Investigating the Role of Platelet-Derived Growth Factor in Plasma Cell Myeloma Patients: A Case-Control Iraqi Study

Abstract

Background: Multiple myeloma (MM) or "plasma cell myeloma", the second most frequent neoplasm after non-Hodgkin lymphomas, is a cancerous proliferation of plasma cells within the bone marrow. Platelets-derived growth factor (PDGF), a mitogenic cytokine extracted from platelets, is one of the cytokines associated with tumor pathogenesis or progression. This research aimed to compare the values of PDGF in cases with MM to control people.

Material and Method: In the current case-control study, fifty-five cases of MM were identified by a professional hematologist. Patients undergoing treatment were separated into two groups: 26 with stage II and 16 with stage III, while the recently diagnosed cases of MM patients were divided into two groups as well: 6 with stage II and 7 with stage III. Furthermore, 25 healthy adults assisted as controls. The ROC-curve analyses were used to distinguish patients from control people and phases II and III.

Results: The total included subjects had a mean age of 60.1 0.7 years (average 47–78 years). The mean PDGF concentrations in the circulatory system were 687.7 ± 80.6 (average 27.2 – 5634.9). Gender found no substantial differences in the distribution of the variables. Except for the platelet counts, no statistically significant variations were found between the MM and the healthy control in any of the research criteria.

To detect MM, PDGF had a reduced accuracy measure (0.424), 95% CI (0.292 - 0.556), P-value >0.05, low sensitivity (0.40), and specificity (0.74). Furthermore, the ROC curve analysis demonstrated that PDGF could not discriminate advanced stages of MM patients.

Conclusion: The authors observed high non-significant levels of PDGF in MM cases compared to control subjects. Also, the poor capability of PDGF to discriminate MM cases from healthy or advanced from the early stages of the tumor. Nevertheless, further studies are desirable for explaining the significance of PDGF as biomarkers in MM.

Keywords: PDGF, Multiple myeloma, bone marrow neoplasm, plasma cells.

Introduction

Multiple myeloma (MM), also known as plasma cell myeloma, is a cancerous growth of plasma cells within the bone marrow that occurs at a rate of 4.5-6/100,000 [1]. MM signifies the 2nd most common neoplasm after non-Hodgkin lymphomas [2, 3]. MM is a result of aberrant bony remodeling that decreases osteoplastic activity and increases osteoplastic activity [2]. Frequently, M-protein presence in urine or plasma is generally associated with MM. As a cancer, MM is not curable, however, its prognosis has improved markedly throughout the preceding two decades on account of the introduction of innovative treatments [3-5]. Plasma cell malignancy has an uncertain etiology, nevertheless, numerous academics suggested various

etiological factors that may have contributed to the etiology of MM such as autoimmune disorders, virus infections, inflammatory disorders, allergic diseases, and hereditary factors [3, 4].

Given the relevance of the angiogenesis pathways in the progression of myeloproliferative disorders, the imbalance between antiangiogenic/proangiogenic elements may be the basis for an angiogenic shift, triggering a vascular phase of the tumor [6]. Among the cytokines that have been associated with etiopathology or the progression of tumors are fibroblast growth factor 2, hepatocyte growth factor, vascular endothelial growth-factor [7], transforming growth factor β, and platelet derived growth factor (PDGF) [7, 8] and others [9-13] at diagnosis have predictive significance. These cytokines might have to regulate multifaceted cell activities including migration, proliferation, differentiation, and cell survival. They can interfere with various biological processes like tumorigenesis, fibrosis, atherothrombosis, asthma, and intellectual activity [8, 11, 14-16]. Likewise, PDGF is a platelet-derived mitogenic cytokine. [8, 17, 18]. The research focused on the expression of PDGF in myeloproliferative tumors has begun since the 1980s [8], despite their controversial outcomes [19, 20].

