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Original Article

Utility of Procalcitonin in the Engraftment Phase of Hematopoietic Stem Cell Transplantation in Children

Koray Yalçın[1], Dayanat Pashayev[1], Suna Çelen[1], Suleimen Zhumatayev[1], Gülsün Karasu[2,3], Vedat Uygun[3], Volkan Hazar[2], Akif Yeşilipek[2,3]

[1]Bahçeşehir University Medical Park Göztepe Hospital, Clinic of Pediatric Bone Marrow Transplantation Unit, İstanbul, Turkey
[2]Medical Park Göztepe Hospital, Clinic of Pediatric Hematology, İstanbul, Turkey
[3]Medical Park Antalya Hospital, Clinic of Pediatric Hematology, Antalya, Turkey

ABSTRACT

Aim: In hematopoietic stem cell transplantation (HSCT), the phase of engraftment which can be described as an "immunogenic storm", is also vulnerable to infections and it has been always very hard to discriminate the cause of fever in this special period of HSCT. In this study, we aim to determine if procalcitonin (PCT) could be used to define the cause of fever in the engraftment phase of HSCT.

Materials and Methods: This study involves 81 patients who consecutively underwent allogeneic HSCT between October 2017-June 2020 in our pediatric HSCT unit. The patients were divided into two groups due to the origin of the fever during engraftment as infectious fever group (n=42) and the non-infectious fever group (n=39).

Results: The median duration of fever for all groups was 4 days (1-11 days) and it was significantly lower in the non-infectious fever group compared to the infectious fever group (3 vs. 4 respectively p=0.001). The median PCT levels was 0.6 ng/mL (0.04-83) for all groups and it was significantly higher in the infectious fever group compared to non-infectious (1.4 vs. 0.3 p<0.001). According to ROC analysis, the cut-off PCT level of 0.515 ng/mL or more had an AUC of 0.817 and may predict the infectious fever with a sensitivity of 81% and a specificity of 76.9%.

Conclusion: We observed that PCT may be used to discriminate infectious fever from non-infectious fever at the engraftment phase of HSCT and PCT could be a useful marker for antibiotic treatment strategy.

Keywords: Engraftment, hematopoetic stem cell transplantation, procalcitonin

Introduction

In hematopoietic stem cell transplantation (HSCT), the phase of engraftment can be described as an "immunogenic storm" and it is susceptible to infections because of severe neutropenia. Fever is the most commonly seen symptom associated with both these faces of engraftment. It has always been very hard to discriminate the cause of the fever in this special period of HSCT. This uncertainty between infectious or immunogenic fever is problematic due to an unnecessary use of antibiotics and delays in choosing the proper therapy.

Procalcitonin (PCT) is produced in C-cells of the thyroid gland and is a propeptide of levels are measured. However, the synthesis of PCT can increase as a result of an increase

Address for Correspondence
Koray Yalçın, Bahçeşehir University Medical Park Göztepe Hospital, Clinic of Pediatric Bone Marrow Transplantation Unit, İstanbul, Turkey
Phone: +90 536 323 64 49 E-mail: koray.ylc@gmail.com ORCID: orcid.org/0000-0003-3454-9870
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in endotoxins and/or cytokines. Increased PCT levels are detected in bacterial, parasitic, and fungal infections but PCT is not observed in healthy individuals, with only small increases seen in viral infections (1,2). Additionally, the diagnostic value of PCT is more discriminative than C-reactive protein (CRP) in differentiating infections from non-infectious processes accompanied by fever including for neutropenic patients (1,3). PCT has a long serum half-life of 25 to 30 hours and in the case of infections, PCT levels increase in 3 to 4 hours while CRP needs 24 to 48 hours to rise significantly (4,5). Apart from infections, CRP can be a more reliable marker for inflammatory processes, as it is well known that CRP significantly increases in engraftment syndrome (6).

In this study, we aimed to determine if PCT could be used to define the cause of fever in the engraftment phase of HSCT. Although inflammatory fever without infections can also cause PCT to increase, the level of this increase is not clear for the engraftment phase of HSCT. We measured the peak PCT level at the first fever episode in the engraftment phase and tried to define a cut-off value for PCT in order to discriminate infectious and non-infectious causes.

