Original Article

Can Procalcitonin Distinguish Infectious Fever From Tumor-Related Fever in Non-Neutropenic Cancer Patients?

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BACKGROUND: Procalcitonin (PCT) has been proposed as a marker of infection and was studied in neutropenic patients. This study investigated its role in non-neutropenic febrile cancer patients (NNCPs). **METHODS:** Between July 2009 and July 2010, a total of 248 NNCPs with fever were studied. PCT was measured in plasma within 24 hours of fever onset and 4 to 7 days thereafter, using a Kryptor system with a lower limit of quantitation of 0.075 ng/mL. Patients' clinical, microbiological, and radiological data were reviewed to make the diagnosis and were correlated with PCT levels. **RESULTS:** This study included 30 patients with bloodstream infection (BSI), 60 with localized bacterial infection, 141 with no documented infection, and 8 with tumor-related fever. Most patients (98%) were inpatients or admitted to the hospital during the study. Patients with BSI had significantly higher PCT levels than did those with documented localized infections ($P = .048$) and no documented infection ($P = .011$). PCT levels were significantly higher in septic patients than in those without sepsis ($P = .012$). Patients with stage IV disease or metastasis had significantly higher baseline PCT levels than did those with early stages of cancer ($P < .05$). PCT levels dropped significantly in patients with bacterial infections in response to antibiotics ($P < .0001$). **CONCLUSIONS:** Baseline PCT levels are predictive of BSI and sepsis in NNCPs. They may be predictors of metastasis and advanced cancer. Subsequent decrease in PCT levels in response to antibiotics is suggestive of bacterial infection. Larger trials are needed to confirm the results of this pilot study. ***Cancer* 2012;118:5823-29.** © *2012 American Cancer Society.*

KEYWORDS: procalcitonin, cancer, non-neutropenics, infectious fever, tumor fever.

BACKGROUND

Procalcitonin (PCT), the precursor of the hormone calcitonin, is a hormokine composed of 116 amino acids that has been proposed as a marker of infection.[1-4] PCT is encoded on the *CALC-11* gene located on chromosome 11, and its transcription is induced universally in all tissues by bacterial infection.[2]

In healthy humans, PCT levels are undetectable, but they rise within 4 hours, peak at 6 hours, and then plateau at 8 to 24 hours after endotoxin injection.[5] PCT has an elimination half-life of approximately 25 to 30 hours.[6]

The role of PCT has been evaluated in numerous studies involving febrile neutropenic cancer patients, which were recently reviewed in a meta-analysis,[7] and where neutropenia is a major risk factor for infection,[8] but there are few studies done in non-neutropenic cancer patients (NNCPs).[9,10] In NNCPs, fever of unknown origin is a challenging diagnosis; malignant tumors can be a source of fever in the absence of infection, particularly in patients with lymphoma and solid tumors with liver metastasis.[11] These patients are commonly exposed to unnecessary antibiotics, with the accompanying risks of toxicity, bacterial resistance, increased medical costs, and delays in the administration of systemic chemotherapy.

This study evaluated the role of PCT as a marker for differentiating infectious from noninfectious fever in NNCPs who had solid tumors, lymphoma, and multiple myeloma.

MATERIALS AND METHODS

We conducted a prospective, observational clinical laboratory study that included 248 NNCPs with solid tumors, lymphoma, or multiple myeloma and fever ($\geq$38.3°C or 2 consecutive $\geq$38°C readings) who were admitted to The University of Texas MD Anderson Cancer Center in Houston, Texas, between July 2009 and July 2010. Patients with leukemia or those who had undergone hematopoietic stem cell transplantation were excluded because of potential bias, because they are more prone to developing infectious rather than tumor-related fevers. The study protocol was approved by the institutional review board, and a waiver of informed consent was requested and provided.