PDGF is a cytokine that has a function in the carcinogenesis of MM. It regulates cellular proliferation, survival, and migration in MM cells. Recent evidence exposed that higher levels of PDGF have been related to enhanced growth and progression of the disease [21]. The PDGF pathway is also involved in the establishment of the tumor microenvironment, which contributes to MM cell viability and resistance to therapy. Inhibitors of the PDGF pathway are being considered as a prospective therapy option for multiple myeloma [22].

The purpose of this study was to evaluate and compare PDGF levels in MM patients and healthy people.

Materials and methods

Study population and setting

The course of this case-control study extended from January to August 2021, and it was conducted in the oncology center at Merjan Medical City, Babylon, Iraq. The present study involved patients with MM (55) and healthy subjects (25), with an average age of 38-72 years. Physicians and oncologists confirmed the MM diagnosis using the "EHA-ESMO Clinical Practice Guidelines for diagnosis of MM" [23]. Each one of the patients in this study was receiving first-line cytotoxic

chemotherapy, either lenalidomide or bortezomib, and was separated into 4-categories. Group I included 26 cases with stage II, and Group II involved 16 cases with stage III. In addition, the newly diagnosed 13 cases formed by the third group of 6 people with stage II and the fourth group of 7 patients with stage III.

Those with type 1-DM, kidney, or hepatic failure were omitted from this study. As well, patients receiving other lines of MM therapy or those who underwent bone marrow transplants were omitted also.

Ethical consideration

Before being registered in the study, all applicants must sign a formal agreement. The hospital and the Babil health directory ratified and legalized the study, which adhered to the Helsinki Declaration's statements.

Data acquirement, PDGF calculation

The basal demographic features, some of the hematological and chemical findings of the participants, as well as the malignant staging, were taken from the patient's files in the hospital. The authors have conducted the PDGF measurements in the research laboratory of the College of Pharmacy. The PDGF levels estimation was done by ELISA technique using "Elabscience® for human PDGF kit".

Statistical examinations

The study collected information was processed, and transferred into an Excel sheet, then filtered before being analyzed by the "SPSS-IBM" software. The parameters were specified and displayed in the findings as mean (SE) or No (%) dependent on their criteria (categorical or continuous). ROC-curve investigations were also performed to assess the accuracy of PDGF in distinguishing between subjects with MM and healthy controls, as well as between stage II and stage III plasma cell myeloma.

Results

The main applicants’ descriptive statistics were demonstrated in (Table 1). The patients' average age was 60.05±0.7 years. The mean circulatory PDGF concentrations were 687.7±80.6 (average 27.2-5634.9). The mean values of platelets, creatinine, and urea were moderately within average values (217.8±15.6, 1.3±0.3, and 48.4±3.4), individually.

Table 1: Main descriptive frequencies of the investigated applicants with MM (N-80)					
	Min.	**Max.**	**Mean**	**Std. Deviation**	**Std. Error**
Age	457	78	60.05	6.9	0.7
PDGF	27.2	5634.9	687.7	721.3	80.6
Platelets	170	320	217.8	30.4	15.6
Creatinine	0.45	3.1	1.3	2.6	0.2
Urea	28.9	220.0	48.4	32.4	3.4

Table-2 shows the possible differences in the reference features of the research variables between the two groups of participants. Gender differences between study groups were not found to be significant. Except for platelet counts, no statistically significant differences were seen between the MM and control groups in any of the research parameters.

