C-reactive protein in critically ill cancer patients with sepsis: influence of neutropenia

Pedro Póvoa1,2*, Vicente Ces Souza-Dantas3, Márcio Soares3,4 and Jorge IF Salluh3,4

Abstract

Introduction: Several biomarkers have been studied in febrile neutropenia. Our aim was to assess C-reactive protein (CRP) concentration in septic critically ill cancer patients and to compare those with and without neutropenia.

Methods: A secondary analysis of a matched case-control study conducted at an oncologic medical-surgical intensive care unit (ICU) was performed, segregating patients with severe sepsis/septic shock. The impact of neutropenia on CRP concentrations at admission and during the first week of ICU stay was assessed.

Results: A total of 154 critically ill septic cancer patients, 86 with neutropenia and 68 without, were included in the present study. At ICU admission, the CRP concentration of neutropenic patients was significantly higher than in non-neutropenic patients, 25.9 ± 11.2 mg/dL vs. 19.7 ± 11.4 mg/dL (P = 0.009). Among neutropenic patients, CRP concentrations at ICU admission were not influenced by the severity of neutropenia (< 100/mm³ vs. ≥ 100/mm³ neutrophils), 25.1 ± 11.6 mg/dL vs. 26.9 ± 10.9 mg/dL (P = 0.527). Time dependent analysis of CRP from Day 1 to Day 7 of antibiotic therapy showed an almost parallel decrease in both groups (P = 0.335), though CRP of neutropenic patients was, on average, always higher in comparison to that of non-neutropenic patients.

Conclusions: In septic critically ill cancer patients CRP concentrations are more elevated in those with neutropenia. However, the CRP course seems to be independent from the presence or absence of neutropenia.
Materials and methods

Design and setting

The present study is a matched case-control study performed in the ICU of Instituto Nacional de Câncer (INCa), Rio de Janeiro, Brazil. The study period (January 2003 to July 2007), every adult (>18 yrs) that required ICU admission in septic cancer patients, like interleukin (IL)-6, IL-8, serum amyloid A, C-reactive protein (CRP), procalcitonin [8,9], with neutropenia were compared [10]. For the present study, cancer patients the concentrations of a widely used biomarker of infection, CRP, comparing the baseline concentrations of infection, CRP, and response to antibiotic therapy in those with and without neutropenia. However, non-neutropenic cancer patients with sepsis are usually excluded from these studies. In the present study, our aim was to assess the diagnostic performance of different biomarkers of infection in septic cancer patients, namely with febrile neutropenia.

Definitions, selection of participants and data collection

Definitions, selection of participants and data collection are provided elsewhere [10]. Briefly, during the study period (N° 10/2003) and the need for informed consent was waived.

Inclusion criteria

- Adults (≥18 yrs) that required ICU admission
- Infection was defined as the presence of a pathogenic microorganism in a sterile milieu (such as blood or cerebrospinal fluid) and/or clinically suspected infection. Infection was defined as the presence of a pathogenic microorganism in a sterile milieu (such as blood or cerebrospinal fluid) and/or clinically suspected infection. Definitions, selection of participants and data collection are provided elsewhere [10]. Briefly, during the study period (N° 10/2003) and the need for informed consent was waived.

Exclusion criteria

- Patients in complete remission of more than 5 yrs, those with an ICU stay less than 24 hrs and readmissions were not considered. The ICU is a 10-bed medical-surgical unit specialized in the care of patients receiving MV or home artificial ventilation.
- Patients in complete remission of more than 5 yrs, those with an ICU stay less than 24 hrs and readmissions were not considered. The ICU is a 10-bed medical-surgical unit specialized in the care of patients receiving MV or home artificial ventilation.

The Institutional Human Research Ethics Committee granted the present research (N° 10/2003) and the need for informed consent was waived.

