CLINICAL SCIENCE

Plasma levels of procalcitonin and eight additional inflammatory molecules in febrile neutropenic patients

Letícia Carvalho Neuenschwander, Henrique Bittencourt, Ana Flávia Tibúrcio Ribeiro, Antônio Lúcio Teixeira, Mauro M. Teixeira, Jairo Cerqueira Teixeira, Vandack Nobre

Postgraduate Course in Infectious Diseases and Tropical Medicine, Internal Medicine Department, School of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte/MG, Brazil.

OBJECTIVE: This study aimed to examine the association between different inflammatory markers and specific clinical endpoints in patients with febrile neutropenia.

METHOD: We prospectively evaluated the expression of procalcitonin (PCT), interleukin 8 (IL-8), induced protein-10, tumor necrosis factor alpha (TNF-α), two soluble TNF-α receptors (sTNF-R I and sTNF-R II), monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein-1 alpha, and eotaxin in 37 episodes of febrile neutropenia occurring in 31 hospitalized adult onco-hematologic patients. Peripheral blood samples were collected in the morning at inclusion (day of fever onset) and on days 1, 3, and 7 after the onset of fever. Approximately 2–3 ml of plasma was obtained from each blood sample and stored at -80°C.

RESULTS: The sTNF-R II level at inclusion (day 1), the PCT level on the day of fever onset, and the change (day 3 - day 1) in the IL-8 and eotaxin levels were significantly higher in patients who died during the 28-day follow-up. A requirement for early adjustment of antimicrobial treatment was associated with higher day 3 levels of IL-8, sTNF-R II, PCT, and MCP-1.

CONCLUSION: Procalcitonin, sTNF-R II, IL-8, MCP-1, and eotaxin could potentially be used to assess the risk of death and the requirement for early adjustment of antimicrobial treatment in febrile, neutropenic onco-hematologic patients. The levels of the other markers showed no association with any of the evaluated endpoints.

KEYWORDS: Febrile neutropenia; Inflammatory markers; Procalcitonin; Sensitivity; Specificity.

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E-mail: vandack@medicina.umg.br

Tel.: 55 31 98310004

INTRODUCTION

Neutropenia, a common feature in onco-hematological patients undergoing chemotherapy, is one of the most important risk factors for bacterial and fungal infections.[1] Due to the potential life-threatening severity of this condition, a low threshold of clinical suspicion and prompt antimicrobial therapy are essential to effectively manage infectious complications in neutropenic patients.[2] However, identifying infections in this population can be challenging, and fever is occasionally the only clinical sign.[3]

Risk stratification is also of the utmost importance when dealing with febrile neutropenic patients, as they constitute a heterogeneous population with a variable risk for serious complications.[4-5] Stratification allows the clinician to identify a subgroup of patients who might be safely treated with oral antibiotics.[6-7] In 1988 and 1992, Talcott et al. proposed and validated, respectively, a risk model for classifying patients with febrile neutropenia according to disease burden (remission *vs.* activity), presence of comorbidities, and the source of fever (i.e., community-acquired fever or nosocomial fever).[8-9] More recently, in a multicenter observational study, the Multinational Association for Supportive Care in Cancer (MASCC) derived a model to identify low-risk neutropenic patients (those with MASCC score ≥21 points), with 71% sensitivity and a 91% positive predictive value.[10] Although useful, the Talcott and MASCC models have several limitations, chiefly their use of subjective, institution-dependent variables and high misclassification rates.[11] Biological markers have been proposed as an additional tool for risk assessment in patients with febrile neutropenia. The accuracy and predictive value of these markers have been tested for clinical and laboratory endpoints (e.g., bacteremia and mortality) in small, single-center studies, but these results have been contradictory.[12-15] In general, these markers are better suited for the identification of

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low-risk patients, as they have high negative predictive values for severe complications.[16]

In this pilot study, we aimed to evaluate the plasma levels of different biological markers in febrile neutropenic patients and assess the relationship between these markers and detrimental clinical events.

