Original Article

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The Predictive and Diagnostic Values of Procalcitonin and C-Reactive Protein for Clinical Outcome in Febrile Neutropenic Patients

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Key Words
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Background. Procalcitonin (PCT) represents a new marker of systemic inflammatory reactions to bacterial infections. The main aim in this study was to determine the diagnostic value of PCT in predicting the clinical severity of febril neutropenic attacks, compare it with that of C-reactive protein (CRP), and clarify its importance in culture-positive attacks.

Methods. Between February 2001 and April 2002, 36 patients who were neutropenic due to various hematologic disorders and febrile were entered into the study. Blood samples were obtained on the first day of fever for the measurement of serum PCT and CRP levels.

Results. In clinically severe neutropenic fever attacks, means of serum PCT and CRP levels were measured as 0.93 ± 1.33 ng/mL and 67 ± 24 mg/L, while they were 0.37 ± 0.23 ng/mL and 32 ± 19 mg/L in clinically mild ones ($p = 0.033$ and $p < 0.001$). On the other hand, no statistical significance was found between culture-positive and negative attacks when either serum PCT or CRP levels were taken into consideration ($p = 0.133$ and $p = 0.141$). The specificity and positive predictive value of the serum PCT test for severe febrile neutropenia was higher than that of the serum CRP test (0.80 *vs.* 0.57 and 0.50 *vs.* 0.39). However, sensitivity and negative predictive value for CRP were higher than the values for PCT (1.00 *vs.* 0.40 and 1.00 *vs.* 0.73). Diagnostic value and positive likelihood ratio of CRP for severe febrile neutropenia were higher than those of PCT (71 *vs.* 67 and 2.32 *vs.* 2.00).

Conclusions. PCT and CRP are comparable with each other in prediction of the clinical severity of febrile neutropenic attacks. Furthermore, serum CRP levels correlate with the duration of fever.

There are various factors that predispose to infection in cancer patients including neutropenia and other phagocytic defenses, cellular immune dysfunction, humoral immune dysfunction, anatomic-barrier (mucosal or integumentary) damage, obstructive phenomena, central nervous system dysfunction and iatrogenic procedures. The incidence of infection began to rise when the neutrophil count was below 500/μL, with a very substantial rise when it was below 100/μL.[1,2]

Fever in a neutropenic patient is always considered an emergency condition. The empiric therapy for all febrile neutropenic patients should be given promptly in the hospital and include broad-spectrum bactericidal antimicrobials.[3] For moderate-risk patients, the availability of expanded-spectrum oral antibiotics has also enabled the clinician to switch from parenteral to oral regimens upon discharge after an initial period of stabilization in the hospital.[4-6] Early discharge might offer a more comfortable management plan for some, particularly those with nausea or mucositis, which might limit oral intake at the onset. Risk groups must be determined in a correct way by using clinical and laboratory methods.[4,7,8]

Procalcitonin (PCT) represents a new marker of systemic inflammatory reactions of the body to bacterial infections.[9-11] The current study was conducted to evaluate the value of PCT as an inflammatory marker in identifi-

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cation of the clinical course of febrile neutropenia. The results were compared with those of another acute phase reactant, C-reactive protein (CRP).

METHODS

Between February 2001 and April 2002, 36 patients who were neutropenic due to various hematologic disorders and febrile were entered into the study. Written informed consents were obtained from all patients.

Definitions

According to 1997 guidelines of the Infectious Diseases Society of America (IDSA), febrile neutropenia was defined when a temperature of > 38.3 °C, or > 38.0 °C for an hour's duration in combination with an absolute neutrophil count less than 500/μL or less than 1000/μL with an anticipated drop to below 500/μL was developed. Each febrile neutropenia episode was classified retrospectively. Severe episodes were defined when fever continued more than 7 days and/or presented with shock or complex infection, whereas episodes in clinically and hemodynamically stable patients with duration of fever less than 7 days were considered as mild.

Guidelines for empiric therapy

Initial management of the neutropenic fever was given according to the guidelines of International Antimicrobial Therapy Cooperative Group and European Organization for Research and Treatment of Cancer (IATCG-EORTC).[8] With respect to the duration of therapy, patients who were afebrile by the third day of treatment with granulocyte recovery could be considered for a 7-day course of therapy. Patients did not receive any antimicrobial prophylaxis during neutropenic period.

Study Design

Blood samples obtained on the first day of fever were stored at -70 °C until the measurement of serum PCT and CRP levels. Serum CRP level was determined using nephelometric method. Serum PCT level was measured by Lumi test-PCT (ILMA Kits BRAHMS Diagnostica GmbH, Berlin, Germany). The analytical assay sensitivity was approximately 0.1 ng/mL. Inter-assay variation co-efficient was 20% and intra-assay variation coefficient was 3.9%.

