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Investigation of hepatocyte growth factor and proinflammatory cytokine levels in patients with febrile neutropenia

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Aim: It has been thought that hepatocyte growth factor (HGF) levels increase during acute phases of infectious diseases. The aim of this study was to determine whether HGF, C-reactive protein (CRP), and proinflammatory cytokines have any diagnostic and prognostic value, and to assess HGF as a biomarker in patients with febrile neutropenia.

Materials and methods: This study included 20 patients with febrile neutropenia as the study group and 20 healthy individuals as the control group. Serial measurements of serum HGF, CRP, and proinflammatory cytokine levels were performed by enzyme-linked immunosorbent assay (ELISA) at the baseline, after 48 h of treatment, and at posttreatment.

Results: It was found that HGF levels at the baseline were significantly higher than those in the healthy controls (P = 0.001). It was also seen that HGF levels 48 h after treatment and at posttreatment were significantly lower than those at the baseline (P = 0.012). High-risk group patients had higher mean serum HGF levels compared with the low-risk group. It was detected that IL-6 and TNF-α levels at the baseline were significantly decreased after treatment (P = 0.02 and P = 0.005).

Conclusion: Our findings suggested that serial measurement of serum HGF levels may be an important marker to identify risk levels of febrile neutropenia and to predict its prognosis.

Key words: Febrile neutropenia, hepatocyte growth factor, CRP, cytokine

1. Introduction

Since bacterial infections are potentially life-threatening in neutropenic patients, empirical antibiotic therapy should be started as soon as possible after the onset of fever without delay in order to obtain microbiological evidence of the infectious agent (1–3). In particular, identifying low- and high-risk groups using clinical parameters alone is not sufficient. Thus, reliable and practical parameters are needed to diagnose infection and to assess risk. C-reactive protein (CRP), an acute phase protein, is a well-known parameter produced after release of proinflammatory cytokines (4). C-reactive protein concentration rises within 24 h and it is found to be elevated in almost all microbial infections. However, its reliability as an indicator of microbial infection is hampered by its low specificity (4). In recent studies, proinflammatory cytokines have been evaluated as a parameter for infections and autoimmune diseases (5). In many studies, interleukin-6 (IL-6) has been suggested as an important indicator of bacteremia (6,7).

Hepatocyte growth factor (HGF) is a multifunctional polypeptide that has growth hormone-like effects in a majority of tissues in addition to mitogenic and morphogenic effects on various epithelial and endothelial cells (8). Hepatocyte growth factor is a heterodimeric protein constituted from 2 subunits, so-called hepatopoietin A and scatter factor, with molecular weights of 34 kDa and 69 kDa, bound by disulfide bonds, and its organotrophic functions has been widely investigated. It plays an important role as an organotrophic factor in the physiological regeneration of the liver, kidneys, and lungs. Accordingly, it has been thought that it is produced by mesenchymal cells in response to injury and plays an essential role in the regeneration of epithelial cells in the injured organ (9,10). Hepatocyte growth factor is angiogenic in systemic tissue. Titrations of HGF are correlated with malignity and metastatic phenotype of certain systemic cancers (11). It has been shown that HGF is accounted for by malign cell transformation, proliferation, invasion,

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and metastasis of cancer cells (12,13). It has been reported that HGF levels are increased in sepsis, inflammatory pulmonary diseases, and pneumonia (14,15). Although HGF levels in serum and local fluids have been particularly investigated in acute and chronic inflammatory diseases, there are a limited number of studies on HGF levels and its prognostic value in infectious diseases.

It has been suggested that the determination of serum HGF, cytokines, and CRP in distinct clinical stages of febrile neutropenia process, and the identification of the relationship between these parameters and clinical and microbiological data, would enable early detection of risk, and aid the identification of treatment approaches and prognosis. Therefore, our study aimed to determine whether HGF, CRP, and proinflammatory cytokines have diagnostic and prognostic value by serial measurements at the baseline, 48 h after treatment, and at posttreatment, and to assess the availability of HGF as a biomarker in patients with febrile neutropenia.

