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ORIGINAL ARTICLE

Prognostic value of procalcitonin in infection-related mortality of cancer patients

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Summary

Purpose: *Infectious diseases are a major cause of morbidity and mortality in cancer patients. Tumor-induced inflammatory responses may increase the value of classical inflammatory markers in blood, so these markers may not be as useful in cancer patients as in non-cancer patients. Serum procalcitonin (PCT) is a sensitive and specific biomarker for severe infection, and has been shown to be unaffected by tumor-induced inflammatory response. In this study we aimed to evaluate the possible role of PCT in mortality in cancer patients with infection.*

Methods: *In total, 104 consecutive adult cancer patients who presented with fever (body temperature ≥ 38.3° C or ≥ 38° C on two consecutive measurements) during follow-up and needing hospitalization for infection were enrolled in this study.*

Results: *The majority (72%) of the patients were male. The most common diagnosis and type of infection were lung cancer (40.4%) and pneumonia (56.7%), respectively. The overall mortality rate was 17%. Statistical analysis showed a significant relationship between PCT levels and mortality (p=0.001), but not between classical inflammatory markers and mortality (p>0.05). The mortality rate of patients with a PCT value > 2 ng/mL was 34.3%, compared with 9.6% in patients with a PCT below this value (p=0.005). Furthermore, PCT predicted in-ward cancer patient mortality with a sensitivity of 66% and a specificity of 76%.*

Conclusion: *PCT is a unique serum biomarker significantly related to infection-related mortality and predicts mortality with a relatively high sensitivity and specificity.*

Key words: *biomarkers. cancer patients, infection, mortality, procalcitonin*

Introduction

Infection with or without neutropenia is a major cause of in-patient mortality in cancer patients. The differential diagnosis between fever of infectious etiology and fever related to disease, therapeutic agents or treatment side-effects must be made quickly because of the high infection-related mortality rate in cancer patients. There is no single proven clinical or laboratory prognostic marker for infection-related mortality, and management of cancer patients with infection remains a continual challenge for oncologists. Cancer itself stimulates a strong immune response and this interaction between cancer and the immune system is usually associated with elevation of inflammatory markers like C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and leukocyte count [1,2]. Results from clinical studies evaluating the prognostic importance of these

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biomarkers were reported to be negative. Therefore, these biomarkers seem to be ineffective in differentiating infection and tumor-induced inflammation [3].

PCT is a prohormone of calcitonin, which was first described in 1989 [4]. PCT is produced by the C-cells of thyroid as part of the systemic response to circulating endotoxins and cytokines during bacterial and fungal infections [5,6]. It has been shown that tumor-induced inflammation does not alter PCT levels [7]. PCT is gaining prominence in distinguishing between bacterial and viral infections, and particularly in identifying serious bacterial infections. In febrile neutropenic patients with solid tumors, PCT was found to be a valuable diagnostic and prognostic test [8-10]. In this study, we examined the role of PCT during follow-up of cancer patients with infection at the Medical Oncology Department of our hospital.

Methods

In total, 104 consecutive cancer patients hospitalized because of fever at the Department of Medical Oncology of the University of Baskent (Adana, Turkey) between June 2013 and October 2013 were retrospectively evaluated. Fever was defined as body temperature ≥ 38.3° C or ≥ 38° C in two consecutive measurements. Description of infection was made from cases with clinical, radiological and microbiological findings according to the definitions of the *'Centers for Disease Control and Prevention'* [11]. Demographic characteristics and laboratory and radiological findings were obtained from patient files. Eastern Cooperative Oncology Group (ECOG) scores were calculated using the ECOG performance scale. PCT measurements were made in the Modular E170 immunology analyzer (Roche Diagnostics GmbH, Mannheim, Germany) with the ECLIA (Electrochemiluminescence immunoassay) method using Elecsys BRAHMS kit (B•R•A•H•M•S Aktiengesellschaft, Hennigsdorf, Germany).

Informed consent was provided from surviving patients. Ethical approval for the study was provided by the University of Baskent Institutional Review Board.

Statistics

All results are presented as rate for categorical values, and as mean and median for continuous variables. Distribution of continuous variables was tested using visual graphics and by the Kolmogorov–Smirnov correction test. Depending on the distribution characteristics, Mann-Whitney U and Wilcoxon tests were used. The adjusted hazard ratios (HRs) and the 95% confidence intervals (95% CIs) were used for making estimations. All data were analyzed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA), and a p value < 0.05 was considered statistically significant.