Statistical Analysis

Student *t*-test was used to compare serum PCT and CRP levels. Cut-off points of both tests for the discrimination of severe febrile episodes from mild ones were determined according to receiver operation characteristics (ROC) curve analysis. The correlation between both markers was studied by means of the Pearson's correlation coefficient. Statistical tests were carried out at a significance level of 0.050. The sensitivity, specificity, positive and negative predictive and diagnostic values, and positive likelihood ratio of PCT and CRP were determined. (*sensitivity* = true positive cases / [true positive cases + false negative cases]; *specificity* = true negative cases / [true negative cases + false positive cases]; *positive predictive value* = true positive cases / [true positive cases + false positive cases]; *negative predictive value* = true negative cases / [true negative cases + false negative cases]; *diagnostic value* = 100 × [true positive cases + true negative cases] / all of the cases*; positive likelihood ratio* = sensitivity / [1-specificity]).

RESULTS

Forty-five febrile neutropenia attacks were noted in 36 patients during the study. The median age was 48 years (range 16-86 years) (Table 1). Hematologic disorders of the patients were classified as 14 acute myeloid leukaemia (39%), 9 acute lymphoblastic leukemia (25%) and 13 non-Hodgkin's lymphoma (36%).

In 9/45 (20%) febrile neutropenia attacks, blood cultures were found positive. The pathogens were *Staphylococcus epidermidis* (n = 2), *Streptococcus* species (n = 2), *Escherichia coli* (n = 3), *Klebsiella* species (n = 1) and *Candida* species (n = 1). The distribution of gram-positive and gram-negative microorganisms was comparable. The median serum PCT and CRP levels in culture positive episodes were 0.28 ng/mL (range 0.10-5.32 ng/mL) and 48 mg/L (range 24-96 mg/L), respectively. No statistical significance was found between culture-positive and negative attacks when either serum PCT or CRP levels were taken into consideration ($p = 0.133$ and $p = 0.141$).

Table 1. Clinical characteristics of the febrile neutropenic patients

	Clinical severity	
	Severe FN (n = 15)	Mild FN (n = 30)
Age		
median (range)	47 (16-86)	36 (16-69)
mean ± SEM	50.20 ± 22.79	38.40 ± 14.73
Gender (male/female)	7/8	20/10
Granulocyte count (/mm^3) [a]	160.00 ± 247.27 (0-900)	209.00 ± 207.98 (0-800)
Diagnosis		
AML	7	12
ALL	3	6
NHL	4	11
Agranulocytosis	1	1
Duration of fever (days) [b]	9 (7-21)	3 (2-6)

AML = acute myeloblastic leukemia; ALL = acute lymphoblastic leukemia; NHL = non-Hodgkin's lymphoma; FN = febrile neutropenia; [a] mean ± SEM (range); [b] median (range).

Table 2. The serum procalcitonin and C-reactive protein levels according to the clinically severity of febrile neutropenia episode

Inflammatory marker	Clinical severity [a]	
	Severe (n = 15)	Mild (n = 30)
Procalcitonin (ng/mL) [b]	0.93 ± 1.33 (0.10 - 5.32)	0.37 ± 0.23 (0.12 - 1.17)
C-reactive protein (mg/L) [c]	67 ± 24 (48 - 96)	32 ± 19 (0 - 48)

[a] mean ± SEM (range); [b] $p = 0.033$; [c] $p = 0.001$.

Table 3. The cut-off points of serum procalcitonin and c-reactive protein levels in febrile neutropenic patients

		Clinical severity	
		Severe (n = 15 [%])	Mild (n = 30 [%])
Procalcitonin (ng/mL) [a]	< 0.50 [b]	9 (60)	24 (80)
	= 0.50	6 (40)	6 (20)
C-reactive protein (mg/L) [c]	< 36 [d]	0 (0)	17 (57)
	= 6	15 (100)	13 (43)

[a] $p = 0.153$; [b] positive likelihood ratio = 2.0; [c] $p < 0.001$; [d] positive likelihood ratio = 2.3.

Fifteen of 45 episodes (33%) were classified as severe clinically and serum PCT and CRP levels were found significantly increased in this group. The mean serum PCT and CRP level among patients with severe attacks were 0.93 ± 1.33 ng/mL and 67 ± 24 mg/L in order, which were 0.37 ± 0.23 ng/mL and 32 ± 19 mg/L in mild episodes, respectively ($p = 0.033$ and $p < 0.001$) (Table 2).

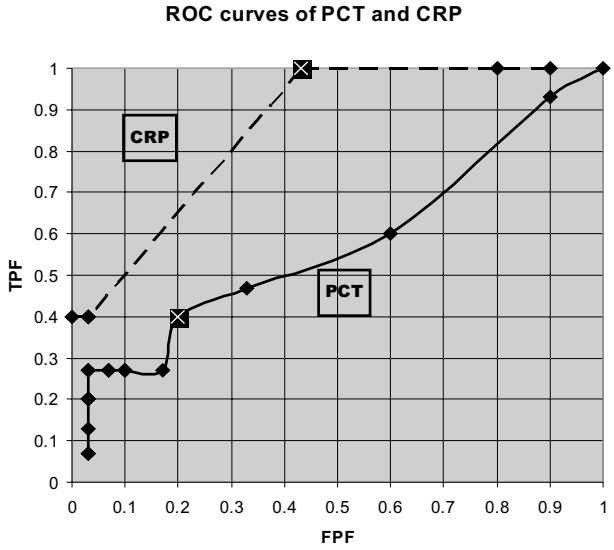

Fig. 1. Receiver operation characteristic (ROC) curve analysis for the assessment of PCT and CRP in predicting the clinical severity of febril neutropenic attacks. Area under curve (AUC) ± SE was 0.603 ± 0.095 for PCT ($p = 0.263$, 95% CI: 0.418-0.789) and was 0.853 ± 0.055 for CRP ($p < 0.001$, 95% CI: 0.746-0.961). PCT = procalcitonin; CRP = C-reactive protein; TPF = true positive fraction; FPF = false positive fraction.