2. Materials and methods

Included in this study were 20 low- and high-risk patients who were managed in the Oncology Clinic of Fırat University, School of Medicine and who developed febrile neutropenia after chemotherapy. Fever was diagnosed in patients with a single axillary body temperature measurement of 38.3 °C or 2 distinct body temperature measurements of 38.0 °C over 24 h. Neutropenia was diagnosed when the neutrophil count was greater than 500 /mm^3 at presentation or was 500–1000/mm^3 but anticipated to fall below 500/mm^3 within the following 48 h (3). The following infection categories were described in patients: fever of unknown origin, bloodstream infection, clinically identified infection, and microbiologically identified infection. In addition, patients were stratified as those with low and high risk according to the Multinational Association for Supportive Care in Cancer (MASCC) score (16). By using a standard data sheet, the following data were recorded: age, sex, received therapies, duration of neutropenia or fever, length of hospital stay, and findings of physical examination. There were 20 age-matched healthy volunteers without any known disease and with normal physical examination and laboratory findings, who were employed as a healthy control group.

Empiric antibiotic therapy, consisting of a beta-lactam antibiotic with antipseudomonal activity alone (2 g IV cefoperazone-sulbactam every 12 h, or 2 g IV piperacillin-tazobactam every 8 h, or 2 g IV cefepime every 12 h, or 2 g IV ceftazidime every 8 h) or in combination with an aminoglycoside (1 g IV amikacin every 24 h), was initiated in patients. Required changes were made in accordance to new pathogens isolated during therapy, whereas an antifungal agent was added when fever extended for 5–7 days. The course of fever and clinical symptoms were evaluated by daily physical examinations and antibiotic therapy was discontinued at the appropriate time after recovery of fever and clinical symptoms caused by infection. Success was defined as at least 5 days without fever, absolute neutrophil count greater than 500/mm^3, and recovery of clinical and laboratory findings after regression of fever. Treatment failure was defined as ongoing fever despite modifications in antimicrobial therapy, no clinical recovery, or progression of existing findings and infection-related mortality.

Three blood samples were taken from patients in the study group: at onset of fever (febrile neutropenic phase), 48 h after treatment, and at the period where fever and neutropenia had ameliorated (recovery period), while a single blood sample was taken in those in the control group. Sera were separated from blood samples and stored at −70 °C until assays. Immunoreactive HGF levels were measured in sera by the micro-ELISA technique using commercially available kits in accordance with the manufacturer's instructions (Biosource International Inc, Camarillo, CA, USA). Results were expressed as pg/mL. Serum IL-1, IL-6, IL-8, and TNF-α levels were evaluated using the ELISA technique.

This study protocol was approved by the local ethics committee and all participants were informed about the study.

SPSS for Windows version 15.0 was used for statistical analysis. Comparison between HGF and proinflammatory cytokine levels at baseline and those 48 h after treatment and at the end of the study was performed by repeated measures analysis of variance analysis. The Wilcoxon signed rank test was used for comparison of dichotomous groups. Fisher's exact test was used to compare differences between categorical variables, while the Spearman test was used for correlation analysis. Student's t test was used for the comparison between study and control groups. $P < 0.05$ was considered statistically significant.

3. Results

The mean age of the study group was 56.4 ± 13.2 (range 23–81) years. Underlying primary disorders were hematological cancers in 8 patients and solid tumors in 12 patients. It was found that the mean absolute neutrophil count was 254.8 ± 48.2/mm^3, whereas the mean duration of neutropenia was 4.12 ± 1.06 days and the mean length of stay was 8.37 ± 2.69 days. Table 1 presents the demographic characteristics and risk factors of the patients. Pneumonia and pyelonephritis were the most common infections among those identified clinically and microbiologically. In 6 patients with a microbiological diagnosis 8 pathogens were isolated. Of the strains isolated, 5 (62.5%) were gram-negative bacteria, whereas 2 were (25%) gram-positive

Table 1. Demographic characteristics and risk factors in patients with febrile neutropenia.