Materials and methods

Design and setting

The present study is a matched case-control study performed in the ICU of Instituto Nacional de Câncer (INCa), Rio de Janeiro, Brazil. The study period (January 2003 to July 2007), every adult (>18 yrs) that required ICU admission in septic cancer patients, like interleukin (IL)-6, IL-8, serum amyloid A, C-reactive protein (CRP), procalcitonin [8,9], with neutropenia were compared [10]. For the present study, cancer patients the concentrations of a widely used biomarker of infection, CRP, comparing the baseline concentrations of infection, CRP, and response to antibiotic therapy in those with and without neutropenia. However, non-neutropenic cancer patients with sepsis are usually excluded from these studies. In the present study, our aim was to assess the diagnostic performance of different biomarkers of infection in septic cancer patients, namely with febrile neutropenia.

Definitions, selection of participants and data collection

Definitions, selection of participants and data collection are provided elsewhere [10]. Briefly, during the study period (N° 10/2003) and the need for informed consent was waived.

Inclusion criteria

- Adults (≥18 yrs) that required ICU admission
- Infection was defined as the presence of a pathogenic microorganism in a sterile milieu (such as blood or cerebrospinal fluid) and/or clinically suspected infection. Infection was defined as the presence of a pathogenic microorganism in a sterile milieu (such as blood or cerebrospinal fluid) and/or clinically suspected infection. Definitions, selection of participants and data collection are provided elsewhere [10]. Briefly, during the study period (N° 10/2003) and the need for informed consent was waived.

Exclusion criteria

- Patients in complete remission of more than 5 yrs, those with an ICU stay less than 24 hrs and readmissions were not considered. The ICU is a 10-bed medical-surgical unit specialized in the care of patients receiving MV or home artificial ventilation.
- Patients in complete remission of more than 5 yrs, those with an ICU stay less than 24 hrs and readmissions were not considered. The ICU is a 10-bed medical-surgical unit specialized in the care of patients receiving MV or home artificial ventilation.

The Institutional Human Research Ethics Committee granted the present research (N° 10/2003) and the need for informed consent was waived.

Materials and methods

Data processing and statistical analysis

The Institutional Human Research Ethics Committee granted the present research (N° 10/2003) and the need for informed consent was waived.

Data processing and statistical analysis

The Institutional Human Research Ethics Committee granted the present research (N° 10/2003) and the need for informed consent was waived.

The Institutional Human Research Ethics Committee granted the present research (N° 10/2003) and the need for informed consent was waived.

The Institutional Human Research Ethics Committee granted the present research (N° 10/2003) and the need for informed consent was waived.

The Institutional Human Research Ethics Committee granted the present research (N° 10/2003) and the need for informed consent was waived.

The Institutional Human Research Ethics Committee granted the present research (N° 10/2003) and the need for informed consent was waived.
The patients had a median age of 68 years (IQR 59, 75). The most frequent malignancy was lymphoma (N = 32, 20.8%), polymorphic (29.1%), gastrointestinal (23.4%), urogenital (10.4%), breast (7.0%), and others (6.5%).

Impact of neutropenia on temperature and C-reactive protein

At ICU admission, temperature in septic critically ill cancer patients was not significantly different in those presenting neutropenia in comparison with non-neutropenic patients. From D3 onwards, neutropenic patients showed a significantly higher concentration, 25.9 ± 11.2°C vs. 26.9 ± 0.9°C (P = 0.009). A similar difference of 0.6°C was observed in comparisons of neutropenic vs. non-neutropenic patients (P = 0.238, comparing neutropenic vs. non-neutropenic patients).

CRP concentrations at ICU admission were not influenced by the severity of neutropenia (< 100/mm³ vs. ≥ 100/mm³) (P = 0.335, between neutropenic and non-neutropenic patients). CRP concentrations, however, showed a significantly higher concentration, 25.9 ± 11.2 mg/dL vs. 26.9 ± 0.9 mg/dL (P = 0.009) in neutropenic patients in comparison with non-neutropenic patients. From D3 onwards, the CRP concentration of neutropenic and non-neutropenic patients decreased from 25.9 ± 11.2 mg/dL to 19.7 ± 11.4 mg/dL (3 < ≥ 100/m³) to 21.5 ± 11.6 mg/dL to 26.9 ± 0.9 mg/dL (P = 0.527, between neutropenic and non-neutropenic patients).

