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ORIGINAL PAPER

Procalcitonin as a predictive marker of infections in chemoinduced neutropenia

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Abstract
Purpose This study was designed to determine the usefulness of procalcitonin (PCT) as a predictive marker of infections in neutropenic patients following chemotherapeutic treatments.
Methods Over a 6-month period, 65 patients (34 affected by a solid tumor, 31 by a hematological disorder) were enrolled. Serum PCT concentrations were measured by an automated immunoassay on the leucocytes nadir and on the third day, when patients were checked for any sign of infection.
Results Procalcitonin values were not affected by gender, age, therapeutic approach, use of G-CSF or performance status and did not differ between patients who subsequently developed a localized infection and those who did not. PCT concentrations resulted higher in patients affected by hematological disorders than in those affected by solid tumors (mean value 0.09 vs. 0.05 μg/L; $p < 0.0015$) and in those who were hospitalized than in the outpatient group (0.10 vs. 0.05 μg/L; $p < 0.0013$). PCT levels correlated with the type of neoplastic disease ($p = 0.016$), the highest concentrations being detected in patients affected by acute leukemia.
Conclusions These findings suggest that PCT is not a useful predictive marker of infection in oncohematologic neutropenic patients, even though higher serum PCT concentrations are associated with hematological tumors as well as in-hospital admission.

Keywords Procalcitonin · Neutropenia · Infection markers · Chemotherapy

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Introduction

In cancer patients morbidity and mortality resulting from infectious complications following aggressive chemotherapy remain a major clinical problem. The treatment-related neutropenia following antineoplastic chemotherapy, or neutropenia resulting from the neoplastic disease itself, are associated with a high risk of infections (Pizzo 1993). Neutropenia, corticotherapy, chemotherapy, anatomic barrier damage, obstructive phenomena and malnutrition increase the risk of infections and reduce the clinical and radiological signs of infection (Talcott et al. 1998). In the majority of neutropenic febrile episodes, causative infection agents cannot be identified. Therefore, specific, rapid and cost-efficient markers indicating early infection are required. Procalcitonin (PCT) has been proposed as an indicator of infection, as its concentration increases very quickly after the onset of infection and it is reliable even in the presence of immunosuppression (Linscheid et al. 2003; Muller et al. 2001; Tang et al. 2007).

The origin of its synthesis is unknown but it is certain that it is independent of the C cells of the thyroid. PCT rises specifically in bacterial and, even to a lesser extent, fungal processes but not in response to other types of inflammation. Concentrations of 0.5–1.0 μg/L are considered to be

associated with localized infections, whereas concentrations >1.0 μg/L are suggestive of bacteriaemia and sepsis (Giamarellou et al. 2004).

The aim of the study was to evaluate the relationships between serum concentrations of PCT and the development of infectious events within 72 h after the first measurement, in asymptomatic patients affected by a solid or hematological tumor, with G3-4 neutropenia following chemotherapy.

Patients and methods

This study was conducted in the oncohematological department of an academic tertiary-care referral hospital. A total of 65 patients neutropenic patients grade G3 and G4 (National Cancer Institute scale) were prospectively included in the study from November 2008 to March 2009. Patients were treated with antineoplastic chemotherapy on an outpatient basis or were admitted to in-hospital ward in the case of more intensive treatment or when neutropenia of longer duration was expected. A preliminary evaluation showed that 35% of patients being treated as outpatients in our hospital developed a neutropenia of grade G3–G4 (data not shown). We enrolled only those patients who, at the time of blood collection, were deeply neutropenic (G3 or G4) but had no signs or symptoms of infection.

Overall we collected 89 samples for PCT serum concentration assessment because some patients experienced more than one neutropenic event, following different cycles of chemotherapy. At the same time as the blood sample was withdrawn, an evaluation form was completed. Collected data were: cancer location, performance status, chemotherapy schedule, line of treatment, neutrophil count, use of G-CSF.

The follow-up of outpatients, directed toward identifying the onset of infection, was carried out by means of a phone interview conducted by a physician 3 days after the measurement of PCT. The inpatients were clinically evaluated every day by the attending physician in the oncohematological ward.

The serum samples obtained on leukocytes' nadir were stored at −20°C until they were measured, using a highly sensitive automated immunofluorescent assay (Brahms PCT Kryptor®, Brahms Diagnostic GmbH, Berlin, Germany). Assay characteristics are: functional sensitivity of 0.06 μg/L, dynamic range up to 1,000 μg/L, within-run and between-run precision of 5.6 and 8.8% at 0.15 μg/L PCT concentration, of 4.2 and 5.7% as well as of 2.5 and 4.9% at 1.7 and 20.3 μg/L, respectively. Healthy individuals without any sign of infection/inflammation usually have serum/plasma PCT levels below 0.5 μg/L. We considered a positive result when PCT serum concentrations were >0.5 μg/L.