MATERIAL AND METHODS

Patients and settings

We conducted a prospective, single-center study of patients with febrile neutropenia admitted to the hematological ward of a tertiary general hospital in Belo Horizonte, Brazil. All adult patients (age ≥18 years) admitted to the University Hospital of the Universidade Federal de Minas Gerais (UH-UFMG) from September 2008 to March 2009 with an onco-hematological diagnosis and febrile neutropenia were evaluated for eligibility. The UH-UFMG is a 460-bed general hospital that is a regional reference center for the management of highly complex conditions, including onco-hematological diseases.

Patients with a neutrophil count less than 1,000/mm^3 were evaluated by two dedicated investigators and invited to participate in the study if they met the following inclusion criteria: *(i)* a primary diagnosis of an onco-hematological disease; *(ii)* a neutrophil count less than 500 per mm^3 or a neutrophil count less than 1,000 per mm^3 that was expected to fall below 500 per mm^3 within the next 48 h, with an anticipated duration of neutropenia of at least six days; *(iii)* fever, defined as an axillary temperature greater than 37.8℃ in two consecutive readings at least one hour apart or a single reading greater than 38.3℃; and *(iv)* either scheduled antibiotic therapy or prior antibiotic therapy for less than one day. Patients were excluded from the study if they presented with a fever that was clearly regarded by the attending physician as being of a non-infectious origin and for which no antibiotic therapy was initiated. Finally, inclusion was considered for individual episodes of febrile neutropenia, and the same patient could be included more than once, provided the episodes of febrile neutropenia occurred during different hospitalization periods.

The exclusion criteria were as follows: *(i)* antibiotic therapy for more than 24 h at the time of inclusion or *(ii)* presentation with severe organ dysfunction (*e.g.*, use of vasoactive amines or mechanical ventilation).

The variables recorded included age, gender, comorbidities, source of infection (when known), primary diagnosis and its state, current antibiotic therapy, and chemotherapeutic regimens. The presence of comorbidities was measured using the modified Charlson's score.[17] We also determined each patient's MASCC risk index, a scoring system for identifying low-risk febrile neutropenic cancer patients[10,18] at baseline. Variables recorded daily during the follow-up included hemodynamic and respiratory parameters and any changes in antibiotic therapy. All-cause 28-day mortality and length of hospital stay were also recorded.

The Ethics Committee of the Universidade Federal de Minas Gerais approved this study, and all included patients provided written, informed consent. In conducting this study and writing this report, we adhered to the Standard for Reporting of Diagnostic Accuracy studies checklist and recommendations.[19]

Endpoints

The evaluated endpoints were *(i)* any change in antibiotic regimen within the first 72 h of therapy, as determined by the attending physician; *(ii)* bacteremia; and *(iii)* all-cause 28-day mortality.

A change of antibiotic regimen was defined as one of the following two situations: *(i)* the addition of a new antimicrobial agent with a broader or different spectrum compared with the current treatment, or *(ii)* a complete change in the antimicrobial regimen for any reason other than adverse effects related to the previous agents.

Bacteremia was defined as the growth of any pathogenic microorganism in one or more blood samples or the growth of representative skin microorganisms (e.g., coagulase-negative staphylococci) in at least two blood samples obtained from different sites.

Procedures

All the included patients underwent a clinical evaluation at baseline, including clinical anamnesis and a physical examination. Peripheral blood samples were collected using vacuum tubes (BD Vacutainer SST II Plus plastic tubes; Becton Dickinson Diagnostic Systems, São Paulo, Brazil) in the morning on the initial day of fever (inclusion or day 0) and subsequently on days 1, 3, and 7. Approximately 2–3 ml of plasma was obtained from each blood sample and stored at -80℃.

The management of patients with febrile neutropenia followed the recommendations proposed by the Infectious Diseases Society of America.[3] Briefly, two blood culture samples were obtained for all neutropenic (see the above inclusion criteria) patients with fever or unexplained clinical deterioration. Urine cultures and imaging were performed as clinically indicated. The empirical antibiotic regimen used for the first episode of febrile neutropenia was monotherapy with cefepime or a combination of ceftazidime and an aminoglycoside. If risk factors for staphylococcal infection were observed (*e.g.*, catheter-related infection, shock, or mucositis), vancomycin was added to the antimicrobial regimen.