Age (mean, years)	56.4 ± 13.2 (23-81)
Sex (female/male)	11/9
Neutrophil count (mean, mm^3)	254.8 ± 48.2
Neutrophil count <100/mm^3 (n)	7
Neutrophil count 100–500/mm^3 (n)	9
Neutrophil count >500/mm^3 (n)	4
Duration of neutropenia (mean, days)	4.12 ± 1.06
Duration of fever (mean, days)	2.6 ± 0.16
Duration of hospitalization (mean, days)	8.37 ± 2.69
The underlying disease (hematological cancer/solid tumor)	8/12
MASCC score (low/high)	8/12
Category of infection (n = 20)	
Clinical	6
Microbiological	6
Fever of unknown origin	8
Treatment (n = 20)	
Monotherapy	12
Combined therapy	8
Duration of treatment (mean, days)	11.7 ± 3.8

MASCC: Multinational Association for Supportive Care in Cancer

bacteria in addition to 1 (12.5%) *Candida* sp. Table 2 presents microorganisms isolated from patients with febrile neutropenia. The control group was composed of 10 females and the same number of males, with a mean age of 53.4 ± 12.42.

Empirical treatments consisted of a single agent therapy in 60% of patients and combined therapy in 40%. In monotherapy, the most commonly used antimicrobial agent was piperacillin-tazobactam (n = 5), followed by carbepenems (imipenem and meropenem; n = 4) and cefoperazone-sulbactam (n = 3). The mean time to response to fever was 2.6 ± 0.16 days. There were 2 patients that died during an episode of febrile neutropenia. It was found that duration of neutropenia was longer (5.8 ± 1.76 days) in patients with microbiologically identified infection. The mean duration of the recovery period was 5.1 ± 1.08 days. Posttreatment samples were not taken from the patients who died. Mean serum HGF levels were 2333.07 ± 474.01 pg/mL at baseline in patients in the study group, whereas they were 401.44 ± 69.75 pg/mL in controls (P = 0.001) (Table 3). It was found that HGF levels 48 after treatment and at posttreatment were significantly decreased when compared to baseline levels (Figure). A significant correlation was found between baseline serum HGF and CRP levels (r = 0.642; P = 0.029). It was also found that mean serum HGF levels in patients

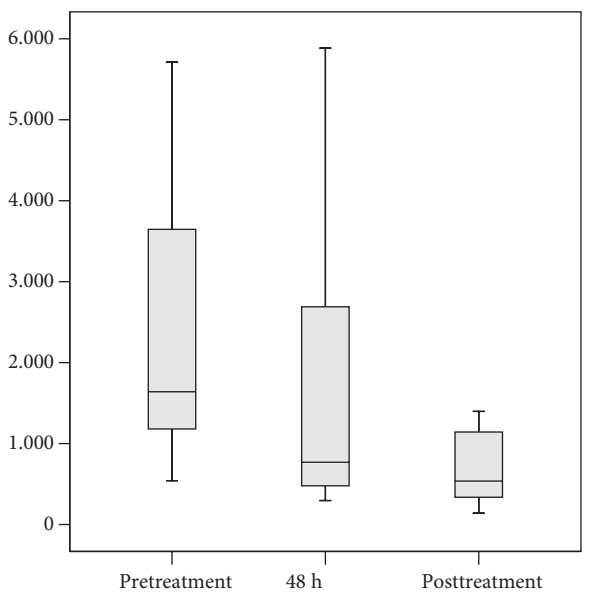

Figure. Mean levels of HGF of patients at the onset, at 48 h, and at posttreatment

in the high-risk group were significantly higher than those in the low-risk group (3649.20 ± 954.72 vs. 1601.88 ± 357.27; P = 0.035). However, no significant difference was detected in mean CRP levels between high- and low-risk

Table 2. Microorganisms isolated from patients with febrile neutropenia.

Microorganisms	Urine n (%)	Blood n (%)	Total n (%)
Gram-negative microorganisms	3 (37.5)	2 (25)	5 (52.5)
Escherichia coli	2 (25)	1 (12.5)	3 (37.5)
Pseudomonas aeruginosa	1 (12.5)	0 (0)	1 (12.5)
Klebsiella spp.	0 (0)	1 (12.5)	1 (12.5)
Gram-positive microorganisms *	0 (0)	2 (25)	2 (25)
Candida spp.	0 (0)	1 (12.5)	1 (12.5)
Total	**3 (37.5)**	**5 (62.5)**	**8 (100)**

* Staphylococcus and streptococcus.

