ejpmr, 2020,7(4), 156-160

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

D. DIMER LEVEL IN MULTIPLE MYELOMA PATIENTS PRE AND POST TREATMENT

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Article Received on 06/02/2020 **Article Revised on 27/02/2020** **Article Accepted on 19/03/2020**

ABSTRACT

Background: Thromboembolism is relatively common and serious event in individuals with malignancy and different type of cancer. Patients with Multiple Myeloma are at higher risk for venous thromboembolism with reported incidences of this complication being up to 30% especially in patients receiving multi agent chemotherapy and anti-angiogenic drugs. This study aimed to evaluate (D. dimer) level among Multiple Myeloma Patients pre and post thalidomide treatment, in Khartoum state -Sudan. **Materials and Methods**: The selection criteria of Sudanese MM patients depend on CBC results, bone marrow examination and hemoglobin electrophoresis. While exclusion criteria include Inflammatory, hypertension and DM to avoid the false positive results .Blood samples from 30 Sudanese MM patients were collected before and after one month of thalidomide treatment .The treatment protocol is thalidomide admitted 100mg/OD, Dexamethasone 40mg every week and Aspirin 100mg/day. 67% were males and 33%were females, with mean age was 44 years. The D. dimer level was measured by I Chroma$^{TM.}$ based on immunoassay principle. Data were analyzed by using statistical package for the social science (SPSS) version 21. **Results and Conclusion:** Our study revealed statistically significant difference of D. dimer level before and after administration of thalidomide treatment. The mean of D. dimer level among Sudanese patients of MM after treatment (1293.96 ng/ml ±928.45) was significantly higher than the level before treatment (478.85ng/ml ±317.37), (P. value 0.001). D. dimer level should be considered as follow up test before and after treatment to monitor the prognostic situation of the patient from the risk of thrombosis.

KEYWORDS: Multiple Myeloma, D. dimer, Sudan.

INTRODUCTION

Normal Plasma Cells are highly specialized cells derived from B-lymphocytes. Every Plasma Cell producing a single type of antibody containing one class of immunoglobin heavy chain (IgG, IgA, IgE or IgD) and one class of light chain (κ or λ). The early B-cells develop from haemopoetic stem cells in the bone marrow, where they rearrange their heavy chain (IgH) gene segments and become precursor B-cells which express IgM and leave the bone marrow. They migrate to the spleen and become either marginal zone B-cells or follicular B-cells. The marginal zone B-cells are short lived and can react quickly on antigen stimulation, producing IgM and then die from apoptosis within one week. Follicular B-cells can also undergo the same quick maturation and become IgM-producing PCs, but can also undergo maturation in the germinal centers, where they would be co-stimulated with dendritic cells and T-cells and subsequently undergo somatic mutations of the immunoglobulin genes.[1]

MM develops from premalignant clonal PCs that have gone through the maturation process in germinal centers , but as PCs lack proliferative capacity, MM may evolve from memory B-cells . These cells would be the myeloma initiating cells and initiate disease but also serve as a reservoir of cells to induce disease relapse.[2]

Myeloma is currently an incurable malignant disease. It stands for about 2% of all cancer deaths and about 20% of all hematological malignancies.[3] It is stated as a systemic malignant disease of the blood and the World Health Organization defines it as a lymphoproliferative B-cell disease. It is characterized as an uncontrolled proliferation of plasma cells (PC) in the bone marrow leading to extensive production of non-functional intact gamma-globulin or parts thereof. It can affect bone structure via enhancing osteoclasts, impair kidney function via hypercalcemia or have direct effect on tubulus of the defect gamma-globulins and cause loss of bone marrow function.[4]

D-dimer is a biomarker that globally indicates the activation of hemostasis and fibrinolysis. It is a degradation product of fibrin, which is produced when cross-linked fibrin is degraded by plasmin-induced fibrinolytic activity. As D-dimer plasma levels are elevated after clot formation, the measurement of D-dimer is routinely used in conjunction with clinical parameters in the initial assessment of suspected acute VTE.[5] Elevated D-dimer levels may also be observed in other clinical settings, such as cancer, pregnancy and infectious diseases or following trauma and surgery.[6] Recently, high D. dimer levels were reported to be predictive of the occurrence of VTE in cancer patients.[7] Both experimental and clinical studies have evidenced an association between cancer and haemostasis.[1] It has been estimated that approximately 15% of all cancer patients develops thrombosis during the course of their disease.[4] In fact, the occurrence of cancer is usually associated with various clinical thrombotic syndromes, including local and systemic venous and arterial thrombosis.[3] Despite the well-established link between cancer and venous thrombosis, anticoagulation is not routine care for these patients.[8] Evaluation of the coagulation profile among cancer patients may help understanding the association of cancers with the coagulation abnormalities also can help in the prediction and management of the complications that arise from the coagulation abnormalities in such patients.[9]