Several biomarkers, such as IL-6, IL-8, CRP, brain natriuretic peptides, procalcitonin, neopterin, have been associated with the severity of sepsis/septic shock in critically ill cancer patients. Among these, CRP concentration is a well-established biomarker for the severity of sepsis/septic shock in critically ill cancer patients. In our study, we found among septic critically ill cancer patients a marked increase in CRP concentrations irrespective of the WCC, at ICU admission. Even though CRP concentrations at ICU admission were not influenced by the severity of neutropenia, we found a poor correlation between WCC and CRP concentration. We found among septic critically ill cancer patients a poor correlation between WCC and CRP concentration. Finally, our findings demonstrate a lack of correlation between WCC and CRP concentration. We found among septic critically ill cancer patients a poor correlation between WCC and CRP concentration. Finally, our findings demonstrate a lack of correlation between WCC and CRP concentration.
evaluated in patients with febrile neutropenia to assess their performance in the diagnosis of infection [18-24], in the identification of the underlying agents [18-20,22,24], in the characterization of sepsis severity and outcome prediction [21,23-27]. However, information on biomarkers comparing neutropenic and non-neutropenic cancer patients are currently limited [28].

Among septic non-cancer patients there is substantial controversy concerning the potential effects of immunosuppression, in particular of corticosteroids, on CRP concentration, decreasing acute phase response independently of the treatment of infection [29-33].

In the present study, we clearly demonstrate that CRP, a major acute phase reactant protein, increases markedly in profoundly immunosuppressed cancer patients with sepsis. In other words, the acute phase reaction seems to remain unaffected by either chemotherapy or radiotherapy. Moreover, we found that septic neutropenic cancer patients had significantly higher CRP concentrations in comparison with non-neutropenic patients at ICU admission. Neutropenia reflects a profound state of immunosuppression representing a markedly increased susceptibility to infections [4]. In addition, neutropenic patients present an increased risk to acquire infections caused not only by "common" bacteria, but also by opportunistic agents, like virus and fungi, secondary to a decrease cellular and humoral immunity [4]. In addition, the size of the inoculum necessary to produce an...

