RESEARCH ARTICLE

Editorial Process: Submission:02/24/2017 Acceptance:07/29/2017

Prognostic Value of IL-10 and Its Relationship with Disease Stage in Iranian Patients with Multiple Myeloma

Ramin Shekarriz[1]*, Ghasem Janbabaei[1], Saeed Abedian Kenari[2]

Abstract

Background: Several studies have demonstrated roles of interleukins in the pathogenesis of multiple myeloma (MM). Objective: Here we considered correlations among serum levels of IL-10, stage of disease and clinical laboratory disease markers in Iranian MM patients to investigate whether the interleukin might have prognostic significance. **Materials and Methods:** In this cross-sectional study, a total of 60 subjects (40 patients and 20 controls) were recruited. After preliminary laboratory tests, disease stage was evaluated and serum levels of IL-10 were measured using an enzyme-linked immunosorbent assay (ELISA). **Results:** The mean concentration of serum IL-10 in patients (2.39±0.82 ng/ml) was significantly higher ($p<0.0001$) than that in healthy controls (0.34±0.15 ng/ml). A positive and significant correlation ($p<0.0001$) was observed with the disease stage. The highest plasma cell proportions were recorded for MM stage III patients (68.8±9.21%), differing significantly from those of stage I patients (50.0±10.0%; $p=0.011$). The Beta-2 microglobulin value in stage III patients (7.7±1.13mg/l) was significantly higher than in those with stage II (4.31±0.64 mg/l; $p<0.0001$) and stage I (2.8±0.4 mg/l; $p<0.0001$). There was also a positive and significant correlation ($p=0.002$) between IL-10 levels and B2M. A trend ($p=0.06$) for positive correlation was observed between IL-10 levels and plasma cells. **Conclusions:** The correlation of IL-10 with disease stage and markers of disease activity indicates important roles in MM pathogenesis and progression. Therefore, measurement of serum IL-10 might be helpful for predicting stage and clinical management of MM.

Keywords: Multiple myeloma- IL−10- disease stages- plasma cells

Asian Pac J Cancer Prev, **19 (1)**, 27-32

Introduction

Multiple myeloma (MM) is a malignant plasma cell disorder which comprises about 10% of all hematologic malignancies (Kyle et al., 2004, Kyle et al., 2008, Palumbo et al., 2011, Shay et al., 2016, Siegel et al., 2016). MM is determined by accumulation of malignant plasma cells within bone marrow. Symptoms of the disease are often nonspecific. The main manifestations include fatigue, unexplained weight loss, anemia of unknown origin, bone pain or fractures due to lytic bone lesions, impaired renal function, coagulation disorders, neurologic symptoms and blood hyper-viscosity (Dolloff et al., 2013, Gerecke et al., 2016, Talamo et al., 2010).

Despite developments in therapeutic factors, MM is still an incurable disease (Ria et al., 2014). This necessitates the need to continue developing new diagnostic and therapeutic options for management of MM. Evidence demonstrated a cytokine network for controlling proliferation and progression of human MM (Otsuki et al., 2000, Tinhofer et al., 2000, Treon et al., 1998). Discovering relations between serum levels of interleukins which contribute to MM activity and severity is of great importance that helps in controlling the disease. Numerous studies focus on methods for controlling expression of key interleukins as considerable factors for reducing symptoms and activity of MM.

Autocrine or paracrine secretions of different mediators are activated by MM cells and bone marrow (BM) microenvironment. Extensive research efforts discovered that several mediators play important roles in MM angiogenic process, leading to tumor growth, invasion and metastasis; for example elevated amounts of Interleukin-16 (IL-16) and IL-17 result in worse MM prognosis(Atanackovic et al., 2012, Noonan et al., 2010). Angiogenesis caused by MM is a complex process which applies different growth factors, adhesion molecules and several factors in the tumor microenvironment. This mechanism includes generation of cytokines by myeloma cells which affects micro-environmental cells (Kyle et al., 2004).

Interleukin 10 (IL-10) is an inflammatory cytokine which is secreted mainly by myeloma-associated macrophages (Alexandrakis et al., 2015, Gu et al., 1996, Lauta 2003, Otsuki et al., 2002, Wang et al., 2016) and plays an important role in proliferation of B cells and their terminal differentiation into plasma cells (Lauta 2003, Mazur et al., 2005, Otsuki et al., 2002). IL-10 has been

[1]*Department of Hematology and Oncology, Gastrointestinal Cancer Research Center,* [2]*Department of Immunology, Immunogenetic Research Center, Mazandaran University of Medical Sciences, Sari, Iran. *For Correspondence: drraminshekarriz@yahoo.com*

implicated in immune suppressive microenvironment in MM and progression of the disease (Moore et al., 2001). However, it is doubtful how serum levels of IL-10 correlates with various stages of MM and clinical symptoms of the disease. Moreover, other malignant B-cells neoplasms like chronic lymphocytic leukemia (CLL) and diffuse large B-cell lymphoma (DLBL) are known to be associated with IL-10, where its serum concentrations are higher among untreated patients and have been associated with poorer outcomes (Fayad et al., 2001).