Thalidomide exhibits immunomodulatory and antiangiogenic characteristics; immunologic effects may vary based on conditions. In multiple myeloma, thalidomide is associated with an increase in natural killer cells and increased levels of interleukin-2 and interferon gamma. Other proposed mechanisms of action include suppression of angiogenesis, prevention of free-radical-mediated DNA damage, increased cell mediated cytotoxic effects, and altered expression of cellular adhesion molecules.[10]

Dexamethasone is a long acting corticosteroid with minimal sodium-retaining potential. It decreases inflammation by suppression of neutrophil migration, decreased production of inflammatory mediators, and reversal of increased capillary permeability; suppresses normal immune response. Dexamethasone's mechanism of antiemetic activity is unknown.[11]

The use of thalidomide in multiple myeloma results in an increased risk of venous thromboembolism, such as deep venous thrombosis and pulmonary embolism. This risk increases significantly when thalidomide is used in combination with standard chemotherapeutic agents including dexamethasone.[10]

MATERIALS AND METHODS

This was a cross sectional study, conducted at AL-Neelain University, faculty of Medical Laboratory, Khartoum. Thirty Citrated blood samples were collected from Multiple myeloma patients (those were anemic, PLT was decreased, Plasma Cell increased more than 5% in bone marrow, and M bands were high). Patients were selected after clinical and laboratory diagnosis based on CBC results, bone marrow examination, hemoglobin electrophoresis and coagulation profile results. About 2.5 ml of venous blood was collected from each (MM) patient to measure the D. Dimer level (Table 1).

D. Dimer measurement by Ichroma™

The test used was a sandwich immunodetection method in which the detector antibody in buffer binds to antigen in sample, forming antigen antibody complexes, then migrates into nitrocellulose matrix to be captured by the other immobilized – antibody complex on test strip. More antigen in sample formed the more antigen antibody complex lead to stronger intensity of fluorescencesignal on detector antibody, which is processed by instrument for Ichroma™. To show D. Dimer concentrations in samples.[9]

Data analysis

Data were analyzed by using statistical package for the social science (SPSS) Version 21. Ethical approval was obtained from ethical committee of Al-Neelain University, and Informed consent was taken from all the participants prior to their inclusion in the study.

RESULTS

The study revealed statistically significant difference of D. dimer level before and after thalidomide treatment. The mean of D. dimer level among Sudanese patients of MM after treatment (1293.96 ng/ml ±928.45) was significantly higher than before treatment (478.85ng/ml ±317.37), (P. value 0.001).

Table 1: Mean, SD, and P. value of the hematological parameter among M.M patients.

Parameters	Mean ±SD	Mean (R.V)	*P-value*
HB (male)	8.71±1.94 mg/dl	14.5 (13.0-16.0)	0.001
HB (female)	8.21±1.44 mg/dl	14 (12.5-15.5)	0.001
TWBC	7220.0±3107.2/cumm	7250 (3500-11000)	0.928
PLT	113033.3±2749.2/cumm	300000 (150000-450000)	0.001
Plasma cell % /BM	23.03±3.44%	<5	0.001
Alpha	1.34±1.16 g/dl	0.2 (0.1-0.3)	0.001
Beta	2.22±1.39g/dl	0.9 (0.6-1.2)	0.001
Gama	6.34±1.59g/dl	1.05 (0.8-1.3)	0.001

Hb was lower in group male and female, WBCs was normal ,PLT was decreased and plasma cell, Alpha, beta and Gama were all higher.

Table (2): The frequencies of M. band, IgM, IgG, and IgA parameters in study

Parameters	Frequency	Percentage (%)
M .band		
Normal	2	6.7
Low	1	3.3
High	27	90.0
IgM		
Normal	4	13.3
Low	1	3.3
High	25	83.3
IgG		
Normal	3	10.0
Low	2	6.7
High	25	83.3
IgA		
Normal	14	46.7
Low	3	10.0
High	13	43.3

The frequency of immunoglobulin light chain was increased in MM patients and serum M protein concentrations were significantly high (IgG was in (83.3%) of patients, IgM in (83.3%), while IgA (43.3%). Regarding M Band found that, (6.7%) of patients were Normal, (3.3%) were low while (90%) were high.

Table 3: Mean concentration of D. dimer level comparison across study groups.

Parameter	After (Mean ± SD)	Before (Mean ± SD)	Mean difference	*P. value*
D. Dimer	1293.96±928.45ng/ml	478.85±317.37	815.103±743.25	0.001
PT	17.9±4.5 /sec	16.6±2.1	1.3±1.2	0.330
APTT	38.6±5.4/sec	38.4±3.6	0.16±0.13	0.923
INR	1.3±0.31	1.2±0.15	0.13±0.11	0.171

D. Dimer, were significantly decreased after treatment, While result of PT, APTT, and INR insignificant before and after treatments.

