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The Efficacy of Procalcitonin in Early Detection of Sepsis in Patients Undergoing Bone Marrow Transplantation

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ABSTRACT

Background: Infections are among the foremost causes of non-relapse mortality in hematopoietic cell grafts recipients and can cause significant morbidity, both in the early and late transplant periods.

Objective: To evaluate the efficacy of serum procalcitonin (PCT) level in early detection of sepsis in patients subjected to hematopoietic stem cell transplantation (SCT).

Patients and Methods: Thirty subjects, from Department of Hematology and Stem Cell transplantation, Maadi Armed Forces Medical Compound, divided into three groups were enrolled. Group I: 10 adult patients with allogenic bone marrow transplantation (BMT). Group II: 10 adult patients with autologous BMT. Group III: 10 healthy adult volunteers, age and sex matched, as controls. Serum PCT was detected by chemiluminescence immunoassay in day 5, day 10 and day 15. Blood cultures were done to all patients during the period of transplantation when sepsis was suspected.

Results: In all the 20 (100%) patients, serum procalcitonin level was positive. In patients with autologous SCT, there were 5 patients (50%) with negative and 5 (50%) with positive cultures. In allogenic stem cell transplantation, there were 2 patients (20%) with negative and 8 (80%) with positive cultures.

Conclusion: PCT is more sensitive and rapid to detect sepsis in the patients as the procalcitonin could detect sepsis in the cases with negative cultures and it was more correlated to fever than cultures in these patients.

Key Words: *Procalcitonin (PCT) – Stem cell transplantation (SCT) – Sepsis – Culture.*

INTRODUCTION

Stem cell transplantation has been described as both intensive investigational therapy for end-stage disease and as standard curative treatment for malignant and non-malignant conditions **[1]**.

Infections are among the foremost causes of non relapse mortality in HSCT recipients and can cause significant morbidity, both in the early and late transplant periods. Immune defects occurring in the post transplant period can be divided into predictable phases based on time from engraftment **[2]**. Procalcitonin (PCT) is a 116 amino acid prohormone of the hormone calcitonin. PCT can be produced by several cell types from a wide range of organs in response to inflammation or infection **[3-5]**.

In patients, after near complete eradication of the leukocytes population by chemotherapy, a microbial infection still induces a ubiquitous increase of CALC-I gene group expression leading to the release of PCT from tissues. Consequently, PCT levels still increase several thousand-fold in severe systemic infections in immuno-compromised patients **[6-7]**. PCT levels have prognostic implications as persistently elevated or increasing levels can be associated with adverse outcome **[8-9]**.

The aim of our study was to evaluate the diagnostic accuracy of PCT in early detection of sepsis in patients undergoing HSCT.

PATIENTS AND METHODS

Patients: The study was carried out on 30 subjects from the Department of Hematology and Stem Cell transplantation, Maadi Armed Forces Medical Compound.

Group I: 10 adult patients were subjected to allogeneic SCT. Group II: 10 adult patients

were subjected to autologous SCT. Group III: 10 healthy adult volunteers, age and sex matched, served as controls. A written informed consent was signed by all subjects before enrollment and the study was approved by the Ethical Committees, Faculty of Medicine, Alexandria University and Maadi Armed Forces Medical Compound.

Patients subjected to SCT (Group I and II) included 13 males (65%) and 7 females (35%) with an age range of 19-50 with a mean of 31.55±9.56 and a median of 32 years. Group III (the healthy control) included 5 males and 5 females with an age range of 25-45 with a mean of 33±8.41 and a median of 31 years.

Methods: All patients were subjected to the following:

1- Full history taking.

2- Complete clinical examination.

3- Radiological investigation (ultrasound, CT scans X-ray and when indicated, positron emission tomography (PET).

4- Laboratory investigations included: (A) Routine investigations (liver and kidney function tests, CBC **[10]**. (B) Bone marrow examination **[10]**. (C) Viral screening for hepatitis B virus (HBV) antigen, hepatitis C (HCV) antibody, cytomegalovirus (CMV) IgM, EBV and IgG **[11]**. (D) Blood cultures weekly or when there is fever or signs of sepsis. (E) Procalcitonin (PCT) assessment on days 5, 10 and 15 post transplant by chemiluminescence immunoassay (DIASORIN)-S.P.A. via crescentino snc-13040 Saluggia (VC)-Italy **[11]**. Procalcitonin level was considered positive if it exceeds the upper limit by 50%.

5- Pulmonary function testing and Echocardiography.

Statistical analysis: Data was statistically analyzed using SPSS (Statistical Package for the Social Sciences) version 20 for windows. Descriptive data were presented as range, mean±SD and frequencies. Mann-Whitney test was used to compare groups. Spearman correlation coefficient was used to test the relationship between various variables *p*-value ≤0.05 was considered significant.

RESULTS

Clinical and demographic data: Our cohort study included 6 patients with AML; 5 with NHL; 2 patients with CML in blastic crisis, Aplastic anemia and relapsed ALL each; and one patient with HD, relapsed HD and relapsed AML post autologous BMT each.

