

Diagnostic value of sTREM-1, IL-8, PCT, and CRP in febrile neutropenia after autologous stem cell transplantation

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Abstract Infections and infectious complications are the major cause of morbidity and mortality in febrile neutropenic patients after autologous stem cell transplantation. Laboratory biomarkers are helpful for early identification of critically ill patients and optimal therapy management. Several studies in adult non-neutropenic patients proposed sTREM-1 as a superior biomarker for identification of septic patients as well as a predictor for survival in these patients compared with procalcitonin (PCT), C-reactive protein (CRP), or interleukin-8 (IL-8). Here, to assess the utility of PCT, CRP, IL-8, and sTREM-1 in febrile neutropenia, 44 patients presenting with febrile neutropenia after autologous stem cell transplantation were recruited in a single-center prospective pilot study. We analyzed PCT and CRP as well as IL-8 and sTREM-1 levels pre- and post-transplantation at defined time points. In 20 of 44 patients, concentration of sTREM-1 was under the detection level at appearance of febrile neutropenia. Mean levels of PCT, IL-8, and CRP were significantly increased in infections of critically ill patients who by dysfunction or failure of one or more organs/system depend on survival from advanced instruments of monitoring and therapy. However, all tested biomarkers could not distinguish between presence and absence of bloodstream infection. The combination of the biomarkers PCT and IL-8 achieved a high sensitivity of 90% and specificity of 74% for the identification of serious complications in febrile neutropenia, whereas the combination of CRP and PCT or IL-8 achieved a high sensitivity of 100%, but with the addition of a low specificity of 47 or 41%. In conclusion,

we found that the measurement of sTREM-1 concentration at presentation of febrile neutropenia is not useful to identify bacterial bloodstream infections and critically ill patients. PCT and IL-8 are useful biomarkers for the early identification of critically ill patients, compared to CRP and sTREM-1 in febrile neutropenia. PCT or IL-8 in combination with clinical parameters should be considered in routine measurement to identify critically ill patients as early as possible.

Keywords Febrile neutropenia · Cancer · Bacterial infection · Soluble TREM-1 · Procalcitonin · Interleukin-8

Introduction

Infections and infection-related complications remain one major cause of morbidity and mortality in patients with febrile neutropenia (FN) after high-dose chemotherapy and autologous stem cell transplantation (auto-SCT) [1]. Thus, standard care for patients with FN consists of frequent monitoring of vital signs and empirical treatment with intravenous broad-spectrum antibiotics. Especially in patients with severe neutropenia, defined as an absolute neutrophil count of less than $0.5 \times 10^9/L$ ($< 500/\mu l$) [2], adequate management on presentation with FN and early identification of critically ill patients might be the most effective strategy to prevent the development of severe complications. Beside clinical scoring systems like the Multinational Association of Supportive Care in Cancer (MASCC) risk index score or the quick sepsis-related organ failure assessment (qSOFA), which may fail in patients with hematological malignancies or due to the presence of FN, the laboratory measurement of circulating markers of inflammation plays an important role in risk stratification [3].

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On a routine basis, the hepatic acute phase reactant C-reactive protein (CRP) is the most commonly used biomarker and recommended by the FN guideline of the European Society of Medical Oncology (ESMO) [2]. Unfortunately, at onset of inflammation, low CRP levels do not exclude development of serious and significant inflammation, demonstrating a low specificity and positive predictive value in earlier FN studies [4].

Along the same line, procalcitonin (PCT) which is induced by bacterial endotoxins and exotoxins has emerged as a biomarker for guiding antibiotic treatment in septic, non-neutropenic adult patients and for distinguishing bacterial from non-bacterial infections [5, 6]. However, up to that point in only one prospective study, PCT-guided antibiotic treatment in neutropenic patients was not useful to reduce the use of antibiotics, but proved to be a marker of bacteremia [7]. Moreover, a correlation between disease severity and serum levels of PCT has been observed previously [8–10]. Nevertheless, the diagnostic accuracy of PCT for the diagnosis of bacterial infections in patients with FN varied in several studies [4]. Beside CRP and PCT, interleukin-8 (IL-8) has been recommended in pediatric and adult FN as an additional useful biomarker, especially for the early detection of a bacterial infection [11, 12]. The combination of PCT and IL-8 reached a sensitivity of 100% for bloodstream infections in pediatric patients [13].