The included patients were followed for 28 days or until death or transfer/discharge from the hospital, whichever occurred first.

Laboratory exams

Plasma levels of nine inflammatory molecules were evaluated in this study: procalcitonin (PCT), induced protein-10 (IP-10), tumor necrosis factor alpha (TNF-α), soluble TNF-α receptors type I and type II (sTNF-R I and sTNF-R II), interleukin 8 (IL-8), monocyte chemotactic protein 1 (MCP-1), macrophage inflammatory protein 1-alpha (MIP-1α), and eotaxin. All assays were performed at the end of the inclusion period; thus, there was no interference in the management of the studied patients. Plasma levels of TNF-α, sTNF-R I, sTNF-R II, MIP-1α, IL-8, eotaxin, IP-10, and MCP-1 were measured using a sandwich enzyme-linked immunoassay (ELISA) (Duoset R & D Systems, Minneapolis, MN, USA). The PCT level was measured using an enzyme-linked fluorescent immunoassay (PCT Vidas Brahms, bioMérieux, France), with an assay sensitivity of 0.05 μg/L, which is approximately four times greater than the mean normal level.

Statistical analysis

Discrete variables are expressed as percentages, and continuous variables are presented as the mean ± SD for

normally distributed variables or as the median and range for non-normally distributed variables. The data were analyzed using a χ^2 test (Yates' test or Fisher's exact test), a two-sample *t*-test, or a Mann-Whitney *U* test, as appropriate. Age, gender, main hematological diagnosis and all-cause 28-day mortality were analyzed for the total number of patients included in the study. All other analyses were performed taking into account the total number of episodes of febrile neutropenia included in the study. ROC curves were constructed to establish the accuracy of each studied marker in predicting the proposed endpoints. Sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios were calculated once the best cut-off levels of these molecules were defined. The collected data were entered into a relational database (Excel 2000; Microsoft, Redmond, WA) and then converted into SPSS files (SPSS 15.0; SPSS, Chicago, United States) for the analyses. A *p*-value less than 0.05 was considered significant.

RESULTS

Characteristics of the patients

Overall, 222 episodes of neutropenia were assessed for eligibility. From these, 37 episodes of febrile neutropenia observed in 31 patients met the enrollment criteria and were included in the final analysis. The main characteristics of the included episodes are shown in Table I. Of the 31 included patients, 23 (74.2%) were male, and the mean (±SD) age of the cohort was 38.5 (±12.3) years. The main hematological diagnoses were acute myeloid leukemia (10 episodes; 32.3%), non-Hodgkin's lymphoma (7 episodes; 22.5%), or multiple myeloma (5 episodes; 16.1%) (Table I).

Of the 37 included episodes of febrile neutropenia, 22 (59%) were secondary to chemotherapy for the hematological disease, and 15 (41%) episodes occurred after bone marrow transplantation (9 allogeneic and 6 autologous). Other than fever, most cases did not present signs or symptoms suggestive of infection. Mucositis was observed in eight (21%) episodes. Two patients (2%) presented with smooth-tissue abscesses.

Table I - Main characteristics of the studied patients.

Characteristic	
Gender, *n (%)*	
Female	8 (25.8)
Male	23 (74.2)
Age, *mean (SD)*	38.5 (12.3)
Hematological diagnosis, *n (%)*	
Acute myeloid leukemia	10 (32.3)
Non-Hodgkin's lymphoma	7 (22.5)
Multiple myeloma	5 (16.1)
Acute lymphoid leukemia	2 (6.5)
Myelodysplastic syndrome	2 (6.5)
Aplastic anemia	2 (6.5)
Hodgkin's lymphoma	2 (6.5)
Chronic myeloid leukemia	1 (3.2)
Disease burden, *n (%)*[	
Remission	16 (43)
Activity	21 (57)
Charlson's score, [*n (%)**	
0	27 (82)
1	3 (9)
2	2 (6)
4	1 (3)

[The total here corresponds to the number of episodes (*n* = 37).
*Charlson's scores were not available for four episodes.

