The Prognostic Value of Serum Procalcitonin Monitoring in Febrile Neutropenic Patients with Hematological Malignancies

Thesis

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by

Caroline Maged Abd Elmessih Hezkial

M.B., B.Ch, Ain Shams University

Under Supervision of

Prof. Dr.Taghreed Hamed Taha Elkhashab

Professor of Medical Microbiology and Immunology
Faculty of Medicine Ain Shams University

Dr. Safaa Mohamed Abdel-Rahman Khattab

Lecturer of Medical Microbiology and Immunology
Faculty of Medicine Ain Shams University

Dr. Walaa Ali Al Salakawy

Lecturer of Internal Medicine and Clinical Haematology
Faculty of Medicine Ain Shams University

Faculty of Medicine
Ain Shams University
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List of Abbreviations

A	**AGR**	**A**ccessory **G**ene **R**egulator
	AML	**A**cute **M**eyloid **L**eukemia
	ANC	**A**bsolute **N**eutrophil **C**ount
	APACHE II	**A**cute **P**hysiology **A**nd **C**hronic **H**ealth **E**valuation II
	ARDS	**A**cute **R**espiratory **D**istress **S**yndrome
	ASCO	**A**merican **S**ociety Of **C**linical **O**ncology
	AUC	**A**rea **U**nder **C**urve
B	**BSI**	**B**lood **S**tream **I**nfections
C	**CAP**	**C**ommunity-**A**cquired **P**neumonia
	CI	**C**onfidence **I**nterval
	CLL	**C**hronic **L**ymphocytic **L**eukemia
	CMV	**C**yto**m**egalo**v**irus
	CoNS	**C**oagulase **N**egative **S**taphylococci
	CRE	**C**arbapenem **R**esistant **E**nterobacteriaceae
	CRP	**C**-**R**eactive **P**rotien
	CSF	**C**olony **S**timulating **F**actor
	CT	**C**alcitonin
E	**ESBL**	**E**xtended **S**pectrum **B**-**L**actamase
	ESMO	**E**uropean **S**ociety For **M**edical **O**ncology
F	**FACS**	**F**luorescence **A**ctivated **C**ell **S**orting
	FDA	**F**ood And **D**rug **A**dministration
	FN	**F**ebrile **N**eutropenia
	FUO	**F**ever Of **U**nknown **O**rigin
H	**HCC**	**H**epatocellular **C**ancer
	HCV	**H**epatitis **C** **V**irus
	HL	**H**odjkin **L**ymphoma
	HSV	**H**erpes **S**implex **V**iruses

I	**ICHS**	**I**mmuno**c**ompromised **H**ost **S**ociety
	ICU	**I**ntensive **C**are **U**nit
	IDSA	**I**nfectious **D**isease **S**ociety Of **A**merica
	IFIs	**I**nvasive **F**ungal **I**nfections
	IL-6	**I**nterleukin -**6**
	IQR	**I**nter **Q**uartile **R**ange
K	**kDa**	**K**ilo**D**alton
	KPC	**K**lebsiella **P**neumoniae **C**arbapenemase
L	**LRTI**	**L**ower **R**espiratory **T**ract **I**nfection
M	**MDR**	**M**ulti **D**rug **R**esistant
	MIC	**M**inimal **I**nhibitory **C**oncentration
	MRSA	**M**ethicillin **R**esistant **S**taphylococcus **a**ureus
N	**NCCN**	**N**ational **C**omprehensive **C**ancer **N**etwork
	NHL	**N**on **H**odjkin **L**ymphoma
P	**PAM**	**P**eptidylglycine **A**lpha-**A**midating **M**onooxygenase
	PCT	**P**rocalcitonin
	PRORATA	**Pro**calcitonin To **R**educe **A**ntibiotic **T**reatment In **A**cutely Ill Patients”
S	**SAPS II**	**S**implified **A**cute **P**hysiology **S**core **II**
	SCT	**S**tem **C**ell **T**ransplantation
	SIRS	**S**ystemic **I**nflammatory **R**esponse **S**yndrome
	SROC	**S**ummary **R**eceiver **O**perating **C**urve
T	**TNF-α**	**T**UMOR **N**ECROSIS **F**ACTOR - **α**
	TRACE	**T**ime **R**esolved **A**mplified **C**ryptate **E**mission
V	**VGS**	**V**iridans **G**roup **S**treptococci
	VRE	**V**ancomycin **R**esistant **E**nterococcus
	VZV	**V**aricella-**Z**oster **V**irus
W	**WBC**	**W**hite **B**lood **C**ells