During the last decade, soluble-triggering receptor expressed on myeloid cells-1 (sTREM-1) has been identified as a novel potential biomarker for the diagnosis of sepsis and/or development of serious infectious complications. TREM-1 has been discovered by Bouchon et al. in 2000 and is a cell-surface receptor expressed on monocytes, macrophages, and neutrophils [14]. TREM-1 expression is increased in infectious bacterial and fungal diseases and associated with the release of its soluble form. Soluble TREM-1 can be directly measured in several human body fluids, including serum, pleural effusion, sputum, and urine during infections [15–17]. The origin of sTREM-1 has been explained with two hypotheses. The first hypothesis relies on a splice variant of the mRNA of TREM-1 [18], whereas in the second hypothesis, sTREM-1 is generated through the proteolytic cleavage of mature cell surface-anchored TREM-1 [19]. Su et al. found that serum sTREM-1 levels at a cut-off value of 64.4 pg/ml yield a sensitivity of 91% and a positive predictive value of 0.989 for distinguishing septic from non-septic patients [20]. Despite the unknown source of sTREM-1, several studies focusing on patients with sepsis in non-neutropenic patients have additionally demonstrated that the value of plasma sTREM-1 is superior to CRP and PCT in early diagnosis and prognosis prediction [21, 22].

Thus, we performed a prospective single-center study to determine the usefulness of sTREM-1, CRP, PCT, and IL-8 for identification of bacterial infection and development of

serious complications among patients with FN after auto-SCT (Fig. 1).

Patients and methods

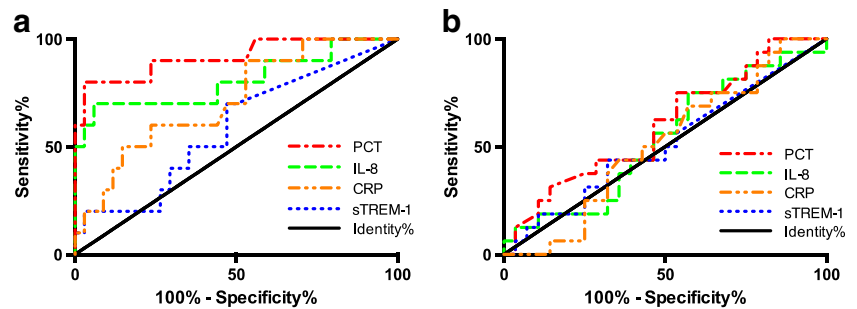
Patient cohort

Patients treated with high-dose chemotherapy followed by auto-SCT from April 2015 to November 2016 at the Department of Hematology and Medical Oncology at the University Medical Center of Mainz, Germany, agreed to participate in the prospective study after reading and signing the written informed consent. The study was carried out in accordance to the principles outlined in the Declaration of Helsinki and was approved by the local ethics committee (Approval no: 837.455.14; Landesärztekammer Rheinland-Pfalz, Mainz, Germany). Sample size of the control and study population has been calculated with a significance level of 0.05 and achieved a power > 80%. Clinical data of all patients were collected from their patient charts. High-dose chemotherapy and auto-SCT were performed in accordance with Joint Accreditation Committee-ISCT & EBMT (JACIE) standards. The patient characteristics relating to age, gender, type of hematological malignancy, remission status, absolute leukocyte counts, duration of febrile episode, and engraftment are shown in Table 1. Febrile neutropenia was defined as leukocytes lower than $0.5 \times 10^9/l$ as well as either with a temperature of > 38.3 °C in a single measurement, or with > 38.0 °C in two consecutive measurements sustained over 1-h period; the temperature was obtained by placing a thermometer in the apex of the axilla with the arm pressed closely to the side of the body for the time recommended by the manufacturer of the thermometer. No prophylactic antibiotic treatment was administered and all patients received a broad-spectrum empirical antibiotic therapy during febrile neutropenia. Prior to the start of antibiotic treatment, standard bacterial cultures of appropriate samples have been taken to check for the presence or absence of bacterial infections. The patients were continuously monitored to determine the development of serious complications in FN including cardiac/respiratory/renal failure, hypotension, confused/altered mental state, intensive care unit (ICU) admission, arrhythmias requiring treatment, and survival [23]. Sera samples for measurement of PCT, IL-8, CRP, and sTREM-1 have been collected within 24 h after appearance of neutropenic fever.