Based on the MASCC model, 75% of the episodes were classified as low risk (score ≥21 points). Furthermore, 21 (59%) episodes had an ECOG of 0 or 1; that is, the patients were fully active or only physically strenuous activity was restricted. Finally, as measured using the modified Charlson's score, most patients did not present with any comorbidities (Table I).

Inflammatory molecules and antibiotic regimen change

In 12 (32%) episodes of febrile neutropenia, a change in antimicrobial regimen was necessary during the first 72 h of treatment. The circulating levels of sTNF-R II ($p = 0.036$), IL-8 ($p = 0.047$), MCP-1 ($p = 0.008$), and PCT ($p = 0.038$), measured at day 3, were significantly higher in patients requiring a change in antibiotic regimen compared with those not requiring a change. Table II depicts the best cut-off levels for these markers, as defined by the receiver operating ROC curve (Figure 1), as well as the corresponding accuracy. Based on these data, the PCT level had the highest positive predictive value for identifying patients requiring an adjustment in antimicrobial therapy (83%).

Inflammatory molecules and bacteremia

Of the 37 episodes of febrile neutropenia, 13 (35%) presented with a positive blood culture during hospitalization. Overall, 15 species were isolated, with two patients presenting with mixed sepsis. Gram-positive (eight cases) and Gram-negative (seven cases) bacteria were similarly represented, with coagulase-negative staphylococci, *S. aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* being the most frequently isolated species. None of the markers examined showed an association with bacteremia.

Inflammatory molecules and all-cause 28-day mortality

Nine (29%) of the thirty-one patients died during the follow-up period. The circulating levels of sTNF-R II measured at day 1 ($p = 0.034$) and the PCT level measured on the day of fever presentation ($p = 0.024$) were lower in patients who survived compared with the levels in patients who died (Table III). Additionally, the eotaxin level increased significantly from day 1 to day 3 (day 3 – day 1) in the patients who died ($p = 0.023$), as shown in Table III. Figure 2 shows the ROC curve used to define the best cut-off levels for these markers using death as an endpoint. Due to technical reasons, only 24 of the 37 (65%) episodes had the plasma PCT level tested at inclusion. Therefore, a ROC curve was independently constructed for this marker (data not shown). Based on this curve, a PCT level greater than 1.2 μg/L was associated with 28-day mortality, with a sensitivity of 77% and a specificity of 54%.

DISCUSSION

Clinical information is often limited when predicting the outcome of neutropenic onco-hematological patients. In this study, 9 (29%) of 31 patients died during the follow-up period, even though their MASCC score was high. Conversely, only one death occurred in the patients classified as high risk based on the MASCC index (data not shown). Inflammatory markers may be a potential tool to enhance the accuracy of risk stratification in neutropenic

Table II - Best cut-off values and accuracy of the inflammatory markers associated with a change in antibiotic therapy within the first 72 h of therapy. The cut-offs were defined using the ROC curve.

Inflammatory marker	Cut-off	Sensitivity	Specificity	PPV'	NPV[/]	+LR[§]	-LR[¶]	*p*-value
IL-8[∞] day 3	218 pg/mL	72%	80%	61%	86%	3.6	0.4	0.047
sTNF-R II[¥] day 3	4000 pg/mL	72%	88%	61%	87%	6.0	0.3	0.036
MCP-1[Δ] day 3	1520 pg/mL	72%	84%	66%	86%	4.5	0.3	0.008
PCT day 3	4.8 μg/L	45%	96%	83%	80%	11.3	0.7	0.038

'Positive predictive value;
[/]Negative predictive value;
[§]Positive likelihood ratio;
[¶]Negative likelihood ratio;
[¥]Soluble TNF receptor type II;
[∞]Interleukine 8;
[Δ]Monocyte chemotactic protein-1.

onco-hematological patients. Several endpoints and multiple inflammatory molecules have been tested in the literature; however, the available data are contradictory, and a reliable biomarker has yet to be found.[12-13,20]

