rapidly proliferating bone marrow cells; reduces neutrophil count besides suppressing their function, and consequently predisposes to infections [4].

Poor nutrition, other organ system dysfunction due to underlying disease, mechanical obstruction, intervention and catheterization causing damage in anatomical barrier, destroyed epithelial and mucosal integrity following cytotoxic chemotherapy (mucositis), bleeding disorders, impaired immune function because of other treatments (e.g. monoclonal antibodies, fludarabine, and glucocorticoids), radiotherapy, flora changes due to prolonged hospital stay and antibiotic use are other significant risk factors for infection in cancer patients [4].

Neutrophil functioning is the leading defence mechanism of the body against microorganisms. Chemotherapy in cancer patients causes reduction in neutrophil count and impairment in their function. Decrease in neutrophil count is associated with increased risk of infection and severity. Bacteremia is present in 20% of patients with severe neutropenia (<100/mm^3) [15].

Chemotherapy induced severe neutropenia in patients with solid tumors lasts less than seven days. Thus, febrile neutropenia incidence in solid tumors does not exceed 5–50%. Neutropenic fever caused by multiple chemotherapeutic agents is seen in 10–50% of solid tumors, and the ratio increases up to 80% in hematologic malignancies [5, 16]. In our study, 11 patients (37%) had hematologic malignancies and six patients (20%) had solid tumors, with lung cancer being in the lead.

Although increased body temperature in cancer patients might be due to the underlying disease itself, chemotherapeutic and antibiotic agents used, or blood transfusions; infections are the reason for fever in two thirds of patients with neutropenia. More than half of those cases are diagnosed with 'fever of unknown origin' [1]. In our study group, most common infections occurred in pulmonary system with eight patients (27%), and source of infection was not determined in nine patients (30%).

Bacterial infections are the most commonly seen infections in neutropenic patients. Gram-negative bacteria used to be responsible for bacteremia about thirty years ago. However, as a result of the increased use of catheterization started in 1980s, gram-positive bacteria in normal skin flora havebeen seen more frequently since then. In the last few years, multidrug resistant Gram-negative microorganisms have been the increasing cause of infection. Recent studies showing Gram-negative bacteria ratios of about 25% extending up to 76% [5–7]. Our data reported Gram-negative bacteria growth in cultures (urine, blood and wound) of eight patients (80%), consistent with literature.

The most frequently obtained bacteria in cultures are Gram-positive coagulase negative *Staphylococci*, Viridans *Streptococci*, *S. Aureus* and *Ecnterococci* species [4, 5]. Gram-positive bacteria isolated in our study patients were Corynebacterium mucifaciens and *S. Epidermiditis*. *E. Coli*, *Klebsiella* species and *Pseudomonas aeruginosa* are the leading causes of Gram-negative infections. Particularly, extended-spectrum beta lactamase producing pathogens, *Klebsiella* species and *E. Coli*, interfere with treatment. Hospital-acquired microorganisms, *Acinetobacter* species and *Stenotrophomonas maltophilia*, show resistance to multiple drugs including carbapenems. Given the increase in the incidence of multi-drug resistant microorganisms in many hospitals; *Acinetobacter*, *Pseudomonas*, carbapenem resistant *Enterobacteriaceae*, methicillin-resistant *Staphylo-*

coccus aureus (MRSA), and vancomycin-resistant *Enterococci* (VRE) have been observed more frequently. Infections caused by these pathogens are more difficult to treat and have increased morbidity [1, 5, 7]. In our study, of eight Gram-negative bacteria grown in cultures, two were *E. Coli*, two were *Klebsiella pneumonia*, two were *Stenotrophomonas maltofilia*, and one was *P. Aeruginosa*.

The source of infection is not determined in about 56% of patients with febrile neutropenia, and the rest consists of blood (34%), upper and lower respiratory tract (23% and 13%, respectively), soft tissue including skin and intravascular devices (18%), and the gastrointestinal tract (7%) [17]. In our analysis of patients admitted with febrile neutropenia, source of infection was not identified in nine patients (30%); five patients (17%) had bacterial growth in blood cultures; and the respiratory system was the primary source of infection in eight patients (27%).

The National Febrile Neutropenia Association Study Group in Turkiye prepared a guideline regarding hospital admission and treatment recommendations, based on the criteria developed by "The Multinational Association for Supportive Care in Cancer" [18]. Point scoring systems are particularly helpful to evaluate low risk patients, whether to hospitalize or undergo an outpatient treatment. When MASCC score >21, mortality is between 1–3% and serious complications risk is below 5%; therefore, it is appropriate to treat at least half of these patients with oral antibiotics and continue with outpatient treatment after 24–48 hours of monitoring [16, 19]. In our study of 30 patients, 23 (77%) were categorized in low-risk group based on MASCC score >21; whereas seven patients were in high-risk group.

Neutropenic fever is an emergent medical condition. Thus, extended-spectrum bactericidal antibiotic treatment, arranged according to the liver and kidney functions, must be initiated immediately in order to prevent progression to sepsis and death. Initial empirical treatment should include anti-pseudomonal activity [20]. Accordingly; 20 patients received piperacillin-tazobactam, five patients received meropenem, and three patients received imipenem, initially, in our 30 patients study group.