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Patients' clinical, microbiological, and radiological data were reviewed to make the diagnosis and were correlated with PCT levels. Patients were classified as having bloodstream infection (BSI; bacteremia or fungemia), localized bacterial infections (ie, pneumonia, wound infection, and urinary tract infection), or no microbiological evidence of infection. Patients were defined as having tumor-related fever if they had no microbiological, radiological, or clinical evidence of infection and did not experience a response to empirical antimicrobial therapy for at least 7 days, or experienced a response to naproxen test.[12] The naproxen test was defined as a prompt, complete lysis of fever with sustained normal temperature (<38°C) while receiving naproxen. Response to antimicrobials was defined as defervescence within 96 hours of treatment. Systemic inflammatory response syndrome (SIRS) was defined as having 2 or more of the following: body temperature >38.5°C or <35.0°C; heart rate of >90 beats per minute; respiratory rate of >20 breaths per minute or $PaCO_2$ (arterial partial pressure of CO_2) of <32 mm Hg; and white blood cell count of >12,000 cells/mL, <4000 cells/mL, or >10% immature (band) forms. Sepsis was defined as SIRS in response to microbiologically documented infection (culture or Gram stain of blood, sputum, urine, or normally sterile body fluid testing positive for pathogenic microorganisms).[13]

Clinical data were collected retrospectively from electronic medical records and included age, sex, underlying cancer and stage, comorbidities, vital signs, pertinent radiological imaging, microbiological data, sepsis status, antimicrobial therapy, response to antimicrobials, and length of hospital stay.

Laboratory Methods

To assess treatment response, we collected 2 residual plasma samples from all patients, 1 within 24 hours of fever onset and the second at 4 to 7 days later. All samples were collected from the University of Texas MD Anderson Cancer Center clinical chemistry laboratory within 4 days of the initial blood draw and immediately frozen at −80°C, according to manufacturer instructions (Brahms ThermoFisher, Middletown, Va). Samples were then thawed and centrifuged for 1 minute at 6708 g to pellet any excess fibrin, and the resulting supernatant was used to measure plasma PCT levels. A PCT immunofluorescent assay was performed using the PCT-sensitive kit on the Kryptor Compact platform (Brahms ThermoFisher) with a lower limit of quantitation of 0.075 ng/mL. Calibrator and control samples were run for maintenance and quality control, as specified by the manufacturer's protocol.

Table 1. Patients' Demographic and Clinical Characteristics

Characteristics	Patients (n = 248)
Age, y, median (range)	56 (5-84)
Male sex, n (%)	142 (57)
Underlying cancer, n (%)	
Gastrointestinal	67 (27)
Genitourinary	41 (17)
Lymphoma	33 (13)
Head and neck	17 (7)
Multiple myeloma	16 (6)
Cancer stage, n/total (%)	
I	17/215 (8)
II	13/215 (6)
III	34/215 (16)
IV	122/215 (57)
Remission	29/215 (13)
Metastasis, n (%)	108/190 (57)
Median absolute neutrophil count at onset, K/UL (range)	6.3 (0.6-49.9)
Bloodstream infection, n (%)	30 (12)
Localized bacterial infections, n (%)	60 (24)
Genitourinary tract infection	28 (11)
Soft tissue infection	16 (6)
Pneumonia	14 (6)
Tumor-related fever, n (%)	8 (3)
Sepsis, n (%)	77 (31)
Systemic inflammatory response syndrome, n (%)	80 (32)

Statistical Methods

Wilcoxon rank-sum tests were used to compare PCT levels between 2 different groups of patients, and Kruskal-Wallis tests were used to compare levels among 3 groups. If a significant result ($P < .05$) was detected on a Kruskal-Wallis test, Wilcoxon rank-sum tests were used for pairwise comparisons. The α levels of the post hoc pairwise comparisons were adjusted using the sequential Bonferroni method to control type 1 error. Patients' initial and follow-up PCT values were compared by using Wilcoxon signed-rank tests, then the diagnostic performance of the PCT test for BSIs was evaluated. First, the best cutoff value was determined using the receiver operating characteristic (ROC) curve method. Sensitivity, specificity, and positive and negative predictive values were calculated on the basis of the best cutoff value. All tests were 2-sided at a significance level of .05. The statistical analyses were performed using SAS, version 9.1 (SAS Institute, Cary, NC).