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INTRODUCTION

Patients affected by hematological malignancies may present sporadic or persistent fever, especially during chemotherapy treatment (well known for its immunosuppressive induced status) or in the later stages of the disease. Moreover, these patients are potential candidates for the development of severe infections. Fever in such patients is extremely common and can have various causes that are not always easy to recognize ***(Macchioni et al., 2013).***

The need of quick, sensitive and reliable tests are fundamental to the diagnosis of infections in patients with hematological malignancies. Unfortunately, routinely available laboratory tests (with a quick turn-around-time, high sensitivity and specificity) to aid in the differential diagnosis, are lacking ***(Magrini et al.,2013).***

C reactive protein (CRP) is often considered a rather non-specific marker of the acute phase inflammatory response rather than infection in particular, and even scoring systems which are used as complementary tools to determine risk of infection (eg: APACHE II, SAPS II) are usually non-specific ***(Chen and Li, 2009).***

Procalcitonin (PCT) is a protein precursor of calcitonin, and its concentration appears to be correlated with the severity of infection. The usefulness of PCT as diagnostic and prognostic marker has been reviewed in some meta-analyses, but the results are still somewhat controversial ***(Tang et al., 2007).***

Although some data have been published on the use of PCT in detecting infectious diseases in hematological malignancies patients, there is relatively little information regarding the diagnosis of sepsis and serial PCT measurements to follow the course of infection in those patients ***(Georgopoulou et al., 2011).***

AIM OF THE STUDY

The aim of this study is to:

- Identify bacterial pathogens causing fever in febrile neutropenic patients with hematological malignancies.
- Monitor serum PCT levels in those patients.
- Correlate between serum Procalcitonin levels and clinical prognosis in those patients in comparison to serum CRP levels.
- Compare sensitivity and specificity of PCT in detection of bacterial infections with CRP.

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Hematological Malignancies and Infections

Hematological malignancies are neoplasms originating in the bone marrow and lymph nodes. The aetiology of most hematological malignancies is not yet known, among the factors increasing the risk of hematologial malignancies are: Ionising radiation, exposure to chemicals and dusts, industrial exposures including benzene, viral infections and genetic predisposition ***(Nørgaard, 2005).***

Over the past 100 years, several classifications have been devised attempting to provide clinically and biologically relevant subdivisions of hematological malignancies. Hematologic malignancies are broadly divided into: myeloid neoplasms, lymphoid neoplasms (leukemias and lymphomas), lymphoproliferative disorders and histiocytic/dendritic cell neoplasms. (They are widely recognized as arising out of specific stages of myeloid or lymphoid development or specific subsets of these types of cells). Immunophenotyping and gene expression profiling studies have been useful tools in distinguishing each type from the others ***(Swerdlow et al., 2008).***

Hematological malignancies in Egypt

Among developing countries, the incidence of Hamatological malignancies is low with Egypt being one of the exceptions. Egypt has one of the highest incidence rates of lymphoma in the world, mainly non Hodgkin lymphoma (NHL), which is higher than even the United States as well as other developed nations where hematological malignancies are more common ***(Curado et al.,2007).***

In Egypt, NHL is the second most common cancer in adults (with cancer breast being the first). A number of studies have been carried out in Egypt, but they mostly contain data from pathology-based laboratories or localized registries from predominantly urban areas. In one of the largest and population-based studies on hematological malignancies in Egypt that was

conducted in Gharbiah governerate, it was observed that a higher urban than rural incidence of hematological malignancies occurred. NHL was the most common type of hematological malignancy with diffuse B-cell neoplasms being the most common type of NHL. Chronic lymphocytic leukemia (CLL) was the most common subtype of leukemia ***(Herzog et al.,2012).***

Prevalence of hepatitis C virus (HCV) infection is about 13.9% of the healthy population with higher rates of up to 15.8% in Northern Egypt, such a high rate of HCV infection is related to the increasing incidence of hepatocellular cancer (HCC) in Egypt while at the same time is also probably responsible for the high rates of NHL, especially B-cell type NHL, the role of HCV infection in NHL is further strengthened by immunohistochemical studies that detected HCV RNA in malignant NHL tissues from Egypt ***(Goldman et al., 2009; Lehman and Wilson,2009 ; Gouda et al., 2010).***