The statistical analysis was carried out using MedCalc software, Version 9.4. Non-parametric tests were applied due to the non-Gaussian distribution of obtained quantitative data in the study population. Accordingly, Spearman rank correlation was used.

Results

The epidemiological and clinical data of the 65 enrolled patients as well as of the 89 episodes of neutropenia observed in this study are shown in Table 1. The median of the 89 PCT determinations was 0.11 μg/L (range 0.02–4.25). In 25 episodes of neutropenia a clinical infection developed after the first measurement of PCT and included fever (13 episodes), mucosites (2 episodes), upper respiratory tract infections (3 episodes), urinary tract infections (2 episodes), gastroenteritis (2 episodes), pneumonia (2 episodes), conjunctivitis (1 episode). Globally, 21 patients developed an infection and 2 patients had infective symptoms in two different neutropenic periods, accounting for 35% of the patients having clinical infection during neutropenia.

In our population PCT values were independent of gender, age, use of G-CSF, grade of neutropenia, and development of infective symptoms (Table 1).

There was a statistically significant difference between patients who were affected by a solid tumor compared with patients affected by a hematological tumor (Fig. 1a). There

Table 1 Characteristics of the study population

Characteristics	*N*	PCT (μg/L)			p^{b}
		N	Median	Range	
Females/males	37/28	51/38	0.05/0.05	(0.02–4.25)/(0.02–0.36)	0.35
Solid/hematologic cancer	34/31	41/48	0.05/0.09	(0.02–0.35)/(0.02–0.42)	0.0015
Outpatients/hospitalized	47/18	60/29	0.05/0.10	(0.02–0.35)/(0.20–4.25)	0.0013
Infection/no infection	23/42	25/64	0.07/0.07	(0.02–0.36)/(0.02–4.25)	0.85
G-CSF/no G-CSF	[a]	49/40	0.06/0.07	(0.02–4.25)/(0.02–1.18)	0.30
G3/G4	[a]	40/49	0.06/0.08	(0.02–0.35)/(0.02–4.25)	0.13

[a] Characteristics that may have changed in different episodes of neutropenia

[b] Mann–Whitney *U* test

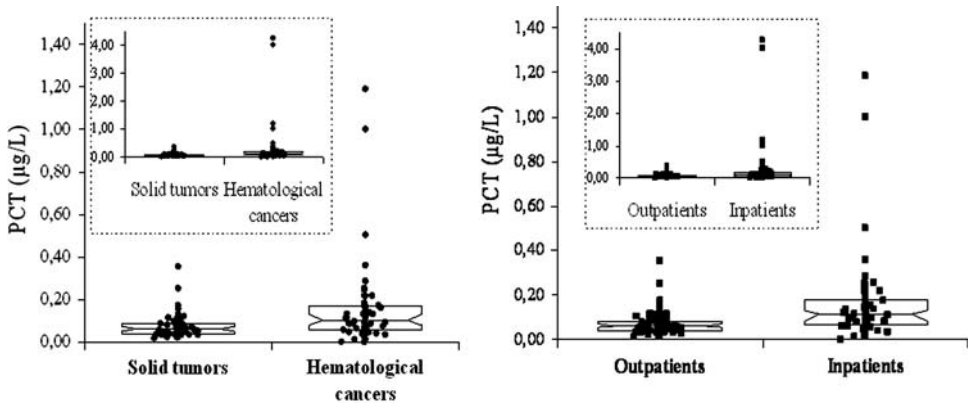

Fig. 1 Notched boxplots (median and 95% CI) of procalcitonin concentrations measured in patient affected by solid tumors and those affected by hematological cancers (*left side*; $p = 0.0015$ by Mann–Whitney *U* test) and in outpatients and hospitalized patients (*right side*; $p = 0.0013$). The *insert boxes* include the two PCT values higher than 1.5 µg/L

