Procalcitonin as a Useful Marker of Infection in Hemato-oncological Patients with Fever

MARIA T. SANDRI[1*], RITA PASSERINI[1*], MARIA E. LEON[2], FEDRO A. PECCATORI[3], LAURA ZORZINO[1], MICHELA SALVATICI[1], DANIELA RIGGIO[1], CRISTINA CASSATELLA[1], SAVERIO CINIERI[3,4] and GIOVANNI MARTINELLI[3]

[1]*Laboratory Medicine Unit,* [2]*Epidemiology and Biostatistics Division and* [3]*Hematoncology Division, European Institute of Oncology, Milan,* [4]*Medical Oncology Division, A. Perrino Hospital, Brindisi, Italy*

Abstract. *Background: The diagnostic utility of procalcitonin (PCT) and C-reactive protein (CRP) to discriminate between infective fever and fever due to inflammation was assessed in hemato-oncological patients treated with aggressive chemotherapy. Patients and Methods: Values of PCT and PCR measured on days -1, 0, 1, 3 and 5 of onset of fever were analyzed using longitudinal regression analysis. Of 236 febrile episodes in 166 patients, 39 were due to bacteremia, 62 to other infections and 135 were classified as fever of unknown origin. Results: PCT concentration increased early only in bacteremia and other infections (p<0.001), with the highest levels at day +1. No different trends were noted in patients with low WBC count (<1,000/μl). CRP increased with a similar trend in all the three groups. Conclusion: PCT determination may contribute significantly to the management of hemato-oncological patients who experience febrile episodes.*

Patients treated with aggressive chemotherapy for malignancy very often experience febrile conditions due to chemotherapy-induced neutropenia. In many cases, fever is due to infection, however in a considerable number of patients, other conditions may be associated with increased temperature, such as the administration of drugs or blood products, and even the tumor itself. As infections are among the major causes of morbidity and mortality in these patients, many efforts have been made to determine laboratory parameters which could help in addressing the diagnosis. These have included C-reactive protein (CRP), the most widely used inflammatory marker (1), which is often found elevated in patients with cancer. Some authors suggest the use of different CRP cut-off levels, but differing results have been reported (2-5). In recent years, procalcitonin (PCT) has been proposed as a new marker of severe bacterial infection (6-8) and to be useful in the discrimination between septic complication and non-infectious fever in transplant patients (9). To assess the value of PCT in the differential diagnosis of febrile conditions in hemato-oncological patients, whether leukopenic or not, PCT and CRP were measured in 166 individuals with solid and hematological tumors who presented febrile episodes during hospitalisation.

Patients and Methods

Data collection. A total of 236 consecutive febrile episodes were recorded in 166 cancer patients treated with high-dose chemotherapy with autologous peripheral blood stem cell transplantation or aggressive chemotherapy for leukemia, lymphoma or solid tumors at the Division of Hematoncology of the European Institute of Oncology; clinical and demographic characteristics of patients are shown in Table I. Longitudinal data on PCT, CRP and WBC determinations during febrile episodes were retrospectively retrieved from laboratory records. Informed consent to use blood samples for research purposes was obtained at hospital admission.

Treatment of patients. All patients were treated *via* central venous catheters. Fever was defined as a single body temperature peak over 38.5˚C or a sustained body temperature of more than 38.0˚C for two observations within 24 hours, not being a consequence of the administration of potentially pyrogenic agents (blood components or drugs). All patients received anti-infection prophylaxis with ciprofloxacin (500 mg twice a day), fluconazole (200 mg daily) and acyclovir (400 mg, three times a day). In the absence of documented infection, ceftazidime, 2 g three times daily and amikacin 15 mg/kg daily were started at fever onset. After 48-72 hours without defervescence, vancomycin at 500 mg four times daily was added. Antifungal empirical therapy with liposomal

*Both these authors contributed equally to this paper.

Correspondence to: Maria Teresa Sandri, MD, Laboratory Medicine Unit, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy, Tel: +39 0257489418 Fax: +39 0294379237, e-mail: maria.sandri@ieo.it

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Table I. *Patient characteristics, underlying solid and haematological tumors.*

Age in years (median/range)	46.8/18-70
Gender, n (female/male)	100/66
Underlying malignancies (n)	
Hodgkin's disease	8
Non-Hodgkin's lymphoma	58
Leukemia (ALL, CLL, AML, CML)	21
Multiple myeloma	16
Breast cancer (adjuvant setting)	53
Other solid tumors	10

ALL, Acute lymphatic leukemia; CLL, Chronic lymphatic leukemia; AML, Acute myeloid leukemia; CML, Chronic myeloid leukemia.

amphotericin B (3-5 mg/kg/daily) was then added after further 48 hours; if clinical conditions did not improve, a thoracic computed tomography (CT) scan was performed.