Detection of PCT, CRP, sTREM-1, and IL-8

Serum concentrations of PCT were determined with TRACE™ Technology on a BRAHMS KRYPTOR compact PLUS. The assay has an analytical sensitivity of 0.02 ng/ml. CRP was measured on a latex-enhanced immunoturbidimetric

Fig. 1 ROC curves for PCT, IL-8, CRP, and sTREM-1. ROC curves were calculated predicting the development of serious complications (a) and absence or presentation of bloodstream infection (b) at presentation with FN



assay on an Architect c8000 Analyzer from Abbott Core Laboratory. IL-8 concentration was analyzed using a commercial, solid phase sandwich ELISA kit (Quantikine R&D Systems, Inc. Minneapolis, MN, USA). Our self-made sTREM-1 ELISA has been established and described previously [24]. After adding standard dilutions (recombinant human TREM-1 in 7.5% BSA-PBS) and samples diluted 1:1.5, the plates were incubated for 1.5 h at room temperature (RT). All dilutions were carried out in blocking buffer and measured in triplicates on a Tecan GENios™ plate reader. Our in-house sTREM-1 ELISA has a limit of detection (LOD) of 4 pg/ml with a total variability of 15%. Patients with sTREM-1 concentration under 4 pg/ml were assessed as not detectable.

Statistical analysis

GraphPad Prism software v6 (GraphPad software, La Jolla, CA, USA) was used for data analysis. Results were expressed as the mean \pm SD if not otherwise specified. Comparisons between groups for testing of statistical significance were calculated using the Mann-Whitney *U* test and Kruskal-Wallis test in combination with Dunn's multiple comparison test for non-parametric data. A *p* value $<$ 0.05 was considered as statistically significant. Receiver operating characteristic (ROC) curves including Youden's index were employed to evaluate sTREM-1, PCT, IL-8, and CRP related to bloodstream infection, microbiologically documented infection (MDI), and development of serious complications in FN.

Results

A total of 44 neutropenic patients were enrolled in the study and blood sera were collected within 24 h after first presentation of fever. Additionally, sera from 27 patients were collected before and after high-dose chemotherapy as well as 1 day after auto-SCT and 48–72 h after first presentation with fever. First time of FN presented on average 6 days after auto-SCT and lasted about 3 days. In 28 of 44 patients (63.6%), proven bloodstream infection was documented. The majority of bloodstream infections were caused by gram-positive (57.1%), followed by gram-negative bacteria (32.2%). No

yeast infections and only one viral bloodstream infection were detected. In the majority of patients, the clinically suspected focus of infection appeared to be abdominal (59.1%). Ten out of 44 patients (22.7%) developed serious complications, i. e., cardiac/respiratory/renal failure, hypotension, confused/ altered mental state, ICU admission, arrhythmias requiring treatment, and death. Unfortunately, one patient died in ICU 8 days after auto-SCT based on acute respiratory failure. All patient characteristics are listed in Table 1.