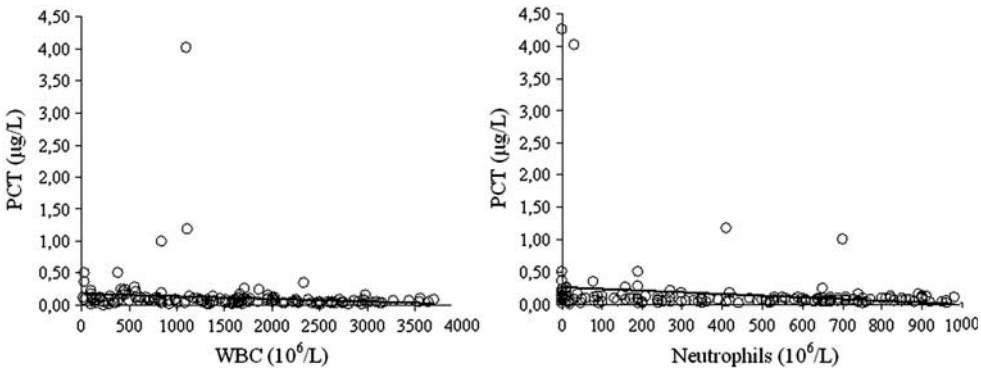

Fig. 2 Correlation between procalcitonin concentrations and the number of leucocytes (*left side*; $N = 156$, $rs = -0.35$ according to Spearman correlation, two-tailed $p < 0.0001$) as well as the neutrophil count (*right side*; $N = 157$, $rs = -0.27$, two-tailed $p = 0.0005$)

were differences also in baseline PCT values in outpatients as compared with inpatients (Fig. 1b). In particular, we found the highest PCT levels in hospitalized patients affected by a hematological disease.

It is interesting to note the statistically significant negative correlation between the number of either leucocytes or neutrophils and PCT values ($p = 0.03$, by Spearman correlation) (Fig. 2) as well as between the type of neoplasia and PCT serum concentrations ($p = 0.016$): patients affected by acute leukemia had higher PCT values in comparison with those affected by other kinds of cancer ($p = 0.0006$ according to Kruskal–Wallis test followed by Bonferroni correction) (Table 2, Fig. 3).

Table 2 Procalcitonin concentrations and the type of cancer disease

Type of cancer	*N*	Number of determinations	PCT (µg/L) Median (range)
Breast cancer	20	50	0.06 (0.02–0.25)
Acute leukemia	6	16	0.12 (0.03–4.26)*
Lymphoma	20	32	0.08 (0.02–0.50)
Myeloma	5	10	0.10 (0.06–4.10)**
Others	14	38	0.07 (0.02–0.35)

* $p = 0.04$ and $p = 0.0026$ with respect to other tumors and breast cancer, respectively, according to Bonferroni correction after Kruskal–Wallis test; ** $p = 0.0012$ versus breast cancer

A comparison analysis of the two episode groups (infection vs. no infection) showed no significant difference in the levels of PCT. However, it is important to highlight that in the group of hospitalized patients, in 2 out of 12 PCT measurements that preceded infective symptoms, PCT concentration resulted >1.0 µg/L and in all

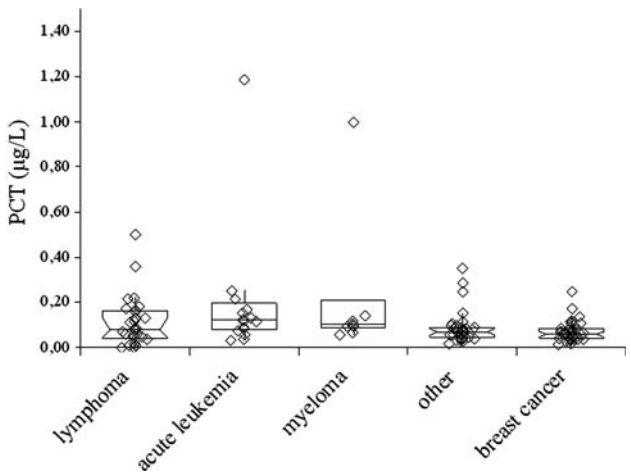

Fig. 3 Notched boxplots (median and 95% CI) of procalcitonin values among different types of neoplasia. The two PCT values higher than 1.5 µg/L, measured in the acute leukemia and in the myeloma groups, respectively, are not shown

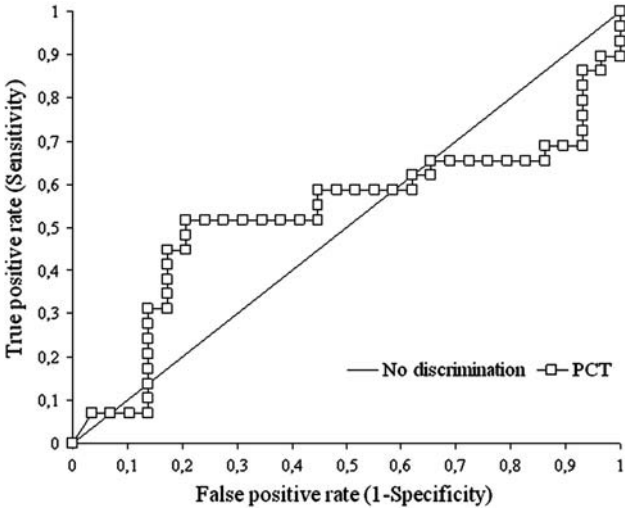

Fig. 4 Receiver-operating characteristic (ROC) plot of procalcitonin baseline concentrations to predict an infectious event in all neutropenic patients. Area under the ROC curve = 0.53

cases of PCT values >0.5 μg/L an infection was taking place.