Viral screening: Six patients (30%) were negative for viral screening, 6 (30%) were CMV +ve, 4 (20%) were HBV +ve (they received lamivudine during the transplantation period) and 6 patients (30%) were HCV +ve (in two of them the transplantation was postponed for 6 months due to elevated liver enzymes and they were treated with interferon and ribavirin).

Complete blood counts: The blood count parameters at different time points are presented in Table (1). There was significant difference in Hb level, platelet counts and WBCs counts among the patients all over the period of follow-up (in days 5, 10 and 15 post transplantation) in comparison to day 0 ($p<0.05$).

The level of procalcitonin in control group and patients all over the period of follow-up is shown in Table (2).

All the 20 patients had positive serum procalcitonin during the period of hospitalization post transplantation. The different levels of procalcitonin were corresponding to the degree of sepsis. There was significant difference between the patients' results, in days 5, 10 and 15 post transplant, and control group ($p=0.001$, 0.001 and 0.0125 respectively).

At day 5, 11 patients were febrile and in all of them PCT levels were above the cut-off except one (patient no. 7) in whom level rose by day 10 and cultures were positive only for the central venous line. Three of these febrile patients failed to grow any positive culture (patients no. 8, 9, 1nd 14) compared to only one who failed to show rise of PCT level by day 5.

At day 10, all the 10 studied patients were febrile and this was also reflected by elevated

PCT levels in all except 2 patients (patients no. 2 and 8); in both fever dropped within 1-3 days. In one of these patients all cultures were negative and in the second, only urine culture was positive denoting limited infection.

Seven out of the 20 febrile patients remained culture negative compared to only 2 of 20 with PCT levels below the cut-off.

At day 15, All the 9 patients with persistent fever had PCT level above the cut-off except one (patients no. 15).

Culture results:

In patients with autologous SCT, there were 5 patients (50%) with negative and 5 (50%) with positive cultures; some of them had positive one type of culture and others had positive more than one type (blood, central venous catheter (CVC), sputum, urine, stool). In allogenic stem cell transplantation, there were 2 patients (20%) with negative and 8 (80%) with positive; some of them had positive results in more than one culture.

Type of organism: Twenty two bacterial isolates were detected with equal numbers of gram positive and gram negative, 11 each. The most common type of organism detected was Staphylococcus aureus (8 patients, 36.4%) followed by E coli (6 patients, 27.3%), Klebsiella Pneumonia (3 patients, 13.6%), Klebsiella Oxytoca and Staphylococcus Epidermidis (2 patients each, 9%) and lastly Enterobacter Cloacie (one patient, 4.5%).

Correlation between procalcitonin levels (ng/l), days of fever and culture results: Elevated procalcitonin was more sensitive and detected sepsis earlier than culture; it was positive in cases with negative cultures. All patients had positive procalcitonin, while only 5/10 with autologous and 8/10 with allogeneic transplantation had positive cultures. The types of positive cultures for the 20 patients are presented in Table (3).

Table (1): Peripheral blood counts of 20 transplanted patients at different time.

Parameter	Day 0	Day 5	Day 10	Day 15
Hb: g/dl	4.70-14.70*	5.30-11.50	5.30-10.30	5.10-9.30
	9.42±2.46	8.29±1.83	6.96±2.12	7.52±0.95
p		0.009	0.011*	0.029*
Platelets	9.00-196.00	7.0-69.00	4.00-61.00	4.00-181.00
x 10^{12}/L	84.70±54.80	26.05±17.04	17.21±14.68	56.06±51.51
p		0.001*	0.001*	0.05*
TLC	0.10-49.20	0.10-0.80	0.10-3.50	1.10-6.30
X 10^{9}/L	8.61±12.49	0.22±0.19	0.49±0.81	2.63±1.55
p		0.002*	0.004*	0.026*

Hb = Haemoglobin. TLC = Total Leukocytic count.

Table (2): Procalcitonin in 20 transplanted patients and control group at different time points.

Procalcitonin (µg/L)	Control	Day 5	Day 10	Day 15
Range	0.025-0.098	0.10-19.60	0.10-12.00	0.10-1.20
Mean±S.D.	0.0325±0.025	1.47±4.41	1.05±2.66	0.27±0.26
p		0.001*	0.001*	0.0125*

Table (3): Correlation between procalcitonin levels (ng/l), days of fever and culture results in 20 transplanted patients.