RESULTS

Patients' Clinical Characteristics

Our study included 248 NNCPs admitted to The University of Texas MD Anderson Cancer Center between July

Table 2. Comparison of Baseline Procalcitonin (PCT) Levels Between Patients With and Without Infections

Group	N	Median PCT (Range)	*P*
Bloodstream infection	30	1.06 (0.075-81.95)	
Localized bacterial infection	60	0.30 (0.075-154.7)	.048
No documented infection	141	0.31 (0.075-68.6)	.011
Tumor-related fever	8	0.67 (0.11-4.14)	.71

P values are the result of comparing PCT levels between patients with bloodstream infection and other groups.

2009 and July 2010. Their basic demographic and clinical characteristics are summarized in Table 1. Median age of patients was 56 years (range, 5-84 years), and 140 patients (57%) were males. The most common underlying cancers were gastrointestinal (27%), genitourinary (17%), lymphoma (13%), head and neck cancers (7%), and multiple myeloma (6%). Most of the patients (98%) were inpatients or admitted to the hospital during the study period. The majority (71%) were not critically ill at enrollment.

Of the 248 patients, 30 had BSIs (12%), 60 had localized bacterial infections (24%), 6 had viremia (2%), 3 had localized viral infections (1%), and the remaining 149 had no microbiological evidence of infection (60%). Of the 149 patients with no documented infection, 8 patients (3%) met the definition of tumor-related fever and were analyzed separately. Seventy-seven patients (31%) had sepsis, 80 (32%) had SIRS, and 91 (37%) had neither SIRS nor sepsis.

Metastatic status could be assessed in 190 patients with solid tumors, and 108 had metastasis (57%). Of the 215 patients with solid tumors, lymphoma, or multiple myeloma in whom cancer stage could be assessed, 122 had stage IV, and 93 had either stages I, II, or III cancer or were in remission.

Of the 89 patients with bacterial infections in our study, 70 (79%) experienced a response to treatment and 18 (20%) did not. One patient experienced defervescence before the initiation of antimicrobial therapy.

PCT in Bloodstream Infections

Baseline PCT levels were compared among patients with BSIs and those with localized bacterial infection, no documented infection, and those with tumor-related fever (Table 2). Patients with bloodstream infections had significantly higher baseline PCT levels than did those with localized bacterial infections (median PCT: 1.06 ng/mL versus 0.30 ng/mL; $P = .048$) and those without infections (median PCT: 1.06 ng/mL versus 0.31 ng/mL; $P = .011$). On the other hand, we found no significant difference in baseline PCT levels between patients with localized bacterial infections and those with no microbiological evidence of infection ($P = .95$).

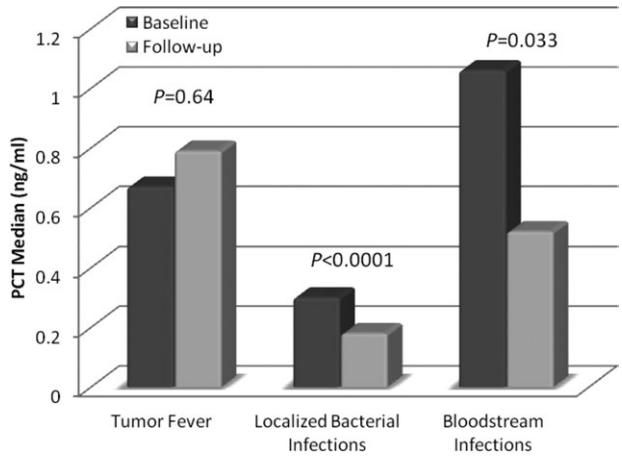

Figure 1. Changes in baseline procalcitonin (PCT) levels are shown for different groups at follow-up.

Next, we evaluated the performance of a baseline PCT test as a diagnostic method for BSIs. On the basis of the ROC curve, the optimal PCT cutoff level was 0.5 ng/mL, and the area under the ROC curve was 0.64 (95% confidence interval, 0.52-0.76). Using 0.5 ng/mL as the cutoff value, the PCT test in our study had a sensitivity of 67%, specificity of 62%, positive predictive value of 26%, and a negative predictive value of 90%.