Table 2: Baseline features of the studied parameters between the two research groups					
Characteristics		**Total (N-80)**	**Multiple myeloma cases (N-55)**	**Healthy controls (N-25)**	Significance
Age (years) mean± SE		60.1±0.7	58.8±0.9	62.1±1.1	> 0.05
Sex N (%)	**Males**	55 (61.1)	33 (60)	22 (62.9)	> 0.05
	Females	35 (38.9)	22 (40)	13 (37.1)	
Platelets mean± SE		236±7.3	204.6±2.6	246.8±6.1	0.001
Blood urea mean± SE		48.4±3.4	46.8±4.6	51.1±5.1	> 0.05
Serum creatinine mean± SE		1.3±0.2	1.7±0.2	1.2±0.7	> 0.05
Serum PDGF mean± SE		687.7±80.6	765.0±113.4	517.7±55.5	> 0.05

The distribution of the study characters in the current study, based on the stages of MM treatment and groups exposed insignificant changes in almost all the variables excluding the counts of thrombocytes (Table 3).

Gender exhibited non-significant differences in all of the research variables (Table 4).

Table 3: The studied parameters distributed in relation to the treated groups and staging of plasma cell myeloma

Characteristics		Treatment Groups				P-value
		Newly diagnosed cases		Treatment group		
		Stage II (n-6)	Stage III (n-7)	Stage II (n-26)	Stage III (n-16)	
Age/years mean± SE		56.7±2.8	63.9±2.1	59.6±1.3	56.3±1.5	> 0.05
Sex	Males	3 (9.1%)	4 (12.1%)	17 (51.5%)	9 (27.3%)	> 0.05
	Females	3 (13.6%)	3 (13.6%)	9 (41%)	7 (31.8%)	
Platelets mean± SE		181.4±4.6	246.8±6.0	211.7±3.6	206.8±4.3	0.001
Blood urea mean± SE		36.7±2.1	39.9±2.6	60.1±9.1	32.1±0.9	> 0.05
Serum creatinine mean± SE		1.8±0.2	1.6±0.2	1.7±0.2	1.7±0.1	> 0.05
PDGF		1579.9±908.2	683.5±117.3	602.1±78.2	759.8±132.1	> 0.05

Table 4: Distribution of the studied parameters according to the gender

Parameters	Gender	Mean	SD. Error	Significance
Age	Males	58.95	1.3	> 0.05
	Females	57.17	1.1	
Creatinine	Males	1.2	0.4	> 0.05
	Females	1.3	0.2	
Blood Urea	Males	51.3	3.6	> 0.05
	Females	50.1	6.3	
RBCs	Males	3.7	0.1	> 0.05
	Females	2.95	0.2	
Leukocytes	Males	6.9	0.4	> 0.05
	Females	7.1	0.4	
PDGF	Males	792.7	101.9	> 0.05
	Females	723.3	242.5	

To estimate the strength of predictability of serum PDGF values to discriminate between healthy patients with MM, a ROC curve analysis was executed that showed an area under the curve measure of 0.424, 95% CI of 0.292 – 0.556, p>5%, low sensitivity (0.40), and specificity (0.74). As well, there was a poor ability of PDGF to differentiate advanced stages of patients with MM (Table 5).

Table 5: Results of ROC-curve analysis for PDGF to distinguish: MM subjects from the healthy, and Stage III from Stage II patients

The ability of PDGF to predict	AUC	Specificity	Sensitivity	Significance	95% CI
Multiple myeloma from the control subjects	0.575	0.625	0.56	0.3	0.444 – 0.707
Stage III from stage-II multiple myeloma	0.586	0.619	0.67	0.3	0.432 – 0.740

Discussion

In the current study, although the mean concentrations of serum PDGF were higher among the MM subjects compared to the healthy control, they were not statistically significant. The second main result of the current study was the poor ability of PDGF levels to discriminate between MM patients and the controls as well as stages 3 from 2 MM patients.

Based on the evidence currently available, it seems fair to validate the role of angiogenesis in the pathogenicity of tumors. Quite a lot of factors share in the progress of angiogenesis and among them is the PDGF. Few revisions have inspected the expression of the PDGF receptors in MM and have shown the correlation and their effect on the prognosis of MM patients [24].