### Table 1 Baseline patients' characteristics and comparison between neutropenic and non-neutropenic patients

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Neutropenic</th>
<th>Non neutropenic</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>154</td>
<td>86</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>48.5 ± 18.1</td>
<td>47.0 ± 17.8</td>
<td>50.4 ± 18.4</td>
<td>0.248</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>94/60</td>
<td>54/32</td>
<td>40/28</td>
<td></td>
</tr>
<tr>
<td>Type of cancer</td>
<td></td>
<td></td>
<td></td>
<td>0.569</td>
</tr>
<tr>
<td>Solid</td>
<td>49</td>
<td>29</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>105</td>
<td>57</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Previous radiotherapy</td>
<td>36</td>
<td>21</td>
<td>15</td>
<td>0.731</td>
</tr>
<tr>
<td>Previous Chemotherapy</td>
<td>112</td>
<td>72</td>
<td>40</td>
<td>0.001</td>
</tr>
<tr>
<td>Previous surgery</td>
<td>6</td>
<td>1</td>
<td>5</td>
<td>0.049</td>
</tr>
<tr>
<td>Non-invasive Ventilation</td>
<td>15</td>
<td>14</td>
<td>1</td>
<td>0.002</td>
</tr>
<tr>
<td>Invasive mechanical Ventilation</td>
<td>135</td>
<td>74</td>
<td>61</td>
<td>0.493</td>
</tr>
<tr>
<td>Vasopressors</td>
<td>112</td>
<td>62</td>
<td>50</td>
<td>0.842</td>
</tr>
<tr>
<td>Type of infection</td>
<td></td>
<td></td>
<td></td>
<td>0.007</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>63</td>
<td>28</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Peritonitis</td>
<td>15</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Urinary</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Blood stream infections</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Skin/Soft tissue infections</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>CNS infections</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other infections</td>
<td>57</td>
<td>43</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>SAPS II (points)</td>
<td>62.2 ± 16.8</td>
<td>62.2 ± 16.7</td>
<td>62.5 ± 16.8</td>
<td>0.827</td>
</tr>
<tr>
<td>SOFA (Day 1) (points)</td>
<td>11.4 ± 3.9</td>
<td>11.6 ± 4.1</td>
<td>11.2 ± 4.1</td>
<td>0.591</td>
</tr>
<tr>
<td>Sepsis severity</td>
<td></td>
<td></td>
<td></td>
<td>0.899</td>
</tr>
<tr>
<td>Sepsis</td>
<td>10 (6.5%)</td>
<td>6 (7%)</td>
<td>4 (5.9%)</td>
<td></td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>29 (18.8%)</td>
<td>17 (19.8%)</td>
<td>12 (17.6%)</td>
<td></td>
</tr>
<tr>
<td>Septic shock</td>
<td>111 (74.7%)</td>
<td>63 (73.3%)</td>
<td>52 (76.5%)</td>
<td></td>
</tr>
<tr>
<td>Total white cell count (/mm³)</td>
<td>1,400 (14,636)</td>
<td>352 (909)</td>
<td>22,100 (35,900)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>37.0 ± 1.5</td>
<td>37.2 ± 1.5</td>
<td>36.8 ± 1.5</td>
<td>0.119</td>
</tr>
<tr>
<td>CRP (Day 1) (mg/dL)</td>
<td>23.6 ± 11.6</td>
<td>25.9 ± 11.2</td>
<td>19.7 ± 11.4</td>
<td>0.009</td>
</tr>
<tr>
<td>Duration of mechanical ventilation (days)</td>
<td>6.0 (9.0)</td>
<td>6.0 (8.0)</td>
<td>6.0 (9.0)</td>
<td>0.616</td>
</tr>
<tr>
<td>ICU length of stay (days)</td>
<td>7.0 (10.3)</td>
<td>7.0 (12.0)</td>
<td>8.0 (10.0)</td>
<td>0.699</td>
</tr>
<tr>
<td>Hospital length of stay (days)</td>
<td>18.5 (23.6)</td>
<td>20.5 (25.0)</td>
<td>16.5 (21.0)</td>
<td>0.111</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>111 (72.1%)</td>
<td>60 (69.8%)</td>
<td>51 (75.0%)</td>
<td>0.472</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>122 (79.2%)</td>
<td>65 (75.6%)</td>
<td>57 (83.8%)</td>
<td>0.211</td>
</tr>
</tbody>
</table>

Values expressed as N (%), mean ± standard deviation or median (interquartile range) according to type of data and data distribution; abbreviations: CNS, central nervous system; CRP, C-reactive protein; ICU, intensive care unit; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment score.
infection is reduced in neutropenic patients. In this context, we could hypothesize that microbiological agents would invade and proliferate easily in neutropenic patients, reaching a higher microbiological burden and also leading to a larger inflammatory response, reflected by a higher CRP concentration [34-36]. Consequently, our findings pointed to the clinical usefulness of CRP in critically ill septic cancer patients irrespective of the presence or absence of neutropenia, as well as the degree of neutropenia. Interestingly, other commonly used biomarkers in non-cancer patients, such as PCT, should be used with some reserve in neutropenia. The origin of PCT in the inflammatory response is not yet fully understood [37]. Moreover, it has been shown that in septic cancer patients with leukopenia PCT concentrations were lower when compared with patients without leukopenia [28]. Consequently, it is possible to observe PCT values < 0.5 ng/ml in infected febrile neutropenic patients [9].

Besides, we recognize that the present study has some limitations. First, our study was an observational single centre study. Second, clinical and laboratory data assessing the recovery phase of neutropenia and factors that could have influenced the CRP course were not routinely collected. Third, since we only assessed CRP course during the first week of antibiotic therapy we cannot draw any conclusion concerning CRP course beyond D7. However, our study has also several important strengths. To date, this is the first study comparing CRP concentrations in septic cancer patients with and without neutropenia, and with a large cohort of septic neutropenic patients.