In this pilot study, we were unable to demonstrate any association between the studied inflammatory molecules and bacteremia. This finding contrasts with the results of previous studies.[13-14] For instance, Kern and colleagues evaluated the association between circulating levels of IL-8 and bacteremia resulting from Gram-negative bacilli in 133 patients with febrile neutropenia. They found that IL-8 levels above 2,000 pg/mL on the day of fever predicted bacteremia, with positive and negative predictive values of 73% and 94%, respectively.[14] Lehrnbecher and colleagues found similar results studying IL-8 and both fungal infections and bacteremia induced by Gram-negative bacilli.[21] In a smaller sample of neutropenic patients, von Lilienfeld-Toal et al. demonstrated that, in contrast with the C-reactive protein level, both the PCT and IL-6 levels were significantly higher in bacteremic patients than in patients presenting with pneumonia but not bacteremia, fever of unknown origin or non-infectious fever.[22]

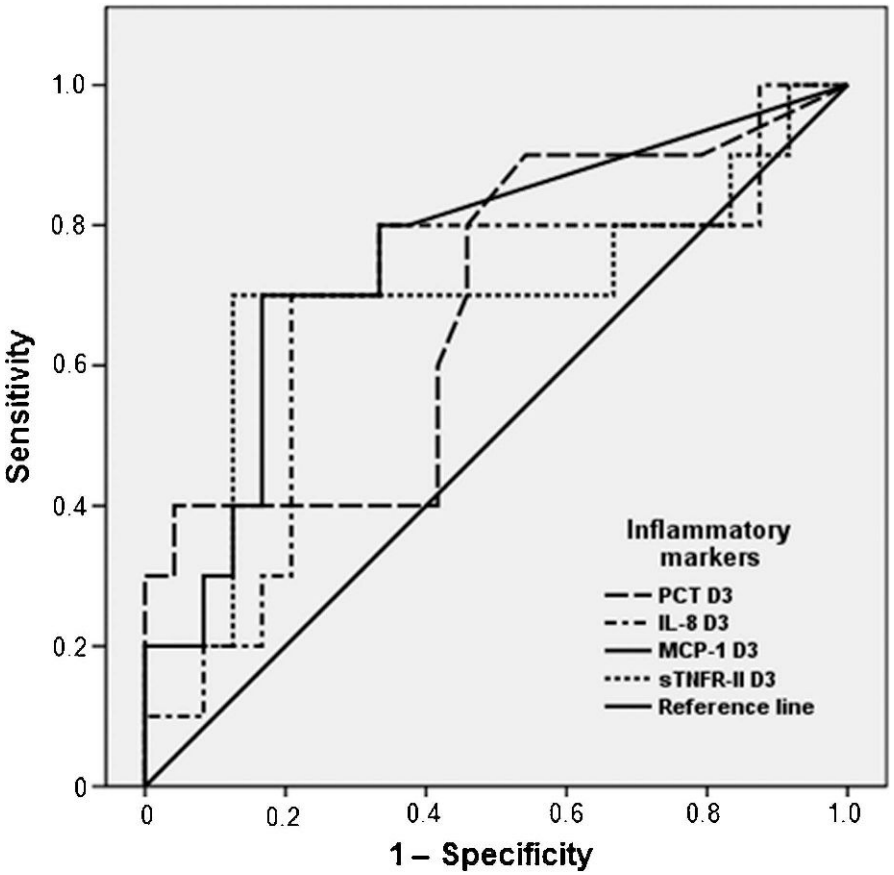

Figure 1 - ROC curve showing the accuracy of the four inflammatory molecules significantly associated with a change in antibiotic therapy within the first 72 h of therapy. The corresponding AUC values were 0.683 (CI 95%: 0.477–0.899) for PCT, 0.758 (CI 95%: 0.572–0.944) for MCP-1, 0.683 (95% CI: 0.470–0.896) for IL-8, and 0.696 (95% CI: 469–922) for sTNF-R II; all data were collected at day 3 following inclusion.

Table III - Best cut-off values and accuracy of the inflammatory markers associated with 28-day all-cause mortality. The cut-offs were defined using the ROC curve.