The median duration of fever was 9 days (7-21 days) in clinically severe attacks and 3 days (2-6 days) in mild ones. Serum PCT level did not correlate with the duration of fever ($p = 0.090$). However, a significant correlation was observed with CRP ($r = 0.45$, $p = 0.002$). No relation was defined between each marker ($p = 0.171$).

The cut-off point for serum PCT was defined as 0.50 ng/mL (Fig. 1). In 6/15 (40%) clinically severe attacks, levels were found higher than the cut-off point, compared with only 6/30 (20%) for clinically mild ones. The cut-off point for serum CRP was defined as 36 mg/L (Fig. 1). In 15/15 (100%) clinically severe attacks, levels were found higher than the cut-off point, which was the case in only 13/30 (43%) for clinically mild ones (Table 3).

The specificity and the positive predictive value of the serum PCT test for severe febrile neutropenia was proved to be higher than those of the serum CRP test (0.80 *vs.* 0.57 and 0.50 *vs.* 0.39). However, the sensitivity and negative predictive value for CRP were higher than

the values for PCT (1.00 *vs.* 0.40 and 1.00 *vs.* 0.73). Diagnostic value and positive likelihood ratio of CRP for severe febrile neutropenia were higher than PCT (71 *vs.* 67 and 2.32 *vs.* 2.00, respectively).

DISCUSSION

There is a gradual increase in the number of the studies regarding febrile neutropenia evaluating those inflammatory markers such as interleukin (IL)-6, IL-8, CRP and PCT to assess their diagnostic values in identifying high-risk patients with sepsis. Cytokines such as tumor necrosis factor (TNF), IL-1, IL-6 and IL-8 were considered as sensitive and early responding markers for infections in patients whether they were neutropenic or not.[12-15] However, there were also contradictory studies.[16] Increased serum PCT levels (> 100 ng/mL) were found in severe bacterial infections and inflammations with systemic signs and symptoms. So, PCT was proposed as an inflammatory marker in the diagnosis of bacterial infections in the recent years.[17]

When compared with other commonly used screening methods such as blood total leukocyte count and other inflammatory markers, procalcitonin and CRP offer better sensitivity and specificity in predicting serious bacterial infections in children with fever without any localizing signs.[18] Kohli *et al.* found that the sensitivity of serum CRP ≥ 40 mg/L for diagnosis of bacteraemia was 95% and the positive predictive value was 67%. On serial monitoring, a decrease in the serum CRP concentration was a sensitive indicator of recovery from infection and provided the earliest clue for the success of the treatment.[19] CRP monitoring may be useful to distinguish between causes of fever. Very high CRP levels tend to be associated with invasive bacterial infections. On the other hand, it was shown that CRP is not an early warning sign.[20] Its late response to inflammation (24-48 hours) and high variety of serum levels related with the amount of tissue injury are disadvantages.[21]

PCT has a serum half-life of 25-30 hours, and serum PCT levels are very low in healthy people (< 0.1 ng/mL). PCT is selectively induced by severe bacterial infections leading to sepsis or multiorgan dysfunction syndrome. Giamarellos-Bourboulis *et al.* reported that the median serum PCT level on the first day of fever was 2.62 ng/mL in patients with clinically severe sepsis compared with 0.57 ng/mL in patients with clinically localized infections ($p < 0.001$). A dramatic decrease in PCT level was documented after resolution of the infection; PCT levels were found to be elevated when the infection worsened. Pronounced PCT levels were also found in patients with fever of unknown origin who were responding to antimicrobial chemotherapy when compared to those without any respond. These findings provided new insight for the application of PCT in clinical trials as a diagnostic measure of the severity of an infection in patients with febrile neutropenia and of the need to change antimicrobial regimen.[17] There are few reports regarding the diagnostic value of PCT in immunosupressive or febrile neutropenic patients.[10,22,23] In our study, we compared sensitivity, specificity, positive and negative predictive values, diagnostic value and positive likelihood ratio of serum PCT and CRP levels in the assessment of severe febrile neutropenic patients. However, the serum levels of these markers were not monitored.

Although serum CRP test is highly sensitive for the assessment of severe neutropenic fever episodes, its specificity was found lower than that of the serum PCT test. Then, while it can discriminate the false positive results of the serum CRP test, serum PCT test can be beneficial when used together with serum CRP test. The results of this study demonstrate that serum PCT and CRP are comparable to predict the clinical severity of febrile neutropenic attacks and furthermore, serum CRP correlates with the duration of the fever.

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