Conclusions

In conclusion, the results of this study provide valuable information concerning the CRP biology and time-course in septic critically ill cancer patients. It was clear from our results that septic cancer patients express a full-blown acute phase response with marked CRP elevations, and that this was particularly significant in the presence of neutropenia. Finally, CRP course was not influenced by the presence or absence of neutropenia. As a result, CRP could be a clinically useful bedside biomarker of infection in cancer patients irrespective of the WCC and the degree of immunosuppression.

Figure 1 Temperature and C-reactive protein of neutropenic and non-neutropenic septic cancer patients at ICU admission. Comparison of temperature (°C) and C-reactive protein concentrations (mg/dL) at ICU admission between neutropenic and non-neutropenic septic critically ill cancer patients (P = 0.119 and P = 0.009, respectively).

Figure 2 C-reactive protein course of neutropenic and non-neutropenic septic critically ill cancer patients. Time course of CRP concentrations (mg/dL) for neutropenic and non-neutropenic septic critically ill cancer patients during the first week of antibiotic therapy (P = 0.335).
Key messages

1. Fever with neutropenia has a low predictive value for the diagnosis of infection.
2. The presence of fever with neutropenia does not influence the management of septic cancer patients.
3. The use of C-reactive protein (CRP) and procalcitonin (PCT) to monitor infection in febrile neutropenic patients is unreliable.

Abbreviations

CRP: C-reactive protein; ICU: intensive care unit; IL: interleukin; IQR: interquartile range; MV: mechanical ventilation; SAPS II: Simplified Acute Physiology Score (SAPS) II; SIRS: systemic inflammatory response syndrome; SOFA: Sequential Organ Failure Assessment; WCC: white cell count.

Acknowledgements

Dr. Márcio Soares is supported in part by individual research grant from CNPq. This work was performed at the ICU of the Instituto Nacional de Câncer, Brazil.

Authors' details

1. Polyvalent Intensive Care Unit, Hospital de São Francisco Xavier, Centro Hospitalar de Lisboa Ocidental, Estrada do Forte do Alto do Duque, 1449-005 Lisbon, Portugal. 2. Cedoc, Faculty of Medical Sciences, New University of Lisbon, Campo dos Mártires da Pátria, 130, 1169-056 Lisbon, Portugal. 3. Postgraduate Program, Instituto Nacional de Câncer - Inca, Centro de Tratamento Intensivo - 10º Andar, Praça Cruz Vermelha, 23, Rio de Janeiro-RJ, CEP: 20220-130, Brazil. 4. D’Or Institute for Research and Education, Rua Diniz Cordeiro, 30, Botafogo, Rio de Janeiro-RJ, Brazil.

Authors’ contributions

PP, VCSD, MS and JIFS contributed to the study conception and design, carried out and participated in data analysis and drafted the manuscript. VCSD, MS and JIFS participated in acquisition of data. All authors read and approved the final version of the manuscript.

Authors’ information

PP is coordinator of the Polyvalent Intensive Care Unit and president of the Antibiotic Commission of São Francisco Xavier Hospital. PP is Professor of Medicine of the Faculty of Medical Sciences from the New University of Lisbon, Portugal. VCSD is assistant physician of the ICU of the Instituto Nacional de Câncer, Rio de Janeiro, Brazil. MS and JIFS are associate investigators of D’Or Institute for Research and Education.

Competing interests

PP has received honoraria and served as advisor of Astra Zeneca, Ely-Lilly, Gilead, Janssen-Cilag, Merck Sharp & Dohme, Novartis and Pfizer and has received an unrestricted research grant from Brahms and Viroagutos. VCSD, MS and JIFS have no competing interests to declare.

Received: 5 March 2011 Revised: 10 April 2011 Accepted: 19 May 2011 Published: 19 May 2011

References


doi:10.1186/cc10242

Cite this article as: Póvoa et al.: C-reactive protein in critically ill cancer patients with sepsis: influence of neutropenia. Critical Care 2011 15:R129.