PCT Levels in Tumor-Related Fever and Metastasis

The 8 patients with tumor-related fever had a median PCT level at baseline of 0.67 ng/mL (range, 0.11-4.14 ng/mL). Seven of the 8 patients (88%) had solid tumors, and 6 (86%) had metastasis. No significant difference was found in baseline PCT levels between patients with tumor-related fever and BSIs ($P = .71$) (Table 2). However, PCT levels in patients with BSIs and those with localized bacterial infections were more likely to decrease by 50% or more on follow-up than were those in patients with tumor-related fever (BSI versus tumor-related fever: 53% versus 0%, $P = .01$; localized bacterial infection versus tumor-related fever: 38% versus 0%, $P = .04$). Figure 1 shows the change in PCT levels in response to antimicrobial therapy in patients with bacterial infections and those with tumor-related fever.

Baseline PCT levels in patients with metastasis were significantly higher than those in patients without metastasis (median PCT: 0.47 ng/mL versus 0.20 ng/mL, $P = .008$). Baseline PCT levels were also compared between patients with metastasis and those with BSIs (after

excluding overlapping patients), and no significant difference was found ($P = .35$).

Patients with stage IV cancer had significantly higher baseline PCT levels than did those with stage I to III cancer or those in remission (median PCT: 0.47 ng/mL versus 0.27 ng/mL, $P = .017$).

PCT in Patients With SIRS or Sepsis

Next, we evaluated PCT levels in patients with SIRS and sepsis. Septic patients (median PCT: 0.60 ng/mL) and patients with SIRS (median PCT: 0.36 ng/mL) had significantly higher baseline PCT levels ($P = .012$ and $P = .032$, respectively) than did those with neither (median PCT: 0.28 ng/mL). However, we found no significant difference in baseline PCT levels between septic patients and those with SIRS ($P = .48$).

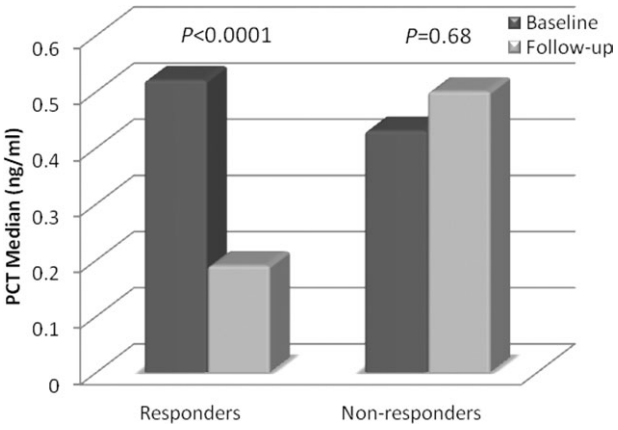

Figure 2. Procalcitonin (PCT) levels in patients with bacterial infections are shown according to response to antimicrobials.

PCT and Patients' Response to Antibiotics

We evaluated the relationship between PCT levels and treatment response in patients with bacterial infections (Fig. 2). PCT levels at 4 to 7 days after fever onset were significantly lower than those at fever onset in the patients who experienced a response (median PCT: 0.19 ng/mL versus 0.52 ng/mL, $P < .0001$). However, PCT levels increased at follow-up in those who did not experience a response, but the increase was not significant (median PCT: 0.50 ng/mL versus 0.43 ng/mL, $P = .68$).

DISCUSSION

To our knowledge, this is the largest study of the role of PCT in febrile NNCPs. Our data demonstrate that baseline PCT level is a predictor of BSIs but not localized infections, and may be a marker of metastatic disease. Our results also showed that baseline PCT levels were significantly higher in septic patients. Furthermore, follow-up PCT levels obtained 4 to 7 days after onset of fever, which show decreased levels upon administration of antibiotics, does suggest bacterial infection (bloodstream or localized); this may help clinicians further distinguish infection-related fever from tumor-related fever.