Table 1. Patient demographic characteristics

Characteristics	*N (%)*
Age, years, median (range)	58 (22-82)
Sex, Male	75
Primary diagnosis	
Lung cancer	42 (40.4)
Breast cancer	10 (9.6)
Gastric cancer	7 (6.7)
Colon cancer	6 (5.8)
Other cancer types	39 (37.5)
Infection type	
Pneumonia	68 (65.4)
Febrile neutropenia	11 (10.6)
Urinary tract infection	7 (6.7)
Cholangitis	6 (5.8)
Abscess	5 (4.8)
Cellulitis	4 (3.8)
Mortality	18 (17.3)

Table 2. Procalcitonin, C-reactive protein, leukocyte counts, erythrocyte sedimentation rate values

Factors assessed	*Laboratory values, median (Normal range)*
Procalcitonin (ng/ml)	0.56 (0-0.05)
CRP (mg/L)	131 (0-6)
Leucocyte count (k/mm^3)	11.3 (4-10)
Erythrocyte sedimentation rate (mm/h)	94 (0-20)

CRP : C-reactive protein

Table 3. Procalcitonin values and mortality

Whole group	*Number of patients at risk*	
Mortality (%)	104	18 (17.3)
Group with mortality (N=18)		
Procalcitonin, N (%)		
<0.5 ng/mL	1	0 (0)
0.5-2.0 ng/mL	68	6 (7.8)
>2.0 ng/mL	35	12 (34.2)

Results

Baseline and demographic characteristics of patients are shown in Table 1. There were 75 (72%) male and 29 (28%) female patients. The median age was 58 years (range 22–88). Lung and breast cancer constituted most of the primary diagnoses (40.4% and 9.6% of the patients, respectively). The most frequently encountered type of infection was pneumonia in 68 (65.4%) patients. Median CRP, ESR, and leukocyte number, and PCT values were 131 mg/dL (normal 3–383), 94

mm/h (normal 0–20), 11,300 /mm^3 (normal 4,000–10,000), and 0.56 ng/mL (normal 0.05–79), respectively (Table 2). PCT values were > 2ng/mL, 0.5–2 ng/mL, and < 0.5 ng/mL in 35 patients, 68 patients and 1 patient, respectively (Table 3).

In statistical analysis, the ECOG performance score and PCT levels showed a significant relationship with mortality (p<0.0001 and p=0.001, respectively). Eighteen patients (17.3%) died during the study. Thirty-five patients had a PCT value >2ng/mL and 69 had a PCT value <2 ng/mL. Statistical analysis showed that mortality rate was significantly higher in the former group than the latter (34.3 vs 8.7%; p=0.005). With the cut-off level of PCT set at 2 ng/mL, PCT predicted infection-related mortality with 66% sensitivity and 76% specificity (Figure 1).

Statistical analysis failed to show a significant relation between mortality and CRP, ESR or leukocyte count (Figure 2). There was also no significant correlation between PCT and ECOG, CRP, ESR or leukocyte count. Also, no significant relationship between PCT levels and length of hospital stay was noticed.

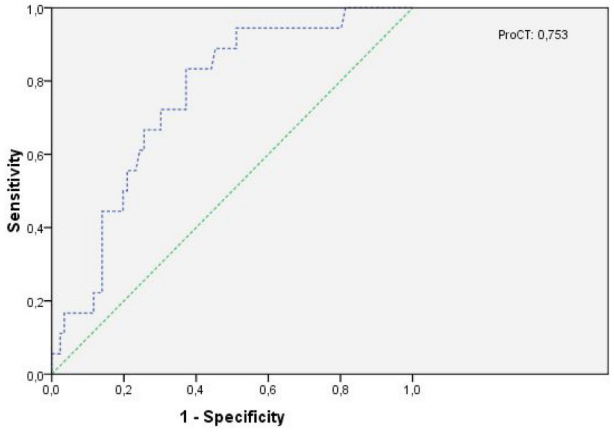

Figure 1. Receiver operating characteristic (ROC) curve for procalcitonin (ProCT) for infection-related mortality. The area under the curve for ProCT is 0.753 with p <0.0001.