In an attempt to establish the optimal PCT cut-off value to be used in the population of our study, the diagnostic sensitivity and specificity of a single baseline PCT value were explored using the ROC curve analysis. The best combination of sensitivity and specificity was achieved at a cut-off value of 0.09 μg/L when considering all patients together, yielding 52% sensitivity and 79% specificity, with 2.50 positive likelihood ratio and 71% positive predictive value (Fig. 4).

Discussion

Symptoms and signs of inflammation may be obscure in patients with severe neutropenia. Early markers of bacterial infections are therefore required when monitoring neutropenic patients (Penel et al. 2004). These markers should be released and regulated independently of neutrophil cell count and the activity of the underlying disease. It is also essential that these markers reflect the severity of the infection and distinguish episodes with high risk of complication from those with low risk. A number of studies among neutropenic patients have been performed, mostly to establish whether different proinflammatory cytokines or acute phase proteins can identify bacteriemia during the first day of fever (Jimeno et al. 2004; Schuttrumpf et al. 2006), but few studies have analyzed if those markers can be used as a predictor of infection or if they can show the presence of infection before the onset of the fever (Hambach et al. 2002). Finding a marker with this characteristic could be helpful in distinguishing, at the onset of neutropenia, those patients who are at low risk of infections and can be treated as outpatients, compared with those who need to be hospitalized or need an empirical antibiotic therapy. There are many clinical factors that can be considered in order to distinguish patients with high risk of complications from those at low risk: age, performance status >2, comorbidity, and poor marrow reserve heighten the risk of severe infectious complications and mortality related to febrile neutropenia. A combined evaluation of the patient using serological markers and clinical features is indicated. Among circulating biomarkers, the potential usefulness of C-reactive protein (CPR) as compared to PCT is still a matter of debate (Simon et al. 2004; van Rossum et al. 2004; Tang et al. 2007). We performed PCR on a group of 40 patients of our study population. As expected, PCR results showed a wide distribution of concentration values (mean 6.08 mg/dL, ranging from <0.04 to 56.1). While PCT levels were always <0.5 ng/mL in these samples, it can be argued that PCR cannot be used due to the occurrence of a high rate of unpredictable "false positive" results in this kind of patients, probably explained by factors associated with their diseases.

Previous studies concerning the use of PCT in neutropenic patients were mainly focused on possible relationships between PCT concentrations and fever and/or other signs or symptoms of infection disorders (Uys et al. 2007; Sakr et al. 2008). We looked at the potential application of PCT assessment as a predictive factor in a cohort of asymptomatic afebrile neutropenic patients.

In the outpatient population we observed an incidence of infectious episodes in 22% of the patients; all of those infections were localized and were correlated with low concentrations of PCT [0.05 μg/L (0.02–0.359)]. In this population it was not possible to verify whether PCT rises in the case of generalized infection, while was only possible to highlight the existence of a correlation between a low level of PCT and a low risk patient. We obtained significantly higher values of PCT in patients affected by a hematological disorder who were treated as inpatients in comparison with the rest of the population. This group of patients had the highest incidence of infection, compared with the rest of the population of the study (37 vs. 22%). In two measurements of PCT, obtained from this same group of patients, we found a PCT level >1 μg/L 24 h before the onset of the symptoms of a bacterial pneumonia; in all cases of PCT concentrations >0.5 μg/L there was a bacterial infection. We may also suppose that the highest PCT values observed in hematological patients may be expression of subclinical infections.

We believe it could be interesting to continue to study PCT or other early marker of infection in this type of patients because they are at higher risk of infection for their own disease that altered the immunological system, compared to

the population affected from a non-hematological disease. It is important in high risk patients, like the hematological patients, to recognize as soon as possible an infection complication and hospitalize the patient if it is necessary.

We confirm that PCT is not a pre-emptive marker of infection. Its levels rise when the infection became systemic because it is released not from leucocytes in the site of localized infection, as it was thought when it was discovered, but from parenchymal cells, mainly by hepatocytes, after the spread of the infection. This evidence is suggested also by our observations of a negative correlation between the number of leucocytes or neutrophil count and PCT levels. Indeed, we find higher PCT concentrations in more deeply neutropenic patients than in patients with neutropenia of lower degree.

The most common infections experienced by patients undergoing chemotherapy are localized infections, therefore PCT in not an efficient marker for those patients because it starts to rise when the infection became systemic. It can just be used to exclude systemic evolution of a clinical localized infection and it can be helpful, when added to a clinical evaluation, in identifying low risk patients who can be treated safely as outpatients.

Conflict of interest statement None among the authors of the article has any financial and personal relationships with other people or organisations that could inappropriately influence the presented work.

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