Our results are consistent with those of previous studies in febrile cancer patients that assessed the diagnostic value of PCT in neutropenic patients who have BSIs (Table 3).[14-25] When using a cutoff point of 0.5 ng/mL, sensitivity ranged from 21% to 92.9%, whereas specificity ranged from 45.5% to 92%. Table 3 summarizes the sensitivity and specificity of PCT in diagnosing BSIs in previous studies. A recent meta-analysis revealed that the diagnostic performance of PCT was moderate for

Table 3. Sensitivity and Specificity of Procalcitonin (PCT) in Diagnosing Bloodstream Infections in Febrile Cancer Patients

Author	Neutropenics/ Non-Neutropenics	PCT Cutoff (ng/mL)	No. of Patients or Episodes	Bloodstream Infection (n)	Sensitivity	Specificity
Jimeno et al[14]	Neutropenics	0.5	104	15	66.7	86.5
Engel et al[15]	Neutropenics	0.51	44	15	73	86
Giamarellou et al[16]	Neutropenics	1	158	52	44.2	64.3
Von Lilienfeld-Toal et al[17]	Neutropenics	0.62	53	18	72	77
Giamarellos-Bourboulis et al[18]	Neutropenics	0.5	115	28	92.9	45.5
Persson et al[19]	Neutropenics	0.5	94	21	58	83
Secmeer et al[20]	Neutropenics	0.4	60	6	33.3	92
Kim et al[21]	Neutropenics	0.5	286	38	60.5	82.3
Koivula et al[22]	Neutropenics	0.5	90	21	57	81
Prat et al[23]	Neutropenics	0.5	57	19	21	75.6
Gac et al[24]	Neutropenics	0.5	39	10	60	65
Fleischhack et al[25]	Mostly neutropenics[a]	0.5	122	13[b]	60	85
Shomali et al[c]	Non-neutropenics	0.5	248	30	67	62

[a] Median absolute neutrophil count was 0.04×10^9/L.
[b] Gram-negative bacteremia only.
[c] Current study.

identifying BSIs in patients presenting to the emergency department.[26] Furthermore, PCT may also be helpful in differentiating contamination from BSI due to coagulase-negative staphylococci, but this finding needs to be confirmed in larger studies.[27]

Our results suggest that PCT levels can be used to enhance clinical judgment by helping clinicians predict BSIs. Blood cultures require 24 to 48 hours to provide meaningful information, but PCT results can be available within 1 hour, and decisions about admission and starting antibiotics can be made immediately thereafter. In addition, PCT can help stratify cancer patients into a low-risk group of having BSI, where outpatient oral therapy may be considered, or into a high-risk group of having BSI, where early and appropriate administration of intravenous antibiotics and possible hospital admission may lead to a better outcome.[28] Muller et al[29] also showed that PCT can help predict bacteremic patients presenting with community-acquired pneumonia, thereby limiting the number of blood cultures drawn. However, the generalizability of the study to our patient population may be limited, because only 13% of patients had underlying cancer, and severely immunosuppressed patients were excluded.

Baseline PCT level was not an absolute predictor of localized bacterial infection in our NNCP population. This finding may be due to the influence of cancer itself. Most of our patients (57%) had stage IV cancer, with a significantly higher PCT levels than those who had stage I to III cancer and remission ($P = .017$). Our findings are consistent with those of Kallio et al,[30] which demonstrated that the discriminatory power of PCT in cancer patients is best for bacteremia, whereas it fails to discriminate minor infections from tumor-related fever.

In our study, patients with metastasis had significantly higher PCT levels than did those without metastasis ($P = .008$). When stratifying patients by cancer stage, we found a significant difference between stage IV and stages I, II, III, or remission combined ($P = .017$). Therefore, in cancer patients with no suspicion of BSI (no fever or chills), PCT may be used as a biomarker of metastasis. However, further studies are needed in nonfebrile cancer patients who have no signs of infection. Given that cancer metastasis is associated with relatively higher PCT levels at baseline, this test is most suggestive of BSI and sepsis in cancer patients with no metastasis.