Laboratory methods. At the onset of fever, 3 sets of blood cultures (two from the central venous catheter, the second after one hour, and one from a peripheral vein) were taken from all patients. Other microbiological cultures were requested depending on the site of suspected infection. Febrile episodes were classified as: i) fever of unknown origin (FUO; fever without documentation of infection - group F); ii) microbiologically or radiologically documented infection without bacteremia (group O); and iii) bacteremia both alone and with other infection (group B). EDTA plasma samples for PCT and CRP determinations were collected prospectively beginning with the day of fever onset and on days 1, 3 and 5. In 172 out of 236 fever episodes, a sample was also available prior to the onset of fever, corresponding to day –1. At the same time, a total white blood cell (WBC) count was performed using an automated hematology analyzer (Toa Medical Electronics Co., Ltd, Kobe, Japan). PCT concentrations were determined using LUMItest PCT (B.R.A.H.M.S.-Diagnostica GmbH, Berlin, Germany) according to the manufacturer's specifications; values >0.5 ng/ml were considered to be pathological. CRP was determined by TINA – QUANT (Integra 800, Roche Diagnostics, Germany); the upper limit of the reference interval was 5 mg/l.

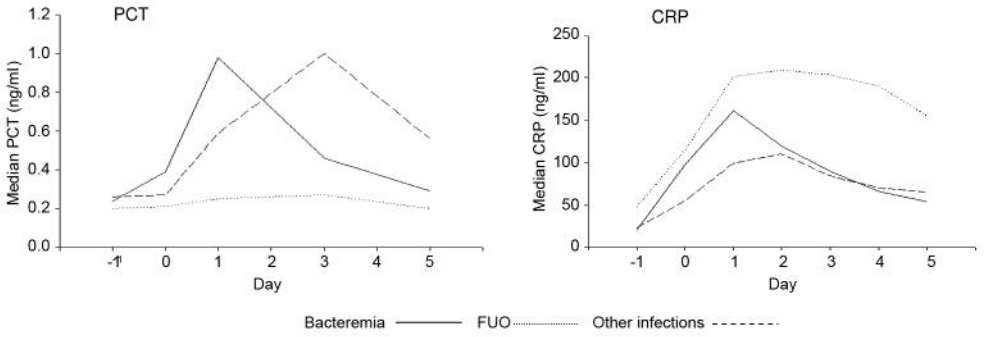
Statistical methods. The statistical analysis was based on data collected on days –1, 0, 1, 3 and 5 of fever onset. Of the 166 patients forming the sample population, 56 contributed with 2 episode of fever, 13 with 3 and one patient contributed with 4 episodes. Both outcome variables analyzed (PCT, PCR) were continuous and non-normally distributed. A logarithmic transformation was used to render the variables approximately normal prior to longitudinal analysis. Patient-specific observations accrued over time were analyzed taking into account patient and between episode correlation for individuals with multiple fever events during the course of treatment. Longitudinal data were analyzed using mixed linear models with time as fixed and patient as random effects respectively. Group and time-specific least-square means were generated with Bonferroni adjusted *p*-values for multiple comparisons of means. In a second phase of the analysis, additional explanatory variables were added to the models, such as etiology of fever and WBC level. All analysis was carried out using SAS (SAS Institute Inc, Cary, NC, USA). *P*-values were derived from two-sided tests. An association was considered statistically significant if $p \leq 0.05$

Results

Clinical and microbiological findings. The 236 febrile episodes recorded were subdivided into three groups, bacteremic episodes (39), other infection episodes (62, of which 30 were respiratory tract infections and 32 urinary tract, gastrointestinal tract, skin and mucosae infections) and 135 FUO. From the positive blood cultures, 24 gram-positive cocci were isolated (13 *Staphylococci* coagulase-negative, 6 *Staphylococcus* aureus, 5 *Streptococcus* species) and 15 gram-negative bacilli (12 *Escherichia coli*, 1 *Pseudomonas aeruginosa*, 1 *Enterobacter cloacae*, 1 *Klebsiella pneumoniae*).