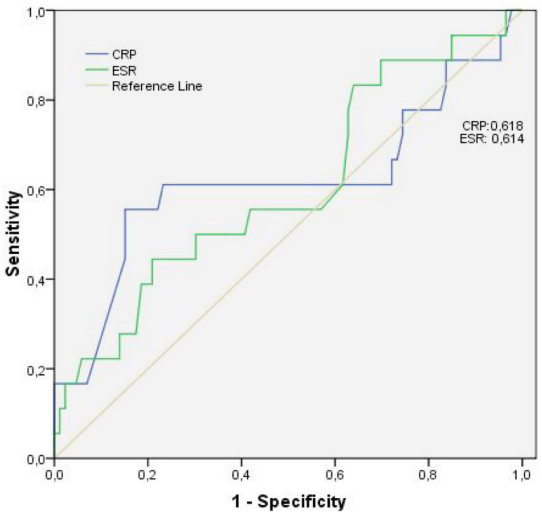

Figure 2. Receiver operating characteristic (ROC) curve for CRP and ESR for infection-related mortality. The area under the curve for CRP and ESR was 0.618 and 0.614, respectively, with p>0.05.

Discussion

Bacterial infection in cancer patients is an important cause of morbidity and mortality. The extent of an infectious risk in cancer patients is highly dependent on the underlying malignancy, situation of mucosal barriers, past history of infections, pathogens and the immunosuppressive effect of antitumor therapy. The European Society for Medical Oncology (ESMO) clinical recommendations and the National Comprehensive Cancer Network (NCCN) guidelines are two major tools actively used by oncologists to optimize cancer patient care. Unfortunately, there is no clear recommendation for the management of non-neutropenic cancer-related infection cases in the ESMO and NCCN guidelines [12,13]. Therefore, infectious diseases in cancer patients are managed using the same principles as in other patients. In cancer patients, the cancer-induced increase in inflammatory biomarkers in the blood and cancer-related factors that severely impair patients' general condition make it more difficult to answer the questions: (i) who truly benefits from antibiotic therapy? (ii) if treated, what is the optimal treatment duration? [14]. Clinical studies have failed to show a significant relation between classical inflammatory biomarkers or culture positivity with infection-related mortality. To be on the safe side, clinicians most often treat their patients with broad spectrum antibiotics in the context of a long hospital stay.

Many markers are seen as indicators of the body's response to a developing infection. One of these markers, CRP, is a very sensitive indicator of inflammation and increases in cases of infection, except for infection with causes such as trauma or autoimmune diseases, and after surgery [15]. PCT increases during a short time after the onset of infection and is not affected by the presence of immunosuppression [16]. PCT is a useful biomarker in determining the severity of infection, estimating prognosis and determining response to therapy. In studies conducted for the diagnosis of infection, PCT has been shown to be more sensitive and specific than CRP [17]. Therefore PCT may be a better prognostic factor than CRP [17].

In this study, we showed that single-value

PCT is significantly related with in-patient mortality. In contrast, statistical analysis failed to show a significant correlation between mortality and CRP, ESR, or leukocyte results. We also found no relationship between PCT and the aforementioned inflammatory markers. In our study, ECOG performance scale was also significantly related to mortality rates, but there was was no significant correlation between ECOG performance scale and PCT levels.

PCT levels are immeasurable in healthy people [18]. PCT values increase above 0.5 ng/mL during infection [18]. In our study, we used a PCT cut-off value of 2 ng/mL. The mortality rate of patients with a PCT value over the cut-off was 34.3%, while that of patients with a PCT value below the cut-off value was 9.6%. With these values, PCT showed sensitivity of 66% and specificity of 75% in predicting in-ward cancer patient mortality. Delevax et al. showed that a PCT value ≥ 1.2 mg/mL is an indication of the emergence of symptoms of bacterial infections and is a sign for the initiation of antibiotic therapy with 80% sensitivity and 96% specificity [19]. In other studies, the sensitivity of PCT was 43–60% and its specificity was 60–96%. PCT was shown to be more specific compared with CRP [3,9,20, 21]. This is important in an era where there is no single biomarker proven to be related to infection-related mortality. Using PCT for predicting infection-related mortality in cancer patients may play a significant role in decision-making. It has the potential for use in managing early hospital discharge and narrowing the spectrum of antibiotics used. However, the design of our study is insufficient to answer these questions and prospective studies are needed.

In conclusion, this is the first clinical study clearly showing that PCT is significantly correlated with infection-related mortality in cancer patients and has a relatively high sensitivity and specificity for infection-related mortality. PCT is a biomarker effective in the assessment of infection severity in patients with malignancy, and it has been used as a parameter to distinguish low and high risk of developing complications. Furthermore, the ease and rapidity of PCT measurement may allow for early recognition of severe infections and permit appropriate selection and stratification of cases to be treated.

Conflict of interests

The authors declare no confict of interests.

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