Inflammatory marker	Cut-off	Sensitivity	Specificity	PPV'	NPV[	+LR[§]	-LR[¶]	*p*-value
sTNF-R II[¥] day 1	3740 pg/μL	89%	60%	50%	92%	2.2	0.2	0.034
Δeotaxin (day 3-day 1)	28 pg/μL	55%	85%	63%	81%	3.6	0.5	0.023

'Positive predictive value;
[Negative predictive value;
[§]Positive likelihood ratio;
[¶]Negative likelihood ratio;
[¥]Soluble TNF receptor type II;
[∞]Interleukin 8.

The requirement for a change in antibiotic regimen was used as a surrogate indicator for an inadequate response to the antimicrobial therapy. The day 3 circulating levels of PCT, sTNF-R II, IL-8, and MCP-1 were significantly higher in patients requiring antibiotic regimen modification compared with the levels in patients who were maintained on their initial regimen. Most importantly, the PCT level on the day of fever presentation (i.e., at inclusion) and the sTNF-R II level on day 1 were also associated with all-cause 28-day mortality, as they were significantly higher in the patients who died. TNF receptors are expressed on the cell membrane of virtually all nucleated cells. Following a bacterial insult, soluble TNF receptors can be detected earlier than TNF-α; however, their half-life is only 6 to 20 minutes.[23] While TNF-R I can mediate almost all TNF-α-associated activities, at physiological levels, TNF-R II only shows signal transduction activity in a few cell types, such as T cells. The inducible expression of TNF-R II might fulfill other important functions, such as the functional neutralization and clearance of TNF from the circulation.[24] To the best of our knowledge, soluble type I and type II TNF receptors have never been tested as markers for clinical risk assessment in adult onco-hematological patients.

PCT is a precursor of calcitonin and is expressed by most parenchymal organs during a systemic inflammatory response, especially responses associated with bacterial