In patients, before the start of high-dose chemotherapy, the concentration of sTREM-1 was 26.9 ± 25.7 pg/ml with corresponding levels of CRP $<$ 5 mg/l and PCT $<$ 0.1 ng/ml. The concentration of sTREM-1 after high-dose chemotherapy and auto-SCT decreased in a minor degree to 21.4 ± 27.8 and 15.5 ± 20.0 pg/ml, respectively. Neutropenic patients with the first presentation of fever had a sTREM-1 concentration of 24.9 ± 47.8 pg/ml. It needs to be pointed out that for 20 of 44 patients, sTREM-1 concentration was under the detection level of 4 pg/ml and altogether significantly reduced compared to patients before the start of high-dose chemotherapy ($p <$ 0.05). In contrast, the corresponding levels of the other inflammatory markers were significantly elevated: CRP was 117.5 ± 93.1 mg/l, PCT was 3.7 ± 8.8 ng/ml, and IL-8 was 66.8 ± 227.4 pg/ml. Concentration of sTREM-1 after 48–72 h of fever was 2.3 ± 4.5 pg/ml and likewise significantly reduced (Fig. 2). For patients with or without bloodstream infection as well as MDI, no significant differences between the groups for concentrations of sTREM-1, IL-8, PCT, and CRP were observed. However, patients developing a serious complication showed significantly elevated levels of PCT (14.2 ± 14.3 ng/ml; $p <$ 0.0001), IL-8 (230.6 ± 454.8 pg/ml; $p = 0.0024$), and CRP (175.3 ± 109.2 mg/l; $p = 0.0388$), whereby CRP demonstrated the lowest statistical significance. Mean sTREM-1 levels did not differ significantly (42.0 ± 76.9 pg/ml; $p = 0.3951$). All values are shown in Table 2.

Table 3 shows the sensitivity and specificity for CRP, IL-8, and PCT for developing a serious complication at cut-off values of 65 mg/l for CRP, 60 pg/ml for IL-8, and 0.5 ng/ml for PCT. These cut-off values were calculated based on the best sensitivity and specificity (Youden's index), as well as according to the literature [25, 26]. For sTREM-1, no reasonable cut-off value could be calculated. The area under the curve demonstrated good individual power for IL-8 and

Table 1 Characteristics of the febrile neutropenia study population

Characteristics	Results
Age (years)	60.09 ± 6.36
Sex	
Male (<i>n</i>)	26
Female (<i>n</i>)	18
Hematological malignancy	
Multiple myeloma (% total)	56.8
B-non-Hodgkin lymphoma (% total)	36.4
T-non-Hodgkin lymphoma (% total)	4.5
Morbus Hodgkin (% total)	2.3
Remission status before auto-SCT (% total)	
Complete remission (CR, nCR, sCR, CRi)	34.1
Partial remission (PR, VGPR)	61.4
Stable disease (SD)	4.5
Engraftment (days)	16.63 ± 4.25
Total white blood cell count (WBC)	0.062 ± 0.050
First presentation of fever after auto-SCT (days)	6.23 ± 2.67
Febrile episode (days)	3.27 ± 2.65
≤ 24 h (% total)	29.5
> 24 h (% total)	70.5
Bloodstream infection (% total)	63.6
Gram-positive bacteria (% of bacterial infection)	57.1
Gram-negative bacteria (% of bacterial infection)	32.2
Mixed bacterial infection (% of bacterial infection)	10.7
Virus (% total)	2.3
Yeast (% total)	0
Microbiologically documented infection (% total)	77.3
No suspected focus of infection (% total)	34.1
Suspected focus of infection	
Lung (% total)	13.6
Abdomen (% total)	59.1
Skin (% total)	13.6
Urinary (% total)	4.5
Serious complication in febrile neutropenia (% total)	22.7
Survivors (<i>n</i>)	43
Non-survivors (<i>n</i>)	1

Results are expressed as the mean ± SD

nCR near complete remission, *sCR* stringent complete remission, *CRi* complete remission with incomplete marrow recovery, *VGPR* very good partial remission

PCT (0.808, 95% CI 0.625 to 0.992; 0.916, 95% CI 0.805 to 1.02) for developing a serious complication in FN. CRP demonstrated lower discriminatory power (0.7162, 95% CI 0.5415 to 0.8908). ROC curves were generated for CRP, IL-8, sTREM-1, and PCT for development of serious complications (Fig. 1a) and absence or presentation of bloodstream infection (Fig. 1b) at presentation with FN.

