Procalcitonin and C-reactive protein as markers of bacterial infection in patients with solid tumours

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ABSTRACT

INTRODUCTION: The diagnosis of bacterial infections in patients with solid tumours can be difficult as both the tumour and its treatment can cause symptoms and signs similar to those of infections. Many patients with solid tumours therefore receive antibiotic treatment without having a bacterial infection. In this prospective study, we wanted to investigate the value of procalcitonin (PCT) compared with C-reactive protein (CRP) as an indicator of bacterial infection in adult patients with solid tumours.

METHODS: A total of 41 patients with solid tumours admitted to hospital due to fever or clinical signs of infection had their PCT and CRP levels measured on and during admission. The patients were classified as having a microbiologically verified infection, a radiologically verified infection or no infection. PCT and CRP were also measured in a control group of 34 out-patients with solid tumours, but with no signs of infection.

RESULTS: Of the 41 admitted patients, 25 were classified as having an infection (either microbiologically or radiologically verified). Among the 25 cases with infection, PCT was within the normal range in 11 cases and only elevated in 14. As nearly half of the patients with infection had PCT within the normal range, PCT is not suited to exclude an infection. CRP was elevated in 20 patients out of the 25.

CONCLUSION: PCT within the normal range cannot exclude an infection and does not appear to be superior to CRP to exclude an infection in patients with solid tumours.

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The diagnosis of bacterial infections in patients with solid tumours remains a difficult clinical problem as patients with solid tumours often experience fever due to their cancer without necessarily having an infection. Also, leucocyte counts may be elevated due to tumour load, antineoplastic treatment or the use of prednisolone.

C-reactive protein (CRP) is produced in response to pro-inflammatory signalling and is therefore often elevated in the presence of a microbiological infection. However, it is not a specific marker, and it is also often elevated due to inflammatory reactions or cancer disease [1]. Furthermore, patients with solid tumours may be infected without showing signs of fever, either due to the use of prednisolone or non-steroidal anti-inflammatory drugs, or due to immunosuppression. Therefore, the usual signs of infection, such as fever, an elevated CRP and a high leukocyte count have only a limited use in patients with solid tumours.

A more specific marker of bacterial infections in patients with solid tumours would be very helpful. This would limit unnecessary use of antibiotics and reduce the risk of inducing multi-resistant bacteria. Likewise, a more certain diagnosis would allow for a faster discharge from hospital and thereby reduce unwarranted delays in the administration of chemotherapy.

Procalcitonin (PCT), the precursor of the hormone calcitonin, is a hormokine, which has been proposed as a very specific marker of bacterial infections and a strong predictor of bloodstream infections in neutropenic patients [2-12]. PCT can be measured within a few hours and would therefore provide valuable, expedient information on whether a patient has a bacterial infection or not. Although many previous reports have investigated the value of PCT in patients with bacterial infections, only a limited number of reports exist on the relevance of PCT for the diagnosis of bacterial infections in patients with solid cancer without neutropenia [12-14].

We initiated a prospective study to investigate the utility of PCT compared with CRP as a predictive marker of bacterial infection in adult patients with solid tumours in anti-neoplastic treatment. As CRP and possibly PCT may be elevated solely due to the cancer process, we also included out-patients with solid tumours but without infection as a control group.

METHODS

Two groups of patients with solid tumours were included from May 2011 to May 2012; Group 1 (in-patients) and group 2 (out-patients).

In-patients

A total of 51 patients hospitalised due to fever or clinical signs of infection were included upon admission to the Department of Oncology. In all, ten patients never had PCT evaluated and were therefore excluded. Upon admission, the following data were obtained: a detailed history of the patients' medical history, documentation of vital signs, physical examination and standard labora-

TABLE 1

Characteristics of patients classified as infection and no infection.

	Infection (N = 25)	No infection (N = 16)
Patients		
Male, n (%)	13 (52)	8 (50)
Female, n (%)	12 (48)	8 (50)
Age, yrs, median (range)	66 (39-84)	68.5 (55-86)
Cancer, n (%)		
Head and neck	1 (4)	1 (6)
Lung	6 (24)	3 (19)
Breast	7 (28)	1 (6)
Gastrointestinal tract	4 (16)	9 (56)
Urogenital	7 (28)	2 (13)
Stage, n (%)		
Localised disease	12 (48)	7 (44)
Metastatic disease	13 (52)	9 (56)
Treatment, n (%)		
Chemotherapy	25 (100)	16 (100)
+ radiotherapy	1 (4)	1 (6)
+ targeted treatment	2 (8)	3 (19)

TABLE 2

Variables and values of procalcitonin and C-reactive protein in 41 in-patients. The values are n (%).