HCV has been attributed as a causal factor in NHL by Some epidemiological studies observing a two to four times higher risk of NHL occurrence among HCV-positive individuals ***(IARC, 2009).***

The association of HCV infection and NHL is clear in Egypt since the pattern of incidence of lymphomas is quite similar to the pattern of incidence of HCC (which can be considered a proxy for HCV infection) in the districts of Gharbiah governerate. In contrast to Gharbiah, cancer incidence in Aswan in South Egypt showed a significantly lower rate of NHL than the rate reported from Gharbiah. However, the rates of Hodjkin lymphoma (HL) and leukemia in Aswan were not significantly different from the rates in Gharbiah. Higher rates of NHL in Gharbiah than South Egypt and other neighboring countries are likely due to the higher infection rate of HCV in Gharbiah than in South Egypt ***(Mazzaro et al., 2005 and Egypt National Cancer Registry, 2010).***

Infections In Patients With Hematological Malignancies

Patients with hematological malignancies are immuno-compromised as a result of the underlying malignancy or due to the therapeutic interventions employed to manage it. Some malignancies are associated with specific immune defects that predispose to infections with particular pathogens. Patients with acute leukemia have increased risk of severe Gram-negative bacterial infections as a result of quantitative or functional neutropenia. Patients with CLL and multiple myeloma are susceptible to invasive bacterial infections from Staphylococci and Streptococci especially encapsulated *Streptococcus pneumoniae* due to the altered humoral immunity. Conversely patients with lymphoma have abnormalities of the cellular immune system resulting in an increased risk of viral infections (e.g. herpes simplex) and fungal infections (e.g. Cryptococcus species) ***(Sharma and Lokeshwar,2005).***

Therapeutic interventions such as corticosteroids, chemotherapy, stem cell transplant, and radiation also produce deficiencies in the host defense. Neutropenia, resulting from cytotoxic chemotherapy is the most common risk factor for severe bacterial infections in hematological malignancies. Similarly common procedures such as venepunctures, bone marrow aspiration and insertion of central venous access devices, disrupt the integument and provide a nidus for colonization ***(Rókusz and László, 2005).***

Mucositis, which is characterized by development of inflammatory or ulcerative lesions in the oral or gastrointestinal tract is a common toxicity of cytotoxic chemotherapy and renders the patient vulnerable to infection by different bacteria that reside in the gastrointestinal tract ***(Martinez et al.,2014).***

The degree of neutropenia either as a consequence of disease or therapy is directly proportional with the incidence of

serious bacterial and fungal infection. The duration of neutropenia also contributes significantly to the risk of serious infections. Qualitative defects in neutrophil function have been described in hematological malignancies. These include defects in chemotaxis, phagocytosis, bactericidal capacity, and absence of respiratory burst that accompanies phagocytosis. Additionally, chemo-therapeutic agents including corticosteroids can decrease phagocytosis and neutrophil migration ***(Sharma and Lokeshwar, 2005).***

Febrile Neutropenia is a clinical syndrome that is characterized by an abnormally low number of neutrophil granulocytes. It is defined by the absolute neutrophil count (ANC) which can be calculated by multiplying total white blood cell count (WBC) by the percentage of polymorphnuclear cells ***(Keng and Sekeres ,2013).***

The Infectious Diseases Society of America (IDSA) and the Immunocompromised Host Society (ICHS)'s definition of neutropenia refers to patient with an absolute neutrophil count (ANC) $<0.5 \times 10^9/L$ or $<1 \times 10^9/L$ that is predicted to fall below $0.5 \times 10^9/L$ within 48 hours of onset of fever or signs of sepsis.

Fever is defined as temperatures of ≥38 °C for at least one hour or a single record of ≥38.3 °C. The ICHS and other scientific societies have also added, as a criterion of fever, the presence of an oral temperature of ≥38 °C measured twice in 12 hours ***(Link et al.,2003).***

With Febrile neutropenia (FN) being the most common life-threatening complication of cancer therapy, the patients treated for hematologic malignancies have an estimated incidence of 43.3 cases per 1000 patients. FN accounts for 50% of deaths in patients receiving chemotherapy for solid tumors. It also accounts for 70% to 75% of deaths in patients receiving chemotherapy for acute leukemia. If not treated in the first 48 hours, mortality approaches 50% ***(Bodey et al., 1985 and Caggiano et al.,2005).***