The analyses were broadened by constructing combinations between CRP, IL-8, and PCT. IL-8 in combination with

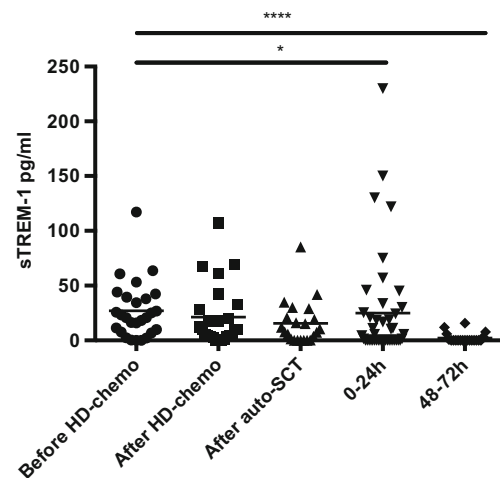


Fig. 2 Concentrations of sTREM-1 before and after HD-chemotherapy (HD-chemo). sTREM-1 levels in sera of patients 1 day after autologous stem cell transplantation (auto-SCT), within the first 24 h with presentation of febrile neutropenia (0–24 h) and 48–72 h after first presentation with febrile neutropenia. Statistical significance was calculated with Kruskal-Wallis test in combination with Dunn's multiple comparisons test (* $p < 0.05$; **** $p < 0.0001$)

PCT documented highly sensitive and specific results. The sensitivity for this combination was 90%, whereas specificity was 74%. The combination of CRP with IL-8 showed the highest sensitivity with 100%, but modest specificity with 47% (Table 4).

Discussion

Several studies have examined biomarkers for the identification of bacterial infections and critically ill patients. Most studies have been performed in non-neutropenic, adult patients. Nevertheless, a number of studies have demonstrated that neutropenic patients can produce a sufficient inflammatory response to release CRP, IL-8, and PCT [27–29]. These results are in line with our findings. In the present study, we further demonstrated that in patients with deep FN, measurement of sTREM-1 concentration is not useful to identify bacterial infections and critically ill patients. Our results in adult febrile neutropenia patients appear to be contrary to the pilot study of Kwofie et al. in 2012, who reported elevated levels of sTREM-1 in high-risk FN patients and proposed sTREM-1 as an alternative biomarker to PCT [30]. On closer examination of the FN patient characteristics in the study of Kwofie et al., mean total leukocyte count was more than ten times higher compared to our FN patients. In pediatric FN patients with similar leukocyte counts to our study population, sTREM-1 was mainly under the detection limit and also not considered as a potential biomarker [13]. It might be reasonable that measuring of sTREM-1 concentration for identifying critically ill or septic patients is depending on total leukocyte count. Unfortunately, we have not collected blood samples of

Table 2 Concentrations of biomarkers. Concentrations of sTREM-1, PCT, CRP, and IL-8 for all patients combined, absence, or development of serious complications, absence or presence of bloodstream, and microbiologically documented infection as well as survivors versus non-survivors. Values are expressed as mean \pm SD combined with *p* values of comparison of groups

	sTREM-1 (pg/ml)	PCT (ng/ml)	CRP (mg/l)	IL-8 (pg/ml)
All patients combined (<i>n</i> = 44)	24.85 \pm 47.76	3.73 \pm 8.78	117.5 \pm 93.05	66.8 \pm 227.4
No serious complication (<i>n</i> = 34)	19.82 \pm 35.29	0.66 \pm 1.47	100.5 \pm 81.99	18.62 \pm 21.88
Serious complication developed (<i>n</i> = 10)	41.97 \pm 76.88 (<i>p</i> = 0.395)	14.16 \pm 14.34 (<i>p</i> < 0.0001)	175.3 \pm 109.2 (<i>p</i> = 0.039)	230.6 \pm 454.8 (<i>p</i> = 0.0024)
No bloodstream infection (<i>n</i> = 16)	26.22 \pm 45.86	1.2 \pm 2.3	109.4 \pm 78.76	121.1 \pm 372.5
Bloodstream infection (<i>n</i> = 28)	24.07 \pm 49.63 (<i>p</i> = 0.874)	5.2 \pm 10.7 (<i>p</i> = 0.278)	122.2 \pm 101.4 (<i>p</i> = 0.889)	35.75 \pm 50.32 (<i>p</i> = 0.724)
No documented infection (<i>n</i> = 10)	30.30 \pm 56.67	0.68 \pm 1.09	104.8 \pm 73.8	35.03 \pm 51.77
Microbiologically documented infection (<i>n</i> = 34)	23.25 \pm 45.66 (<i>p</i> = 0.767)	4.63 \pm 9.84 (<i>p</i> = 0.235)	121.3 \pm 98.7 (<i>p</i> = 0.918)	76.14 \pm 257.4 (<i>p</i> = 0.972)
Survivors (<i>n</i> = 43)	24.87 \pm 48.32	3.61 \pm 8.87	115.5 \pm 93.18	33.25 \pm 47.50
Non-survivors (<i>n</i> = 1)	24.33	8.9	204	1509.44