Table 3. Mean levels of HGF and CRP of patients at the onset, at 48 h and at posttreatment, and control groups.

	Febrile neutropenia (n = 20)			Control group (n = 20)
	Pretreatment	48 h	Posttreatment	
HGF (pg/mL)	2333.07 ± 474.01*	1897.66 ± 591.19**	785.75 ± 160.23	401.44 ± 69.75
CRP (mg/L)	52.5 ± 14.8[£]	19.1 ± 3.5	5.6 ± 0.9	2.8 ± 0.3

HGF: Hepatocyte growth factor, CRP: C-reactive protein
* vs. 48 h P = 0.012, posttreatment P = 0.001, ** vs. posttreatment P = 0.028
[£] vs. 48 h P = 0.004, posttreatment P = 0.0001

groups. HGF levels were significantly different in patients with microbiologically identified infection (4815.36 ± 862.16 vs. 1769.41 ± 346.2) compared to those not having a microbiologically identified infection. A positive correlation was found between fever and HGF levels (r = 0.649; P = 0.026).

It was found that baseline IL-6 levels were significantly decreased after treatment and there was no significant difference between levels at posttreatment and those in the control group (P > 0.05) (Table 4). It was also found that baseline TNF-α was significantly decreased at 48 h and at posttreatment (P = 0.005). It was seen that levels of IL-1 and IL-8 didn't significantly differ by treatment (P > 0.05). It was found that TNF-α and IL-6 levels at baseline were significantly correlated with baseline CRP levels (P = 0.031). When comparing by risk category, no difference was observed between the groups for the values of cytokines and CRP (Table 5).

4. Discussion

Infection-related symptoms and signs may be vague in patients with febrile neutropenia. Fever is the first symptom in most neutropenic patients with infection. A careful evaluation should be undertaken because of the lack of or reduced inflammatory response in these patients. Several risk factors have to be taken into consideration in patients with febrile neutropenia in order to identify a prognosis. Although it is a widely used practice to hospitalize and to give broad-spectrum antibiotics to patients with fever during episodes of neutropenia, patients in the low-risk group may be managed on an outpatient basis or by short durations of hospitalization (17). The use of a rapid and easy diagnostic test that would identify the risk, is important (18,19). Among these, the most widely accepted one is the risk stratification developed by MASCC and used to discriminate patients as those at low and high risk (16). The different existing approaches need to be improved as they do not have satisfactory sensitivity. Thus, reliable and practical parameters are needed to diagnose infection and to assess risk. C-reactive protein (CRP) is an acute phase protein and a well-known parameter produced after the release of proinflammatory cytokines (4). However, the reliability of CRP as an indicator of a microbial infection is diminished due to its low specificity (4). It has been reported that levels of HGF, a multifunctional protein, are increased in several infection diseases such as sepsis, brucellosis, pneumonia, and urinary infections as well as cancers (14,15).

It is thought that HGF levels are increased during the acute phase of infection diseases, which reflects the regeneration process in injured organs (20,21). In an investigation performed in 60 patients with acute

Table 4. Mean levels of IL-1, IL-6, IL-8, and TNF-α in patients at the onset, at 48 h and at posttreatment in febrile neutropenia compared with the control group.

	Febrile neutropenia (n=20)			Control group (n=20)
	Pretreatment	48 h	Posttreatment	
IL-1 (pg/mL)	21.86 ± 3.09	22.20 ± 2.13	22.58 ± 2.11	13.2 ± 5.86
IL-6 (pg/mL)	185.37 ± 46.74 *	178.81 ± 71.68	143.87 ± 26.67	110.6 ± 18.43
Il-8 (pg/mL)	236.50 ± 31.52	225.60 ± 37.9	161.31 ± 11.02	144.32 ± 29.41
TNF-α (pg/mL)	127.68 ± 12.97*	123.92 ± 9.73$^{£}$	109.87 ± 11.79	110.6 ± 22.80

* vs. posttreatment P = 0.02, $^{£}$ vs. posttreatment P = 0.005

Table 5. Mean levels of HGF, IL-1, IL-6, IL-8, and TNF-α of patients by risk group.