Materials and Methods

This retrospective study involved 81 pediatric patients who consecutively underwent allogeneic HSCT between October 2017 and June 2020 in our pediatric HSCT unit. This study was approved by the Medical Research Ethics Committee (13.10.2021-16/01).

Those patients who had at least one febrile episode in the engraftment phase (within 4 days of engraftment) were included. Those patients with no febrile episode or febrile episodes where PCT and CRP levels were not assessed were excluded. Additionally, febrile episodes before or after the engraftment phase were excluded from this study. Although this study only focused on fever at the engraftment phase, other clinical findings besides fever were evaluated and engraftment syndrome was defined as mentioned in the Spitzer Criteria (7).

The patients were divided into two groups according to the origin of their fever. The infectious fever group consisted of those patients who had infectious events as defined below and the non-infectious fever group was comprised of all the other patients who had no infectious events. We compared these two groups regarding the the day of the fever, the duration of the fever, and their PCT, and CRP levels.

Infectious Events

A single oral temperature of ≥38.3 C or ≥38 C sustained over one hour was defined as a fever (8). Positive blood culture was defined as bacteremia (two positive cultures were needed for coagulase-negative staphylococci). Urinary tract infection was considered when >100,000 colonies of bacteria/mL were observed in a urine culture. Cytomegalovirus (CMV) reactivation was defined as quantitative polymerase chain reaction (PCR) >1,000 copy (Anatolia Bosphore CMV Quantification Kit Istanbul, Turkey). Pulmonary infiltrates on chest X-ray/computerized tomography which could not be explained by any other reasons were defined as pneumonia. Any other localized inflammation except for pneumonia was defined as a local infection.

Supportive Care and Management of Febrile Episodes

Bone marrow transplantation was performed in HEPA filtered air-conditioned single rooms. All patients received fluconazole and acyclovir as prophylaxis from the initiation of conditioning, co-trimoxazole prophylaxis was initiated after engraftment. Broad-spectrum antibiotics were initiated in case of any febrile episodes and blood, urine cultures or clinical samples as indicated such as pus culture or swab were taken. Viral screening via PCR, influenza, and severe acute respiratory syndrome-coronavirus-2 were analyzed if necessary. Antibiotics consisting of an antipseudomonal β-lactam, a fourth-generation cephalosporin, or a carbapenem were preferred as the first-line therapy. This was revised later depending on microbiological information or clinical evolution. If the fever persisted for more than 96 hours, empirical broad-spectrum antifungal treatment was initiated.

PCT and CRP Measurements

For each episode of fever, we had a measurement of PCT and CRP within 24 hours from its onset. We continued PCT and CRP measurements as clinically indicated within the engraftment phase. Due to the variable duration of serial measurements, we only included the peak PCT and CRP levels within the engraftment phase. PCT was measured by PCT fast test kit immunofluorescence assay (Getein Biotech, Inc. Nanjing, China) and CRP by turbidimetry (Sentinel Milan, Italy). Normal values are <0.5 ng/mL for PCT and <5 mg/L for CRP. According to the manufacturer's recommendation, we kept in mind any interferents which might have influenced the test results.

Statistical Analysis

The Mann-Whitney U test was used to assess any differences between the two groups. The diagnostic relevance was estimated as sensitivity, specificity, and the positive and negative predictive values. Levels of sensitivity and specificity were plotted on the receiver operator characteristic (ROC) curve. The area under the curve (AUC), was calculated by trapezoid integration. While an area of 0.5 denotes no discrimination, an area of one denotes full discrimination. According to optimized sensitivity and specificity, the best cut-off value was chosen. Kaplan and Meier was used to analyze overall survival (OS). The Statistical Program for Social Science (IBM Corp. Released 2011, Version 20.0, Armonk, NY) was used in calculations.