Patient / Parameter	Day 5	Day 10	Day 15	Days of fever	Culture results				
					Blood	Urine	CVC	Sputum	Stool
1	<0.1	0.43	0.24	$D_7 \rightarrow D_{15}$	(+ve)	–ve	+ve	–ve	–ve
2	0.10	0.13	0.12	$D_6 \rightarrow D_{13}$	–ve	(+ve)	–ve	–ve	–ve
3	0.52	0.71	0.2	$D_4 \rightarrow D_{15}$	(+ve)	–ve	(+ve)	–ve	–ve
4	0.41	0.9	0.3	$D_3 \rightarrow D_{16}$	–ve	–ve	(+ve)	–ve	–ve
5	0.15	12	1.2	$D_4 \rightarrow D_{17}$	(+ve)	–ve	(+ve)	–ve	–ve
6	0.11	0.18	<0.1	$D_{10} \rightarrow D_{13}$	–ve	–ve	–ve	–ve	–ve
7	<0.1	0.42	0.19	$D_4 \rightarrow D_{14}$	(+ve)	–ve	(+ve)	–ve	–ve
8	0.69	0.1	–	$D_4 \rightarrow D_{11}$	–ve	–ve	–ve	–ve	–ve
9	0.36	0.64	0.15	$D_4 \rightarrow D_{14}$	–ve	–ve	–ve	–ve	–ve
10	0.29	0.76	0.3	$D_5 \rightarrow D_{17}$	–ve	–ve	(+ve)	–ve	–ve
11	0.11	0.53	0.41	$D_7 \rightarrow D_{16}$	–ve	–ve	–ve	–ve	–ve
12	<0.1	0.16	0.5	$D_6 \rightarrow D_{17}$	–ve	–ve	–ve	(+ve)	–ve
13	<0.1	0.75	0.24	$D_8 \rightarrow D_{16}$	(+ve)	–ve	–ve	–ve	–ve
14	0.38	0.59	0.17	$D_4 \rightarrow D_{14}$	–ve	–ve	–ve	–ve	–ve
15	0.23	0.46	0.13	$D_2 \rightarrow D_{15}$	(+ve)	–ve	–ve	(+ve)	–ve
16	<0.1	0.36	0.1	$D_8 \rightarrow D_{13}$	(+ve)	(+ve)	–ve	–ve	–ve
17	5.2	0.28	0.16	$D_3 \rightarrow D_{14}$	(+ve)	–ve	(+ve)	–ve	–ve
18	19.6	–	–	D_7	–ve	–ve	–ve	–ve	–ve
19	0.67	0.34	0.13	$D_3 \rightarrow D_{13}$	(+ve)	–ve	–ve	(+ve)	–ve
20	0.12	0.21	0.14	$D_{76} \rightarrow D_{13}$	–ve	–ve	–ve	–ve	–ve

D: Day. CVC: Central venous catheter.

DISCUSSION

Infections contribute significantly to morbidity and mortality after hematopoietic stem cell transplantation (HSCT). Gram positive bacteria now account for 70% of bacterial infections compared with 30%, 25 years ago. This increase is in large part attributable to the nearly universal use of indwelling central venous catheters, and the wide spread use of antibiotics with gram-negative coverage to decontaminate the gut and reduce gram negative infections which has also contributed to the proliferation of gram-positive organisms **[13]**.

Boulad et al., (1998) found that infection is the result of a shift in the equilibrium between host defenses and microorganism pathogenecity. Patients undergoing HSCT are at risk of granulocytopenia, impairement of barrier defenses, and impairement of cell-mediated immunity and humoral immunity this will allowing microorganisms to cause infection more easily **[14]**.

Until recently no biomarker has been able to differentiate bacterial infection from a viral or non-infectious inflammatory reaction. Procalcitonin (PCT) is one of the first to offer this possibility **[15,16]**. Bacterial infections induce a ubiquitous increase of CALC-1 gene expression and a constitutive release of PCT from all parenchymal tissues, so that significant concentrations of PCT can be detected in the blood of patients with severe bacterial infection and sepsis **[17,18]**.

Procalcitonin increases 2-3 hours post induction by endotoxin levels then rises rapidly up to several hundreds in severe sepsis and septic shock. It remains high for up to 48 hours, falling to baseline values within the following 2 days **[19,20]**.

In our study, there was significant difference in the procalcitonin levels between patients in day 5, day 10, and day 15 due to the wide range detected. In all patients, the PCT results were positive, and reflecting the degree of septicemia in all patients.

PCT was positive with negative culture at early time points while with overt infection both PCT and cultures are positive.

This highlights the possibility that PCT levels may be better than cultures only for detecting infection early rather than late persistent infections.

In agreement with our results, PCT is superior to cultures in detection of sepsis with a sensitivity and specificity of 94 and (90%) at a cut-off of 0.5ng/1. Similar results were obtained in other studies **[21,22]**.

In our results, only 50% of patients with autologous and 80% of patients with allogeneic transplantation had positive cultures, while all patients had fever and had (except one) positive PCT achieving 90% sensitivity.

In clinical practice, the use of PCT as a diagnostic marker was shown to be of benefit in detection of sepsis. Because the up-regulation of PCT is attenuated by interferon-gamma, a cytokine released in response to viral infections, PCT is more specific for bacterial infections and may help to distinguish bacterial infections from viral illnesses.

In addition, PCT levels correlate with bacterial load and severity of infection which may help to guide the need for antimicrobial therapy more definitively **[23]**.

Among our patients, 13 (65%) had positive cultures compared to the serum PCT which was elevated in the vast majority of our patients with infectious fever.

This is in agreement with the results of other studies establishing the superior diagnostic accuracy of PCT in early infection compared with other markers **[24-26]**.

In conclusion, PCT is more sensitive and rapid to detect sepsis in the patients as the procalcitonin could detect sepsis in the cases with negative cultures and it was more correlated to fever than cultures in these patients.

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