Table (4) Frequency and percentage of normal and abnormal D. Dimer in study group

D. Dimer	Frequency (%)	Mean ± SD	*P. value*
Before treatment			
Normal	18 (60.0)	261.32±206.84	0.001
Abnormal	12 (40.0)	805.14±446.73	
After treatment			
Normal	8 (26.7%)	280.70 ±122.65	0.009
Abnormal	22 (73.3)	1379.71±1270.90	

Table (5): Frequency of NN, AA, AN, NA variables in study.

Variable	Frequency	Percentage (%)
NN	5	16.7
AA	10	33.3
AN	2	6.7
NA	13	43.3
Total	30	100.0
NN= normal before and after treatment AA= abnormal before and after treatment AN= abnormal before and normal after treatment NA= normal before and abnormal after treatment		

The frequency of **NA** (43.3%) then **AA** was (33.3%) ,**NN**(16.7%)and **AN** (6.7%).

Table 6: Correlation between study variables and change in D. Dimer level.

Variables	*R-value*	*P. value*
Age	-0.273	0.144
HB	0.115	0.547
TWB	0.264	0.158
PLT	0.529**	0.003
PLA	-0.082	0.666
Alpha	0.100	0.601
Beta	0.370*	0.044

Table 7: Distributions of D. Dimer normality value according to gender and treatment in study.

Gender	Before		*P-value*	After		*P .value*
	Normal	Abnormal		Normal	Abnormal	
Male	9 (30.0%)	11 (36.7%)	0.021	5 (16.7%)	15 (50.0%)	0.011
Female	9 (30.0%)	1 (3.3%)		3 (10.0%)	7 (23.3%)	
Total	18 (60.0%)	12 (40.0%)		8 (26.7%)	22 (73.3%)	

DISCUSSION

Multiple Myeloma (MM) is a neoplastic plasma cell disorder characterized by the clonal proliferation of plasma cells in the bone marrow and presence of monoclonal protein in the blood or urine. Worldwide, it accounts for 1% of all malignancies, 10-13% of all hematological malignancies and 1% of all cancer deaths every years.[12]

This study evaluated D. dimer in 30 Sudanese patients of Multiple Myeloma. Our finding results of D. Dimer before treatment was (478.85ng/ml) and after treatment was (1293.96 ng/ ml) that matched with finding of a study conducted by M. Robak et al., 2012, was performed on 31 MM patients to assess certain aspects of platelet activation and coagulation activation, as well as angiogenesis markers in patients with multiple myeloma: firstly on diagnosis and then in relation to anti myeloma therapy. Results of previous study revealed that after 1 month of TD therapy, a markedly increased sTM concentration was observed (3.3 ng/ml vs. 4.2 ng/ml; p = 0,006). Additionally, at that time, a significant positive correlation was found between sTM concentration and vWF: Ag (r = 0.34, p = 0.02), as well as between sTM and D-dimer concentration (r = 0.36, p = 0.01). Four weeks of thalidomide therapy resulted in no significant change in the percentage of platelet CD62P expression, while therapy with TD resulted in a marked increase (3.6 vs. 4.5 %; p = 0.04).[13]

However, in another a study conducted by Juraj Sokol. A 36 patients (18 men, 18 women) were initially examined and tested at the Department of Hematology and Transfusion Medicine in Martin University Hospital during a period from April 2012 to May 2014. The aim of this study was to measure the concentrations of serum levels of vascular endothelial growth factor, D-dimer, and von Willebr and factor in patients with newly diagnosed or relapsed multiple myeloma before treatment, during therapy, and after successful therapy. The study indicates that, the levels of D-dimer were significantly higher in patient with newly diagnosed versus relapsed MM.[14] These finding not agreement with our results it may be due to different therapeutic protocol such as Thromboprophylaxis consisting of low-dose molecular weight heparin was given to all patients in previous study; the current study excluded hypertensive and diabetic patients however, in previous study it may be didn't ; in addition, the level of D. Dimer was measured after one month in this study while it was measured after six months in the previous study.

CONCLUSION

Our study indicates that, the D. dimer level where is significantly higher in case before and after thalidomide treatment (p.value:0.001).

Recommendation

Based on the results of the study, the following recommendations are proposed:

- There is need to increase sample size for more accurate and generalize the finding results.
- Further mechanistic research, rigorously designed pharmacological evaluation, and multicenter clinical trials are warranted.

ACKNOWLEDGMENT

We are indebted to the staff of Heamatology Department (Al-Neelain University). We are grateful to the staff of Military Hospital for their collaboration. Finally, special thanks to the patients for being cooperative.

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