	Infection		
	microbiologically verified (N = 14)	radiologically verified (N = 11)	No infection (N = 16)
Bacteriaemia	6 (43)	0	0
Localised infection	8 (57)	11 (100)	0
Neutropenic fever[a]	3 (21)	6 (55)	7 (44)
Procalcitonin			
> 0.5 µg/l	8 (57)	6 (55)	2 (13)
≤ 0.5 µg/l	6 (43)	5 (45)	14 (87)
C-reactive protein			
> 50 µg/l	13 (93)	10 (91)	11 (69)
≤ 50 µg/l	1 (7)	1 (9)	5 (31)

a) Defined as a leucocyte count < 1.0×10^9 /l and/or neutrophils < 0.5×10^9 /l and a temperature > 38.5 °C.

tory tests. Fever was defined as a temperature > 38.5 °C. In the presence of pulmonary symptoms or in the absence of a bacterial focus, a chest X-ray was performed at the discretion of the treating physician. Samples of blood and urine from all in-patients and, when relevant, material from other sites suspected of infection, were cultured before initiation of antibiotic treatment. Levels of CRP and PCT were measured on days one, two and three. Treatment decisions regarding the use of antibiotic treatment were made irrespective of the level of PCT and, if necessary, treatment was initiated before the PCT blood sample was taken. We independently reviewed the clinical, microbiological and radiological data of all in-patients in order to classify the patients into three groups: microbiologically verified infection, radiologically verified infection and no infection (the PCT and CRP values were blinded during this process). The following diagnostic criteria of infection were used:

A) Patients were classified as having a microbiologically verified infection in case of a positive bacterial culture (bloodstream infection identified as "likely contamination" by the microbiologist was not characterised as a positive bacterial culture). Positive urine cultures were defined as microbiologically verified infection depending on the concentration of bacteria and the patients' symptoms: A concentration of any type of bacteria > 100,000/ml, with or without urinary tract symptoms, and a concentration of any type of bacteria > 10,000/ml if the patient had symptoms consistent with urinary tract infection was characterised as microbiologically verified infection. A concentration of any type of bacteria < 10,000/ml was characterised as no infection.

B) Patients were classified as having a radiologically verified infection if there were positive radiological findings and symptoms consistent with pneumonia or clinical findings consistent with a bacterial infection.

C) Patients were classified as having no infection if there were no microbiological or radiological evidence of a bacterial infection.

In order to calculate the sensitivity and specificity of PCT and CRP, groups A) and B) were combined (infection).

Out-patients

A total of 40 patients with solid tumours, but without any signs of infection, were included irrespective of disease status. PCT and CRP were measured in 34 patients once during a routine visit and could be used for evaluation.

Laboratory tests

PCT was measured from serum using a BRAHMS Kryptor with a quantification limit of 0.02 microgram/l to 50.00 microgram/l. Calibration and control samples were run for maintenance and quality control as specified by the manufacturer's protocol.

Elevated values of PCT were defined from a cut-off level at 0.5 microgram/l [12]. The usual cut-off level for CRP in our laboratory was 3.0, but such a low cut-off may not be relevant in a population of cancer patients. For this study, a cut-off level of 50 microgram/l was c hosen based on the literature [15, 16].

Statistical analyses

The primary endpoint was to evaluate if a PCT within the

normal range could exclude a bacterial infection. This was expressed as the negative predictive value of PCT. Further, we compared PCT with CRP, and the diagnostic accuracy of detecting infection was expressed as the area under the receiver-operating characteristic (ROC) curve, and the respective areas were calculated with a 95% confidence interval (CI). The statistical analysis was performed with IBM SPSS Statistics Version 19 (SPSS Inc., Chicago, Illinois).

Ethical approval

The study was approved by the Ethical Committee H-4-2010-133 (2011-02-02) and by the Danish Data Protection Agency. The study was conducted in accordance to good clinical practice. All patients provided written, informed consent.

Trial registration: Clinicaltrials.gov, NCT01227109.

RESULTS

A total of 25 in-patients were classified as having an infection; 14 had a microbiologically verified and 11 had a radiologically verified infection (see **Table 1** and **Table 2**). Of the 25 patients with an infection, 11 had PCT within the normal range, corresponding to a negative predictive value of 0.56 (see Table 2 and **Table 3**). Of the 11 patients with PCT within the normal range, five had a radiologically verified infection and six a microbiologically verified infection; among the latter, three had a positive blood culture and three had a positive urine culture.

The median PCT value in all in-patients with infection was 0.74. In in-patients with localised disease and infection, the median PCT value was 0.225, whereas the median PCT value in in-patients with metastatic disease and infection was 2.07.

Sixteen in-patients were classified as having no infection. Despite being classified as having no infection, two of the 16 patients had a PCT > 0.5 microgram/l, corresponding to a positive predictive value of 0.88 (see Table 2 and Table 3).

The area under the ROC curve was 0.836, (95% CI = 0.735-0.937) for PCT and 0.847 (95% CI = 0.754-0.940) for CRP (see **Figure 1**).

Serial blood samples of procalcitonin in in-patients

Of the 26 patients who had more than one sample of PCT, 11 patients (42%) had higher second levels of PCT and 15 patients (58%) had lower second levels. None of the patients went from an elevated level of PCT to a normal level or vice versa.