patients during recovering of ANC and cannot add this aspect to the manuscript. Therefore, further studies with different leukocyte counts could decipher a cut-off value for reasonable measurements of sTREM-1 in daily routine. Additionally, it has to be mentioned that there is a lack of standardization for different sTREM-1 assays and concentration levels of different sTREM-1 assays might be difficult to compare [24].

In our study, PCT and IL-8 were the most favorable biomarkers for discrimination of critically ill patients. This finding is supported by recently published studies in critically ill neutropenic patients [31, 32]. CRP is commonly used in clinical practice and recommended as the only biomarker in the ESMO FN guidelines. However, in our study, CRP demonstrated to be the weakest biomarker for identifying critically ill patients in comparison to PCT and IL-8. In addition, we found that the combination of the biomarkers IL-8 and PCT might provide an opportunity to receive a highly sensitive and specific test to identify patients developing a serious infection.

Unfortunately, all tested biomarkers could not distinguish between bloodstream and no bloodstream infection. Among

the tested biomarkers, PCT still showed best discrimination. In our study, we detected more positive blood cultures (63.6%) in comparison to other FN studies (20–30%) [33, 34]. The differences might be related to usage of antibiotic prophylaxis in almost half of these study patients compared to the absence of antibiotic prophylaxis in our study. The present bloodstream infections were predominantly due to gram-positive coagulase-negative *Staphylococcus* (CNS). In general, CNS isolated from blood cultures are associated with lower levels of inflammation compared with bloodstream infections because of gram-negative bacteria and are comparable with levels in patients with negative cultures [35]. Thus, PCT, IL-8, and CRP seem to be not or slightly changed due to CNS bloodstream infection in FN.

In conclusion, PCT might be the best biomarker for identifying critically ill patients with febrile neutropenia. In combination with an additional biomarker like IL-8, high sensitivity and specificity are achieved, while sTREM-1 is not a useful marker for the identification of critically ill patients in deep FN. Testing of PCT and/or IL-8 with CRP is a biomarker tool to define which FN patients are at high risk of developing serious complications in FN and need continuous monitoring.

Table 3 Cut-off values of individual inflammatory markers for the detection of serious complications in FN Sensitivity, specificity, area under the curve (AUC), and 95% confidence interval (CI) as well as *p* value of PCT, IL-8, and CRP for development of serious medical complications

	Cut-off	Sensitivity	Specificity	AUC (95% CI)	<i>p</i> value
PCT	0.5 ng/ml	80%	76%	0.9162 (0.8051 to 1.027)	< 0.0001
IL-8	60 pg/ml	80%	94%	0.8088 (0.6250 to 0.9926)	0.0033
CRP	65 mg/l	90%	47%	0.7162 (0.5415 to 0.8908)	0.0396

Table 4 Sensitivity and specificity of combined inflammatory markers for the detection of critically ill patients Comparison of combinations of PCT, IL-8, and CRP and their sensitivity and specificity to identify critically ill patients

	Sensitivity	Specificity
PCT > 0.5 and/or IL-8 > 60	90%	74%
CRP > 65 and/or IL-8 > 60	100%	47%
CRP > 65 and/or PCT > 0.5	100%	41%

Further studies with more patients and in multiple centers are needed to evaluate whether PCT or IL-8 should be considered to be included in future FN guidelines.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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