	Low-risk (n: 8)	High-risk (n: 12)
HGF (pg/mL)	3649.20 ± 954.72*	1601.88 ± 357.27
IL-1 (pg/mL)	22.44 ± 3.81	21.11 ± 1.85
IL-6 (pg/mL)	189.66 ± 51.17	179.85 ± 43.68
Il-8 (pg/mL)	268.55 ± 47.93	195.28 ± 35.17
TNF-α (pg/mL)	129.66 ± 12.73	125.14 ± 13.82

* vs. high-risk P = 0.035

myelocytic leukemia, serum concentrations of HGF were measured and it was found that 28% of the patients had elevated HGF concentrations, with a correlation between HGF levels and the presence of disseminated intravascular coagulation (22). Again, it is proposed that low HGF levels, reflecting insufficient production, may be a predictor of a poor prognosis (14,15). In a study of HGF levels in patients with acute pancreatitis, it was reported that HGF is similar to CRP, and more useful than IL-6, in the detection of severe pancreatitis, whereas it is better than both CRP and IL-6 in prognosis determination (23). In our patients, serum HGF, cytokines, and CRP levels were measured 3 times, including during the neutropenic period without fever after chemotherapy, at the onset of fever (neutropenic period with fever), at 48 h, and at the period where fever and neutropenia had ameliorated (recovery). In our study, mean serum HGF levels were significantly higher in the study group than in the controls and there was a significant correlation between baseline HGF and CRP levels.

There are studies suggesting that procalcitonins and some cytokines are valuable in the prediction of severe infections, especially in gram-negative bacteremia (24). Recent data support this, particularly that procalcitonin and IL-8 are the most promising biomarkers for management and prognostication of patients with febrile neutropenia (25). In a study of procalcitonin, CRP, and IL-6 levels as indicators for bacteremia in patients with febrile neutropenia, levels of procalcitonin and IL-6 were significantly higher in patients with bacteremia than in those without bacteremia, but CRP levels did not significantly change among groups. Authors suggested that procalcitonin and IL-6 are more reliable markers than CRP in the prediction of bacteremia in patients with febrile neutropenia (26). However, it was found that procalcitonin levels do not reach high levels in febrile neutropenia and do not show significant differences in microbiologically documented cases and in those with unknown origin of fever (27). In a study of 26 patients, serum IL-8 levels were found to be higher in patients with febrile neutropenia when compared to cancer patients with newly diagnosed fever but no neutropenia, or to those with infection but no diagnosis of cancer. No such relationship was found for CRP and procalcitonin (27). Although HGF levels were found to be low in neutropenia and neutropenic infections, it was reported that high HGF levels were correlated with increased early mortality, with levels normalizing during posttreatment in responders (22). In our study, serum HGF, IL-6, and TNF-α were higher before treatment and began to decrease 48 h after

treatment and approximated to normal control levels in posttreatment after effective treatment. It was seen that HGF levels were decreased by the regression of fever and had a correlation with fever. Particularly, there were significantly higher HGF levels in patients in the high-risk group when compared to those in the low-risk group, suggesting that HGF may be a more important biomarker than other known biomarkers for determination of risk level and prognostication. Again, significant HGF levels in our patients with microbiologically identified infection show that HGF may be an important parameter for diagnosis in addition to its prognostic value.

It has been reported that levels of IL-8 are increased in several infectious diseases such as brucellosis and that high IL-8 value may be an indicator of relapse (28). Data regarding the duration of antibiotic therapy are controversial in cases of febrile neutropenia. Particularly, it has been reported that IL-8 may be a useful marker in low-risk patients for the discontinuation of antibiotic therapy. It has been reported that IL-8 may be used in risk assessment and may be an early indicator of, febrile neutropenia (29). It was seen that serum TNF-α, IL-1, IL-6, and IL-8 concentrations are increased in patients with febrile neutropenia induced by chemotherapy (30). It was seen that IL-6 and TNF-α levels were significantly decreased after 48 h and at the end of treatment compared to baseline levels in our patients with febrile neutropenia. No significant difference was detected among IL-8 and IL-1 levels before and after treatment or in the control group in our study.