Results of PCT measurements. A total of 1,041 PCT determinations were performed. PCT level changed significantly with sampling day in groups O (other infections) and B (bacteremia) but not in group F (FUO), showing a significant day by group interaction ($p<0.0001$). PCT levels increased with time reaching the highest value on day 1 in groups B and on day 3 in group O, subsequently dropping. In patients with FUO, PCT level varied little over time (no significant change). No differences in PCT level were noted among the three groups at day –1 (Figure 1). Considering patients with bacteremia, PCT was more frequently increased and reached the highest concentration in cases of gram-negative bacteremia [12 out of 15, 80%; 95% confidence interval (CI): 52-96%; day +1 median value 2.08 ng/ml] than in cases of gram-positive (13 out of 24, 54%; 95% CI: 33-74%; day +1 median value 0.60 ng/ml). Among gram-positive cases, PCT was increased in 4 out of 5 patients with *Streptococci* bacteremia (80%; 95% CI: 28-99%) and in 9 out of 12 patients with *Staphylococci* bacteremia (75%; 95% CI: 43-94%): the frequency of occurrence did not differ between *Streptococci* and *Staphylococci*. In other infections (group O), increased concentrations of PCT were found in 38 out of 62 episodes (61%; 95% CI: 73-98%); patients with pneumonia showed the highest median levels of PCT (from 0.28 ng/ml on day 0 to 1.07 ng/ml on day 2). Twenty-six episodes (20%) classified as FUO showed increased levels of PCT.

Considering a cut-off of 0.5 ng/ml, PCT showed a sensitivity of 62.3% and a specificity of 80.7%, to differentiate patients with infection from those with FUO. The positive predictive value was 70.7% and the negative predictive value was 74.1%. Two hundred and six episodes of fever (87%; 95% CI: 82-91%) developed in deeply leukopenic patients (WBC less than 500/μl or less than 1,000/μl with an expected decline to 500). In patients with documented infection, PCT was elevated both in patients



PCT expressed in ng/ml

Day	FUO (group F)			Bacteremia (group B)				Other infections (group A)			
	n	Median	Range	n	Median	Range	*p*	n	Median	Range	*p*
-1	102	0.20	0.08-1.16	24	0.24	0.08-76.71	ns	45	0.26	0.08-1.66	ns
0	121	0.21	0.09-30.1	32	0.39	0.08-49.17	0.009	59	0.27	0.09-16.47	ns
1	99	0.25	0.08-8.91	30	0.98	0.09-34.13	<0.0001	52	0.59	0.09-14.20	0.0006
3	97	0.27	0.08-7.13	31	0.46	0.09-10.15	ns	50	1.00	0.08-14.68	<0.0001
5	66	0.20	0.09-1.86	23	0.29	0.12-2.48	ns	40	0.56	0.09-21.49	<0.0001

p-values are Bonferroni adjusted and compare differences of least square means between group B and F and between group A and F, respectively.

CPR expressed in mg/L

Day	FUO (group F)			Bacteremia (group B)				Other infections (group A)			
	n	Median	Range	n	Median	Range	*p*	n	Median	Range	*p*
-1	103	23	0 - 353	24	21	1 - 174	ns	44	48	0 - 396	ns
0	120	55	4 - 364	32	97	5 - 238	ns	56	115	5 - 440	ns
1	98	99	16 - 324	30	161	22 - 357	ns	51	201	9 - 379	ns
3	95	84	6 - 289	31	90	31 - 277	ns	50	203	9 - 406	0.029
5	63	65	1 - 285	24	54	6 - 228	ns	40	155	9 - 424	0.025

p-values are Bonferroni adjusted and compare differences of least square means between group B and F and between group A and F, respectively.

Figure 1. *Procalcitonin (PCT) and C reactive protein (CPR) concentrations from day –1 to day +5 in patients with FUO, in patients with bacteremia and in patients with other infections. PCT level changed significantly by sampling day in groups A and B but not in group F ($p<0.0001$). CRP changes were similar in all groups of patients.*

with low and normal WBC count (Figure 2), without any significant difference between the two groups ($p=0.71$). There was a significant change in PCT levels over time ($p<0.0001$) in both groups.