The specific immunological mechanism of monoclonal immunoglobulin gammopathy in MM patients is undisclosed. [25]. The progress of myeloma cells is controlled by a diversity of body cytokines [26]. PDGF, which can enhance chemotactic migration of endothelial cells, has recently emerged as a significant cytokine in the pathogenesis of MM. A range of neoplastic cells, as well as normal cells such as macrophages and stromal cells, induce PDGF synthesis [27]. Unlike

our outcomes, Bilalis A. et al. reported a high expression of PDGF receptors among MM patients was correlated with advanced-stage disease.

On the other hand, several cytokines comprising PDGF-BB were considerably lower among myeloma patients compared to controls in other studies [28]. Another case-control study reported non-significant alterations between the serum and bone marrow levels of PDGF [7].

Platelets not only promote tumor development [29] and migration, but they can also drive cancers to become chemotherapy-resistant [30]. Recently, numerous studies have been dedicated to the relationship between blood platelets and therapy resistance. However, platelet reactivity is increased in multiple myeloma [31]. This could be one of the confounders in the current study since there were considerable differences in platelet numbers between the study two groups.

In the current analysis, there was no grouping based on the drugs or the administered regimes that had been received by the patients. Nonetheless, we should remark that all the selected patients had treated uniformly as the study was single-center, to overcome this cause of bias.

There is a piece of evidence that PDGF is crucial for pericytes and vascular smooth muscle cells, which aid to stabilize the microvascular environment. PDGF receptor Block results in the degeneration of vascular smooth muscle and pericytes, in that way, stimulating angiogenesis [32]. Current studies reported that PDGF-β could be a latent angiogenic promoter in many types of hematological tumors. Tsirakis et al. exposed that in MM patients, serum PDGF-β positively correlated with microvascular density, i.e. patients with increased density of microvasculature exhibited greater plasma PDGF-β levels [33]. Inconsistent with the findings of our study, a major difference was observed by other researchers in circulatory PDGF levels in MM subjects before and after chemotherapy. These researchers have shown that PDGF may be an imperative marker of the immune state among MM patients but are of higher value in the advanced stages [34].

The data generated by the present study exposed that the ages of MM subjects were similar to the ages described by other scholars [35]. A previous Iraqi analysis of the incidence of MM described 41-72 years of age ranges of the patients [25]. Last year, another Iraqi analysis exposed equivalent ages of MM cases in the current revision and the in the bordering states, though lower than western populations [5].

The gender influence on the MM outcomes is unknown. Nevertheless, the males were considered dominant in the present study, consistent with the USA study included 78,351 MM patients of different ages [36], and with another survey that involved newly diagnosed 2268 multiple myeloma [37]. Given that males are more likely than women to get plasma cell myeloma, a study of all malignancies conducted through the "National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program" predicted that myeloma men may have a lower survival rate [38].

There have been increased efforts to explore and pinpoint pathways, growth factors, machinery proteins, or, targets that may contribute to the facilitation of MM progression. Furthermore, the necessity for innovative therapeutic targets always exists. This study endeavored not to directly cover and justify but to inspect PDGF as a new biomarker.

Recent developments in molecular genetics can better explain PDGF's carcinogenic actions and provide a solid foundation for targeting PDGF signaling pathways to initiate innovative MM treatments. Nonetheless, the specific mechanisms of PDGF involved in the pathogenesis of malignancy obligate further interpretation, which could be the horizon of future works.

Conclusion

The authors observed high non-significant levels of PDGF in MM cases compared to control subjects. As well, there was the poor capability of PDGF to discriminate MM cases from healthy or advanced from the early stages of the tumor.
Nevertheless, further studies are desirable for explaining the significance of PDGF as biomarkers in MM.

Limitations:

The lower number of cases and the single-center source of data can be considered at the top of the study limitations. Additional newly discussed cytokines involved in myeloid tumor formation (such as VEGF, TGFB, and IL-6) are much more useful and determinant. Their analysis in upcoming works would strengthen our findings.

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