Results

Patient Characteristics

The patient group consisted of 81 consecutive pediatric patients (55 males; 67%, 26 females; 33%) with a median age of 64 months (range 1-248 months) who underwent allogeneic HSCT for malign disease (n=26, 33%) or non-malign disease (n=55, 67%). The patients received stem cell transplants from a matched unrelated donor (n=45; 56%), a matched sibling donor (n=19; 23%), a matched family donor (n=10; 12%) or a haploidentical donor (n=7; 9%). Stem cell sources included bone marrow (n=33), peripheral blood (n=44), both bone marrow and cord blood (n=3) and both bone marrow and peripheral blood (n=1). The conditioning was myeloablative for 77 patients and only four patients had a non-myeloablative regimen. The patient characteristics are given in Table I.

Origin of Fever

The patients were divided into two groups according to the origin of their fever during engraftment. Those patients with infectious fever (n=42) had either bacteremia (n=30), CMV reactivation (n=10), bacteriuria (n=1) or pneumonia (n=1). According to their blood cultures, 17 patients had gram-positive bacteria, and 13 patients had gram-negative bacteria. There was no significant difference between the type of bacteria in terms of CRP levels, PCT levels, duration of fever, or the post-transplant day of fever.

Table I. Characteristics of patients according to their origin of fever

Patient characteristics	All (n=81)	Infectious fever (n=42)	Non-infectious fever (n=39)	p-value
Median age at transplant, months	64 (1-248)	56 (6-252)	80 (1-248)	0.057
Disease type				0.268
Malign	26 (33%)	11 (26%)	15 (38%)	
Non-Malign	55 (67%)	31 (74%)	24 (62%)	
Gender				0.320
Female	26 (33%)	12 (28%)	14 (36%)	
Male	55 (67%)	30 (72%)	25 (64%)	
Donor type				0.527
Matched unrelated	45 (56%)	22 (52%)	23 (59%)	
Matched sibling	19 (23%)	10 (24%)	9 (23%)	
Matched family	10 (12%)	6 (14%)	4 (10%)	
Haploidentical	7 (9%)	4 (10%)	3 (8%)	
Stem cell source				0.317
Peripheral blood	44 (54%)	19 (45%)	25 (64%)	
Bone marrow	33 (40%)	20 (47%)	13 (33%)	
Bone marrow + Cord blood	3 (4%)	2 (5%)	1 (3%)	
Bone marrow + Peripheral blood	1 (2%)	1 (3%)	-	
Conditioning regimen				0.926
Myeloablative	77 (95%)	40 (95%)	37 (95%)	
Non-myeloablative	4 (5%)	2 (5%)	2 (5%)	

The median day of post-transplant CMV reactivation was 13 (8-17) days. In the group with infectious fever, the duration of fever was significantly lower in those patients with CMV reactivation compared to those patients without reactivation (3 days vs. 5 days respectively, p=0.04). Regarding the duration of fever, those patients with or without CMV reactivation had similar findings regarding their post-transplant day of fever, PCT, and CRP levels (Table II).

All of the 39 patients in the non-infectious fever group had no positive blood/urine culture, no CMV reactivation, and no infiltration in the radiological work-up of the chest. Amongst these 39 patients, only 16 met the criteria for engraftment syndrome, while the rest only had fever which could not be explained by an infectious origin.

Comparison of the Infectious Fever Versus the Non-infectious Fever Groups

According to the transplant characteristics, there were no significant differences between the two groups regarding gender, age, type of disease, stem cell source, or donor type.

The median neutrophil engraftment time and post-transplant days of fever of the whole group were 11 days (8-18 days) and 9 days (4-21 days), respectively. There were no significant differences between the groups regarding neutrophil engraftment time or post-transplant days of fever.

The median duration of fever for all groups was 4 days (1-11 days) and it was significantly lower in the non-infectious fever group compared to the infectious fever group (3 vs. 4 respectively p=0.001). The median PCT level was 0.6 ng/mL (0.04-83) for all groups and it was significantly higher in the infectious fever group compared to non-infectious (1.4 vs. 0.3: p<0.001). The median CRP levels was 72 mg/dL (0.3-306) and it was significantly higher in the infectious group (85.5 vs. 60: p=0.026) (Table III).