The discovery of biomarkers that are predictive of the progression and metastasis of cancer can have a major impact on patient care and outcome, because at present, clinicians rely on expensive radiographic procedures such as computed tomography and positron emission tomography scans in patients with solid tumors and lymphoma. Ghillani et al[31] previously reported that calcitonin precursors were frequently elevated in patients with various malignant tumors, ranging from 7% in breast tumors to 62% in hepatocellular carcinoma, depending on the cell type and tumor stage. These results were confirmed by Matzaraki et al[32] in a study that included 43 patients with solid tumors and no evidence of infection. PCT was shown to be a marker of metastatic disease, because serum PCT levels in patients with generalized metastatic carcinoma were significantly higher than those in healthy control subjects and cancer control patients without metastasis.

Another important finding is that in our patient population, PCT levels were significantly higher in patients with SIRS and sepsis than in patients with no SIRS or sepsis. However, PCT did not differentiate between SIRS and sepsis. This finding is consistent with the study by Brunkhorst et al[33] but contrasts with other studies[34,35] in which PCT levels were significantly higher in septic patients than in those with SIRS. This may be because potentially infected patients with negative cultures were misclassified into the SIRS group. Distinguishing between infectious and noninfectious etiology of SIRS is often difficult, especially in immunocompromised cancer patients, who are at high risk for occult infections that are often not revealed through positive cultures. In a study by Meisner et al[36] that compared PCT and C-reactive protein at different stages of sepsis and multiple organ dysfunction syndrome, patients with SIRS and sepsis were not separately analyzed, because the infectious etiology cannot always be identified, and culture-negative (clinically suspected) sepsis has a similar mortality rate to that of culture-proven sepsis.[37]

As an epidemic of bacterial resistance is emerging, where the overuse and misuse of antimicrobials lead to the increased selection of resistant organisms, effective antibiotic stewardship programs are strongly needed.[38] PCT-guided algorithms for the management of critically ill septic patients were shown in a recent meta-analysis of randomized controlled trials to be associated with decreased antibiotic exposure and adverse events.[39] Hence, PCT may be useful for guiding and enforcing antimicrobial stewardship programs in cancer patients, leading to shorter durations of antimicrobial therapy and decreasing the emergence of resistance, as well as lowering treatment costs. This was demonstrated in our study through PCT kinetics, which revealed a significant decrease in association with response to successful antimicrobial therapy in patients with bacterial infections

($P < .0001$). In addition, follow-up analysis of PCT levels can help in predicting bacterial infection (bloodstream or localized), in which PCT levels decrease significantly over time, whereas patients with tumor-related fever experience a nonsignificant increase in PCT levels (Fig. 1), thereby helping clinicians choose the appropriate antibiotic agents and therapy durations. PCT algorithms have been recently proposed for determining appropriate antibiotic treatments in different patient populations, and these to be evaluated in future trials.[40]

Our study has several limitations that should be mentioned. First, it was a single-institution study, which limits the generalizability of the results. Second, given its observational design, whereby clinical data were extracted retrospectively, the effect of confounding variables cannot be excluded.[41] Third, we relied on positive cultures to determine whether patients had sepsis or infection (including BSI). However, cancer patients may have an unapparent infection despite negative cultures, because many factors limit culture sensitivity.[42]

Conclusions

On the basis of our results, we conclude that baseline PCT level is a predictor of BSI and sepsis in NNCPs. It may also be a predictor of metastasis and advanced cancer, but confirmatory studies are warranted in nonfebrile patients with no signs of infection. A decrease in follow-up PCT levels in response to antibiotics may help differentiate infectious fever from tumor-related fever. Finally, implementation of PCT testing in the care of cancer patients should be studied in randomized controlled trials, because it may lead to more efficient antibiotic use, with possible reduction in antibiotic therapy duration, emergence of resistance, and cost.

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CONFLICT OF INTEREST DISCLOSURE

The authors made no disclosure.

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