Baseline values of procalcitonin and C-reactive protein in out-patients

Only one out-patient had a PCT > 0.5 microgram/l. This confirms the high specificity of PCT also found in the 16 in-patients without infection. The median value of PCT in all out-patients was 0.07, and the median values of PCT in out-patients with localised and metastatic disease were 0.07 and 0.08, respectively.

TABLE 3

Sensitivity, specificity, positive predictive value and negative predictive value of procalcitonin and C-reactive protein in 41 in-patients.

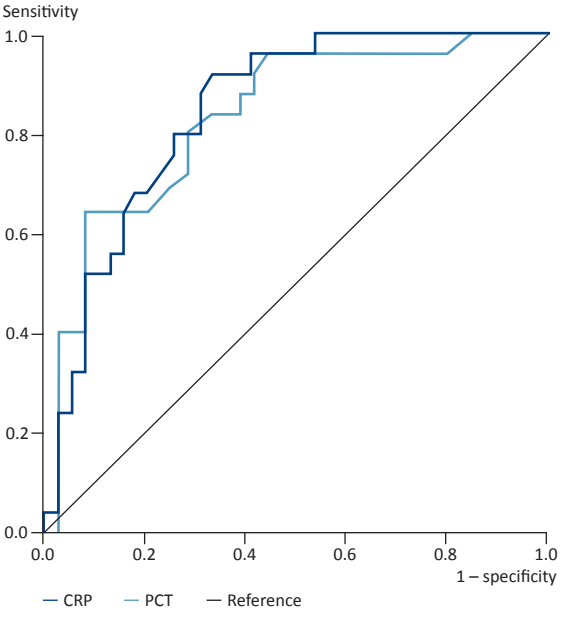
	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Procalcitonin	0.56 (14/25)	0.88 (14/16)	0.88 (14/16)	0.56 (14/25)
C-reactive protein	0.92 (23/25)	0.31 (5/16)	0.68 (23/34)	0.71 (5/7)

DISCUSSION

This study was initiated to examine if the value of PCT could be used to differentiate between bacterial and non-bacterial infections in patients with solid tumours only. In our study, 16 patients out of 41 in-patients did not have a bacterial infection and could therefore have avoided antibiotic treatment. Unfortunately, we found PCT to be a poor predictive marker for exclusion of bacterial infections in patients with solid tumours who were brought to the hospital with a suspected infection, as the negative predictive value of PCT within the normal range was 0.56. Also, in six patients with a microbiologically verified infection, of whom three had a bloodstream infection, PCT was within the normal range. Shomali et al [12] found 30 patients with bloodstream infection of whom ten had a PCT within the normal range. In patients with a localised infection, they found that the mean PCT level was not higher than in patients without infection. They also summarised the results of PCT levels in cancer patients from other trials and reported a sensitivity ranging from 21% to 93% and a specificity ranging from 46% to 92%. These variations might be caused by a difference in the classification of infections which makes comparisons difficult. Furthermore, most of the studies included both patients with haematological malignancies as well as patients with solid tumours. Shomali et al also reported that febrile cancer patients with metastases had higher levels of PCT than patients without metastatic disease, indicating that PCT is not only specific of bacterial infection, but also specific of the extent of disease. In our study, we found a similar trend with a higher median PCT (2.07) in in-patients with infection and metastatic disease than in in-patients with infection and localised disease (median PCT 0.225 microgram/l), whereas there was no difference in out-patients. Other studies have found that a higher PCT level was, indeed, associated with infection [2-13], but no studies have found that PCT within the normal range

FIGURE 1

Receiver-operating characteristic (ROC) curve demonstrating the sensitivity as a function of 1 – specificity for discriminating patients with infection based on C-reactive protein (CRP) and procalcitonin (PCT) levels. The area under the ROC curve for CRP and PCT is 0.847 (95% confidence interval (CI): 0.754-0.940), and 0.836 (95% CI: 0.735-0.937), respectively.



could exclude an infection. The conclusions of the various studies vary considerably; from claiming that PCT could help differentiating between infection and no infection, contending that PCT has no diagnostic value at all [4]. In this study, antibiotic treatment could be started before the initial PCT sample was measured. The half-life of PCT is approximately 25-30 hours [17, 18], and all of our patients except for one had their PCT measured within the first 24 hours. Thus, it is unlikely that the level of PCT should have converted to the normal range before being measured. Furthermore, none of the 26 patients who had more than one measurement of PCT went from normal levels of PCT to elevated levels or vice versa. The main limitation of this study was a small sample size. However, it is unlikely that a larger study would have produced findings that may justify the use of PCT since we observed cases with bacteraemia and PCT ≤ 0.5 microgram/l.

CONCLUSION

In this prospective study, PCT within the normal range could not exclude an infection, thus, in daily clinical practice, PCT cannot help in the decision of whether to initiate antibiotic treatment or not. Our study indicates that PCT is probably not superior to CRP and thus probably has no role as a standard marker of bacterial infection in patients with solid tumours.

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