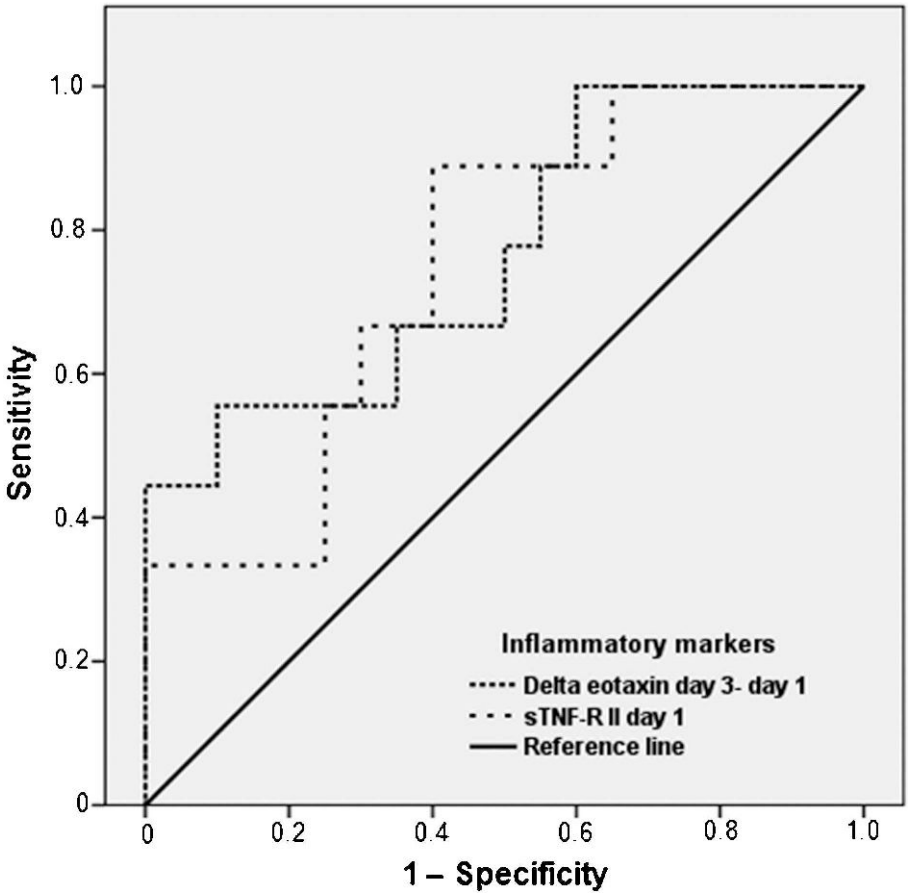

Figure 2 - ROC curve showing the accuracy of the three inflammatory molecules significantly associated with 28-day all-cause mortality. The AUC values were 0.728 (95% CI: 0.508–0.948) for ΔIL-8 (day3 - day1), 0.767 (CI 95%: 0.575–0.958) for Δeotaxin (day3 – day 1), and 0.750 (95% CI: 565–935) for sTNF-R II measured at day 1.

infections.[25] PCT has been investigated in several clinical settings and has been shown to be a useful diagnostic and prognostic marker[26] as well as a potential therapeutic guide.[27] Along with IL-8 and IL-6, PCT is one of the most studied biomarkers in neutropenic patients. Even though some negative results have been published,[20] most studies suggest that PCT has diagnostic potential in neutropenic patients. In this context, Persson and colleagues demonstrated that the PCT level rose within two days of the onset of febrile neutropenia and was sustained in patients who were more likely to develop severe or unstable infections compared with patients who presented with no complications.[28] In another study, the same group demonstrated that the PCT level was more accurate than the C-reactive protein level in discriminating febrile neutropenic patients with bacteremia from those without bacteremia;[13] similar results have been published by Massaro et al.[29] Finally, in an observational, multicenter European study with 158 neutropenic patients, Giamarellou and colleagues showed that a PCT level above 5 ng/mL strongly suggests the presence of severe sepsis.[30]

In addition to sTNF-R II, MCP-1, and PCT, the change in eotaxin levels from day 1 to day 3 was significantly associated with all-cause 28-day mortality. The eotaxin level significantly increased from inclusion to the third day of follow-up in patients who did not survive. This association between eotaxin level and 28-day mortality in neutropenic patients was a surprising finding. Eotaxin acts primarily as a chemokine, recruiting eosinophils via CCR3. Eotaxin has been shown to play a role in human allergic diseases[31] and can attract cell types other than eosinophils under certain circumstances.[32] However, neither the sTNF receptors nor eotaxin has been evaluated as a risk factor in febrile neutropenia.

It should be noted that there are limitations to this study. First, this was a single-center study with a small number of patients, which limits the generalizability of the results. For instance, the small sample size, along with the low frequency of bacteremia (35%) observed among the studied patients, might have prevented us from detecting any association between bacteremia and the investigated markers. However, this was a pilot study, and these results will be verified in a larger cohort with a pre-defined sample of patients. Second, some patients with more than one neutropenic episode were included, potentially leading to an underestimation of the number of deaths. Third, only 35% of the studied episodes presented with bacteremia; most cases of fever were not microbiologically confirmed as infectious fever. Due to the small number of patients, we were unable to evaluate patient subgroups (e.g., confirmed and unconfirmed infections) for the other studied endpoints. Finally, some patients had undergone blood marrow transplantation, which increases the heterogeneity of the studied population. As this was an initial, pilot study, some of these limitations were anticipated. Our group is currently conducting complementary studies with a larger number of patients, focusing on the most promising markers.

In conclusion, in this pilot study, we examined the predictive potential of different biological markers in 37 episodes of febrile neutropenia occurring in 31 patients with an onco-hematological diagnosis. The PCT, sTNF-R II, IL-8, eotaxin, and MCP-1 levels, measured at different times during the first three days of follow-up were significantly associated with all-cause 28-day mortality and/or the requirement for a change in antibiotic therapy. None of the studied molecules were able to differentiate febrile neutropenic patients with bacteremia from those patients without bacteremia. Because this was a pilot study, our findings must be confirmed in a larger prospective, multicenter cohort.

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