Adding vancomycin to empirical therapy has been discussed as a result of increased Gram-positive bacterial infections in neutropenic patients. However, in a meta-analysis of randomized controlled studies, adding vancomycin to empirical therapy did not decrease mortality, on the contrary increased adverse event incidence, renal dysfunction being in the first place [21]. Of our 30 patients, vancomycin was added in only one patient unresponsive to initial meropenem treatment.

Teicoplanin, another glycopeptide antibiotic, can also be used for the same purpose as vancomycin. Nevertheless, linezolid which is effective against MRSA and VRE, and daptomycin, whichis effective against multi-drug resistant Gram-positive bacteria, have not been proven their efficient in empirical treatment yet. However, for the purpose of targeted treatment, linezolid therapy should be preferred in MRSA pneumonia by reason of its higher pulmonary tissue penetration compared to other glycopeptides. Daptomycin is commonly used because it shows rapid bactericidal activity in addition to good transition to foreign-bodies (catheter, vascular port) and other tissues [1, 5]. In our study group of 30 patients, daptomycin therapy was added considering MRSA infection in two patients (one with initial piperacillin-tazobactam and one with initial imipenem treatment).

Malnutrition in the elderly population is a major problem with many aspects resulting in biological, psychological, social, and economical issues. It presents with decreased total body and muscle mass (sarcopenia); and consequently, causes frailty, falls and hip fractures, prolonged healing time, increased susceptibility to infection, decubitus ulcers and poor wound healing in the elderly. In such circumstances; hospital stays happen to recur and last longer, drug use increases, patient care gets more difficult and expensive along with decreased quality of life. Besides, malnutrition has been proven as an independent risk factor for mortality [22].

Protein malnutrition is a condition resulting from a lack of protein intake or absorption, leading to different pathophysiological changes, such as physical and cognitive impairment. Protein malnutrition can impair all tissues, especially those with high cellular turnover, such as hematopoietic tissue. Protein malnutrition causes changes in hematopoietic organs and leads to anemia, leukopenia and impaired immune response. In addition, protein malnutrition induces arrest phase of hematopoietic progenitors and may cause bone marrow hypoplasia [23]. Malnutrition is a common problem in cancer patients and occurs in 80% of patients with advanced cancer. Although the mechanisms underlying nutritional alterations in cancer are not fully understood, the host's proinflammatory reaction and production of catabolic factors may result in weight loss and ultimately malnutrition. Therefore, individuals with high tumor burden may be more vulnerable to malnutrition and at higher risk of chemotherapy-related toxicity [24].

Weight change is alarming for malnutrition and a simple tool to assess the effectivity of treatment. Malnutrition should be considered in case of unintentional weight loss of 5% of the total body weight in the last month or 10% in the last six months. Moreover, adequate food consumption should be evaluated cautiously in terms of both calorie and protein intake [25]. In our study patients, mean weight loss in the last three months was 3.89±2.37.

Sarcopenia is the progressive loss of muscle mass, strength, and function. It is considered as a part of the aging process; thus, it is a geriatric syndrome. However, it can also develop in consequence of non-use/immobilization, malnutrition and cachexia [26]. Physical inactivity, decreased mobility, and poor physical strength usually accompanies sarcopenia. In the pathogenesis; loss of muscle mass and fibers, increased inflammation, change in hormone levels, poor nutritional status, impaired renin-angiotensin system, and many other factors play an important role [27]. The assessment of muscle strength in our patients with anthropometric measurements was in the normal range: mean mid-upper arm circumference was 26.96±4.6 cm and mean mid-calf circumference was 42.15±8.57 cm. On the other hand, hand grip strength was reduced with the mean measurement of 17.6±8 kg. Screening methods in malnutrition are easy and quick to apply, convenient for the patient, and does not require a qualified practitioner. They usually refer to presence of malnutrition alone; and more information in regards to cause and severity of malnutrition is necessary for patients under risk [28, 29]. In our study, mean MNA score was 16.2±5 and 17.0±5 (during admission and at discharge, respectively); indicating malnutrition. Based on NRS 2002 test, mean score was 2.8±1.5 and 2.9±1.7 (during admission and at discharge, respectively); not consistent with malnutrition. Taking into account the mean age of our patients (58.3) and the accuracy of MNA testing in elderly population; one can consider our patients had malnutrition.

Conclusion

Febrile neutropenia is a critical condition in patients with malignancy, requiring oral and/or parenteral antibiotic treatment and hospital admission; and a significant cause of mortality and morbidity. Prolonged hospital stays of the patients result in drug resistance in microorganisms due to inappropriate and unnecessary antibiotic use, and increased cost. We consider the malnutrition in these patients are due to underlying malignancy and lack of awareness of nutritional assessment. In our study, there was no correlation between MASCC score and nutritional assessment tools (NRS 2002, MNA, hand grip strength, mid-upper arm and mid-calf circumference). However, we believe that true assessment of nutritional status in patients with febrile neutropenia and compensation of any needs will be helpful to improve the treatment and reduce the length of stay in hospital.

Ethics Committee Approval: The Umraniye Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 06.05.2016, number: 6905).

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