According to ROC analysis, a cut-off PCT level of 0.515 ng/mL or more had an AUC of 0.817 and may predict infectious fever with a sensitivity of 81% and a specificity of 76.9% (Figure 1).

OS (3 years) for all the patient groups was 80.2% (±4.7). Regarding the cut-off PCT level (0.515 ng/mL), 3 year OS for those patients whose PCT level was <0.515 ng/mL was 82.0% (±7.0) and for those patients whose PCT level was ≥0.515 ng/mL was 78.1% (±6.5) (p=0.585).

Discussion

Our aim in this study was to show whether PCT could be used as a marker to differentiate between infectious and non-infectious fevers at the engraftment phase of HSCT. The engraftment phase of HSCT has two challenging characteristics to test a marker for such discrimination; (1) the last period of aplasia just before the neutrophil

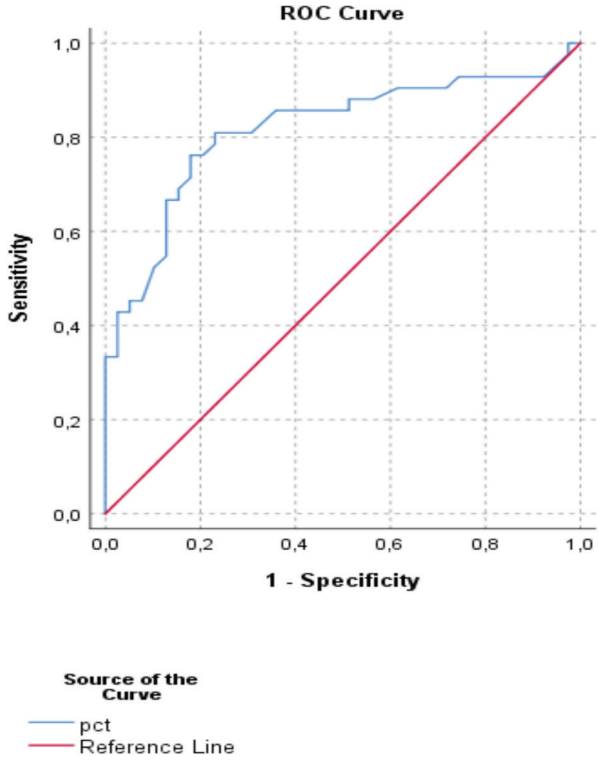

Figure 1. PCT level of 0.515 ng/mL or more had an AUC of 0.817 and may predict the infectious fever with a sensitivity of 81% and a specificity of 76.9%

PCT: Procalcitonin, AUC: Area under the curve

Table II. Comparison of the patients regarding CMV reactivation

	No CMV reactivation (n=31)	CMV reactivation (n=11)	p-value
PCT (ng/mL)	1.40 (0.05-83.00)	1.40 (0.17-11.30)	0.466
CRP (mg/L)	92.00 (4.90-306.00)	72.00 (17.00-192.00)	0.271
Post-HSCT day of fever	9.00 (3.00-21.00)	11.00 (7.00-14.00)	0.124
Duration of fever (day)	5.00 (1.00-11.00)	3.00 (1.00-8.00)	0.040

CMV: Cytomegalovirus, PCT: Procalcitonin, CRP: C-reactive protein, HSCT: Hematopoietic stem cell transplantation

Table III. Comparison of characteristics of infectious and non-infectious fever

	Infectious fever median (range)	Non-infectious fever median (range)	p-value
PCT (ng/mL)	1.40 (0.05-83.00)	0.30 (0.04-3.60)	<0.001
CRP (mg/L)	85.50 (4.90-306.00)	60.0 (0.30-236.00)	0.026
Post-HSCT day of fever	10.00 (3.00-21.00)	9.00 (4.00-19.00)	0.383
Duration of fever (day)	4.00 (1.00-11.00)	3.00 (1.00-8.00)	0.001

PCT: Procalcitonin, CRP: C-reactive protein, HSCT: Hematopoietic stem cell transplantation

increments and (2) high cytokine release just after the neutrophil increments.