CRP measurements. A total of 1,045 CPR determinations were performed. CRP increased with time, reaching its highest value on day 1 in all the groups of patients, subsequently dropping (no significant day by group interaction) (Figure 1). Among patients with bacteremia, those due to gram-negative infection showed higher levels of CRP compared to those due to gram-positive infection (median values 187 mg/l and 89 mg/l respectively). The other infections group (group O) showed the highest CRP levels, with pneumonia reaching the highest values (from 118 mg/l at day 0 to 223 mg/l at day 2, median values).

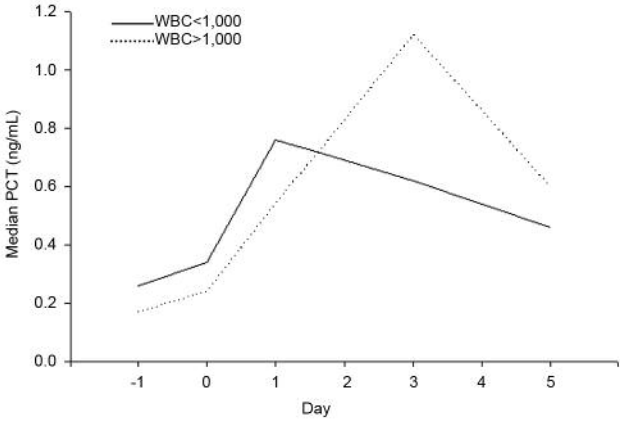


Figure 2. *Comparison of procalcitonin levels in patients with WBC below or above 1000/μl (patients with bacteremia and other infections).*

Discussion

Many previous reports have pointed out that PCT is an early marker of severe infections in various clinical settings, but mainly in non-leukopenic patients. This study describes the PCT concentration prior, during and after onset of fever, also analyzing its diagnostic usefulness as an early marker discriminating between severe or mild infections and FUO, in patients treated with intensive chemotherapy for aggressive malignancy. Some previous reports suggested that although PCT is recognized as a marker of severe infection, it did not give adequate information in leukopenic patients (10-13). Oberhoffer *et al*. demonstrated that peripheral blood mononuclear cells are among the main sources of PCT in patients with sepsis (14). Conversely, other authors have underlined the ability of PCT in discriminating between leukopenic patients with fever due to severe infection and those with fever due to mild infection or which is tumor-related (15-21). In our study, 87% of the episodes developed during the leukopenic period; we found that PCT measurement early after fever onset could be a useful tool in the evaluation of leukopenic patients in association with

clinical examination, discriminating between patients with bacterial infections (severe or mild) and patients with FUO. In the FUO group, the vast majority of patients (80%) showed low levels of the marker at day 0 and +1 (and also thereafter), while patients with bacteremia or other infections showed increasing levels on the first and on the third day, respectively. Considering the FUO group, 26 patients (20%) showed augmented PCT levels in two or more samples. Mild increases of PCT in patients with FUO have also been reported by Giamarellos-Bourboulis *et al.* (18), however they found that these patients, differently from patients with FUO and low levels of PCT, responded to antimicrobial chemotherapy, hence they speculated that the increase of PCT levels was probably due to an underlying bacterial infection which could not be documented. The same explanation could be considered valid for our patients (22).

In 14 patients of the bacteremic group, PCT concentrations did not increase: in 11 of them a gram-positive bacterium was responsible for the bacteremia, confirming that PCT increased particularly in gram-negative infection (23, 24). In particular, we found increased median PCT values in patients with *Streptococcus* species bacteremia, similar though lower than those found in gram-negative bacteremia, and in individuals with *S. aureus*. On the other hand, the majority of patients with *Staphylococci* coagulase-negative bacteremia (7/10) had low PCT levels, in agreement with previous reports (25). Moreover, PCT was more frequently increased in patients in whom, beside the bacteremia, a second infection was documented (14/16, 87.5%). Increased levels of PCT were also found in the group of patients with other infections, confirming previous studies (12, 17, 24).

Regarding CRP, as already reported (12, 26), its levels before the onset of the febrile episode were well above the reference range and increased from day –1 to day +1 in all the patients, with a wide overlap among different groups and not discriminating between the different febrile conditions.

In summary, PCT seems to be an early marker of bacterial infection, also in cases of leukopenic oncological patients who experience febrile episodes, thus providing the clinician with very quick and early information about the etiology of the episode and allowing more appropriate management of the patient.

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