This is the first study in which HGF levels were serially evaluated at different clinical phases in patients with febrile neutropenia. However, the use of markers such as HGF and CRP is limited, as patients with febrile neutropenia form a heterogeneous group in terms of infection and risk score. In particular, it is expected that biomarkers that would be used in febrile neutropenia should be as sensitive as and more specific than fever. It is also known that mortality is caused by delayed diagnosis and antibiotic therapy rather than long-term use of antibiotics in patients with febrile neutropenia. Thus, randomized, controlled studies with larger sample sizes are needed to determine if HGF can be used as an early diagnostic tool as well as for prognosis and risk score in febrile neutropenia.

References

1. Chanock SJ, Pizzo MD. Fever in the neutropenic host. Infectious Diseases Emergencies. Infect Dis Clin North Am 1996; 10: 777–96.
2. Pizzo PA. Fever in immunosuppressed patients. N Engl J Med 1999; 341: 893–900.
3. Febril Nötropenik Hastalarda Tanı ve Tedavi Kılavuzu. Febril Nötropeni Çalışma Grubu. Flora 2004; 9: 5–28. (In Turkish).
4. Sudhoff T, Giagounidis A, Karthaus M. Serum and plasma parameters in clinical evaluation of neutropenic fever. Antibiot Chemother 2000; 50: 10–9.
5. Karadağ R, Koca C, Totan Y, Yağcı R, Aydın M, Karadağ AS et al. Comparison of serum levels of IL-6, IL-8, TNF-α, C reactive protein and heat shock protein 70 in patients with active or inactive Behçet's disease. Turk J Med Sci 2010; 40: 57–62.
6. Abrahamsson J, Pahlman M, Mellander L. Interleukin 6, but not tumour necrosis factor-alpha, is a good predictor of severe infection in febrile neutropenic and non-neutropenic children with malignancy. Acta Paediatr 1997; 86: 1059–64.
7. Engel A, Mack E, Kern P, Kern WV. An analysis of interleukin-8, interleukin-6 and C-reactive protein serum concentrations to predict fever, gram-negative bacteremia and complicated infection in neutropenic cancer patients. Infection 1998; 26: 213–21.
8. Gohda E, Tsubouchi H, Nakayama H, Hirono S, Sakiyama O, Takahashi K et al. Purification and partial characterization of hepatocyte growth factor from plasma of a patient with fulminant hepatic failure. J Clin Invest 1988; 81: 414–9.
9. Boros P, Miller CM. Hepatocyte growth factor; a multifunctional cytokine. Lancet 1995; 345: 293–5.
10. Dudek K, Koziak K, Placha G, Kornasiewicz O, Zieniewicz K, Zurakowski J et al. Early expression of hepatocyte growth factor, interleukin-6, and transforming growth factor-beta 1 and -beta 2 in symptomatic infection in patients who have undergone liver transplantation. Transplant Proc 2009; 41: 240–5.
11. Laterra J, Nam M, Rosen E, Rao JS, Lamszus K, Goldberg ID et al. Scatterfactor/hepatocyte growth factor gene transfer enhances glioma growth and angiogenesis in vivo. Lab Invest 1997; 76: 565–77.
12. Motoki T, Takami Y, Yagi Y, Tai A, Yamamoto I, Gohda E. Inhibition of hepatocyte growth factor induction in human dermal fibroblasts by tryptanthrin. Biol Pharm Bull 2005; 28: 260–6.
13. Hou XZ, Liu W, Fan HT, Liu B, Pang B, Xin T et al. Expression of hepatocyte growth factor and its receptor c-Met in human pituitary adenomas. Neuro Oncol 2010; 12: 799–803.
14. Nayeri F, Brudin L, Darelid J, Nilsson I, Fryden A, Söderström C et al. Hepatocyte growth factor may act as an early therapeutic predictor in pneumonia. Scand J Infect Dis 2002; 34: 500–4.
15. Abednazari H, Xu J, Millinger E, Brudin L, Forsberg P, Nayeri F. Hepatocyte growth factor is a better indicator of therapeutic response than C-reactive protein with in the first day of treatment in pneumonia. Chemotherapy 2006; 52: 260–3.