The effectiveness of PCT in the follow-up of neutropenic patients is controversial in the literature. Although it has been shown that peripheral blood mononuclear cells are a major source of PCT, we detected high PCT levels in the neutropenic phase of HSCT. Our findings were also consistent with those studies in which PCT levels seemed to be independent of the cell count (9-11).

As previously reported, cytokine release was the main component of the engraftment phase so we may easily hypothesize that the cytokine release was the most probable etiology of inflammatory fever in our non-infectious group (12,13). Additionally, it may be acceptable to test PCT as a marker to differentiate between infections and inflammations which are caused by this cytokine release. In one of the early studies on the role of PCT in HSCT to discriminate infection from inflammation, it was found that PCT was non-effective (14). That study had two main limitations as it only involved 12 patients and it analyzed all inflammatory complications after HSCT rather than focusing on a certain complications or periods. In another study, PCT was defined as a biomarker for engraftment syndrome which could be accepted as an inflammatory process (13). Although it was known that even PCT could increase in cases of inflammation, these changes can be distinguished from infections with a cut-off value (15). In our study, we not only evaluated PCT changes in patients diagnosed with engraftment syndrome, but we also tried to show its discriminative value for infectious and non-infectious fever in the engraftment phase by defining a cut-off value.

CMV reactivation is closely followed up especially in the early phases of stem cell transplantation. It is not one of the prominent reasons for fever, but previously, CMV was solely associated with fever in stem cell transplantation (16). Although viral infections are known to be related to small/modest PCT increases, in our study, we included CMV reactivation in the infectious fever group (15). Additionally, we found that CMV reactivation had similar median PCT values to the other causes of infectious fever consistent with our study design.

In our study group, anti-thymocyte globulin (ATG) was used in conditioning before HSCT and it is well known that ATG impacts inflammatory markers such as CRP and PCT (17). As mentioned in previous studies, the impact of ATG is transient and it is expected that the inflammatory markers reach their baseline values after approximately 4 days (18). All the patients in this study had fever after the cut-off time of ATG so we can exclude the impact of ATG on this study.

Although we focused on the PCT for the discrimination between infectious and non-infectious fever at the engraftment phase, CRP levels were also significantly higher for the infectious fever group. This data was consistent with the findings of Hambach et al. (19) regarding the comparison of PCT and CRP in HSCT. Unlike well-accepted data, Hambach et al. (19) showed that for the detection of bacterial or fungal infections in HSCT, PCT did not have a superior diagnostic value to that of CRP. We could not explain the exact dynamics of these inflammatory markers in HSCT, but both of them may predict infectious disease at the engraftment phase, with PCT having a statistical superiority over CRP.

Study Limitations

There are some limitations for this study, namely; (1) this is a retrospective study (2) we have no serial measurements of PCT and CRP so we used the peak values in the fever episode and (3) although we assumed that cytokine release in the engraftment phase was the main reason for non-infectious fever, we had no cytokine measurements.

Conclusion

In this study, we observed that PCT and CRP may be used to discriminate infectious fever from non-infectious fever at the engraftment phase of HSCT. Within the engraftment phase, PCT levels <0.515 ng/mL for the first fever episode may predict non-infectious etiology with a sensitivity and specificity of 81% and 76.9%, respectively and PCT may

be a useful marker for antibiotic treatment strategy. CMV reactivation can also cause a modest change in PCT levels. Although these results are promising for the proper therapy of fever in this phase, our results should be confirmed in prospective studies with more patients.

Ethics

Ethics Committee Approval: This study was approved by the Medical Research Ethics Committee (13.10.2021-16/01).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Data Collection or Processing: K.Y., D.P., S.Ç., S.Z., Analysis or Interpretation: K.Y., G.K., V.U., V.H., A.Y., Writing: K.Y., V.U.

Conflict of Interest: The authors declared that there were no conflicts of interest.

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