16. Klastersky J, Paesmans M, Rubenstein EB, Boyer M, Elting L, Feld R et al. The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low risk febrile neutropenic cancer patients. J Clin Oncol 2000; 18: 3038–51.

17. Bayram I, Erbey F, Alabaz D, Yılmaz S, Tanyeli A. Cefoperazone-sulbactam plus amikacin empirical therapy for febrile neutropenia in children with cancer. Turk J Med Sci 2009; 39: 635–40.

18. Chamilos G, Bamias A, Efstathiou E, Zorzou PM, Kastritis E, Kostis E et al. Outpatient treatment of low-risk neutropenic fever in cancer patients using oral moxifloxacin. Cancer 2005; 103: 2629–35.

19. Morres KG. Safe and effective outpatient treatment of adults with chemotherapy-induced febrile neutropenia. Am J Health Syst Pharm 2007; 64: 712–7.

20. Ozden M, Kalkan A, Demirdag K, Kilic SS, Denk A, Yuce P. Hepatocyte growth factor (HGF) in patients with acute brucellosis. Scand J Infect Dis 2004; 36: 109–13.

21. Ozden M, Kalkan A, Demirdag K, Denk A, Kiliç SS. Hepatocyte growth factor (HGF) in patients with hepatitis B and meningitis. J Infect 2004; 49: 229–5.

22. Hjorth-Hansen H, Seidel C, Lamvik J, Börset M, Sundan A, Waage A. Elevated serum concentrations of hepatocyte growth factor in acute myelocytic leukaemia. Eur J Haematol 1999; 62: 129–34.

23. Ueda T, Takeyama Y, Hori Y, Nishikawa J, Yamamoto M, Saitoh Y. Hepatocyte growth factor in assessment of acute pancreatitis: comparison with C-reactive protein and interleukin-6. J Gastroenterol 1997; 32: 63–70.

24. Neuenschwander LC, Bittencourt H, Ribeiro AF, Teixeira AL, Teixeira MM, Teixeira JC et al. Plasma levels of procalcitonin and eight additional inflammatory molecules in febrile neutropenic patients. Clinics 2011; 66: 1699–705.

25. Banacloche JG. Biomarkers in fever and neutropenia: A solution in search of a problem? Crit Care Med 2011; 39: 1205–6.

26. von Lilienfeld-Toal M, Dietrich MP, Glasmacher A, Lehmann L, Breig P, Hahn C et al. Markers of bacteremia in febrile neutropenic patients with hematological malignancies: procalcitonin and IL-6 are more reliable than C-reactive protein. Eur J Clin Microbiol Infect Dis 2004; 23: 539–44.

27. Bilgir O, Bilgir F, Kebapcilar L, Bozkaya G, Çalan M, Kırbıyık H et al. Comparative levels of macrophage migration inhibitory factor, procalcitonin, osteoprotegerin, interleukin-8, hs-C reactive protein, D-dimer in febrile neutropenia, newly diagnosed cancer patients, and infectious fever. Transfusion and Apheresis Science 2012; 46: 19–24.

28. Demir NA, Ural O. Serum interleukin-8 levels may predict relapse in brucellosis. Turk J Med Sci 2012; 42: 796–801.

29. Tromp YH, Daenen Simon MGJ, Sluiter WJ, Vellenga E. The predictive value of interleukin-8 (IL-8) in hospitalised patients with fever and chemotherapy-induced neutropenia. Eur J Cancer 2009; 45: 596–600.

30. Sakr Y, Sponholz C, Tuche F, Brunkhorst F, Reinhart K. The role of procalcitonin in febrile neutropenic patients: Review of the literature. Infection 2008; 36: 396–407.