The aim of this study is to measure serum concentrations of IL-10 in Iranian MM patients with various stages of disease to investigate whether pre-treatment serum levels of IL-10 could predict MM severity. We also attempted to evaluate any relationship between IL-10 levels and several clinical as well as laboratory disease markers in a group of MM patients and healthy controls among Iranian populations. Results of this study may help us to find out clinical importance of interleukins in the process of MM and reveal new diagnostic aspects in the approach of hematological malignancies. Furthermore, we should point out that up to now this is the first study on the correlation between IL-10 and MM severity which has been done in Iran.

Materials and Methods

Study subjects

A total of 60 subjects (40 patients and 20 controls) were recruited to Tooba Clinic and Imam Hospital at the Mazandaran University of Medical Sciences (Sari-Iran) between 2015 and 2016. This cross-sectional survey was approved by the institutional review board and ethical committee of Mazandaran University of Medical Sciences. Written informed consents were also obtained from all patients and controls for the use of their clinical data just for research purposes before participation. Patients were selected from those suspicious for MM referred to our Oncology clinic. Questionnaires containing demographic data of the study population were filled before laboratory evaluations. Diagnostic criteria for MM patients described previously (Pettersson et al., 1981). According to the mentioned criteria a total of 40 patients with symptomatic MM and 20 healthy individuals as controls were enrolled in the study. Healthy controls were selected from those who just came to our center for checkup and no abnormalities were found in clinical examination or laboratory results. They were also didn't have any considerable history of previous medical diseases. Inclusion criteria for patients including: (1) newly diagnosed patients with MM based on the mentioned criteria; (2) no history of previous malignancy or treatments; (3) had measurable monoclonal protein (M protein); (4) complete clinical information; and (5) available serum specimens before initiation of treatment. Subjects who met the following criteria were excluded from the study: (1) history of smoking; (2) history of previous inflammatory disease such as infections, collagen-vascular disease, and neoplasms; (3) previous treatment for MM; (4) history of chronic disease like diabetes mellitus, liver disease, and etc.; (5) history of non-steroidal anti-inflammatory drugs (NSAIDs) intake. Patients suspicious for MM were admitted at Imam Hospital for bone marrow aspiration. Three patients with stage 1, 21 with stage 2 and 16 with stage 3 among 40 MM cases were diagnosed according to the international staging system (ISS) (Durie et al., 1975).

Laboratory evaluations

Serum samples, from patients, before starting any myeloma-related therapy, and healthy controls, were collected and stored at -80 °C for further evaluations. Serum concentrations of IL-10 were evaluated with Sandwich enzyme-linked immunosorbent assay (ELISA) kits (eBioscience, Germany, NO: BE53101), as described by manufacturer instructions.

Additionally, blood samples were assessed for complete blood count (CBC), erythrocyte sedimentation rate (ESR), calcium (Ca), β-2 microglobulin (β-2M), M protein, immunoglobulin type (IgG and IgA), type of light chain (Kappa, Lambda). Bone marrow biopsy was also taken from each patient during local anesthesia and Giemsa staining was performed to assessment of plasma cells percentage. Skull X-ray was performed for each patient to evaluate osteolytic lesion. Kidney failure was also recorded when creatinine clearance were less than 50 ml/min.

Statistical analysis

Demographic and clinical characteristics of all patients are reported as means ±SD. An independent t-test was considered to compare the mean of each of the parameters between the patients and control groups. The Pearson correlation test and linear regression were used to analyze and examine the relationship between the IL-10 and other parameters. Graph Pad Prism software (version 7) was used to draw all graphs. Data were analyzed using SPSS (version 19) and a $p<0.05$ was considered as significant.

Results

The basic and clinical characteristics of all patients are summarized in Table 1. In total, 40 patients (23 male and 17 female) with mean age of 66.72±7.64 years met the inclusion criteria. More than half of the patients (57.5%) were >65 years old. The percentage of patients with stages I, II and III were 7.5%, 52.5% and 40%, respectively. Types of monoclonal protein were: IgG for 27 (67.5%) patients, IgA for 10 (25%) patients, and light chain disease for 3 (7.5%) patients. Sixty percent of patients presented Kappa light chain and 40% of patients presented Lambda light chain. Mean of serum B2M concentrations in patients was 5.55±2 mg/l. The mean percentage of plasma cells in bone marrow of the patients was 63.5±10.81%. M protein mean level in patient was 7.02±2.08 g/dl. 42.5% patients were presented with kidney failure, while 72.5% patients had osteolytic lesions.

The mean concentration of serum IL-10 for all patients was 2.39±0.82 ng/ml (range 0.4-4.2 ng/ml). Serum IL-10 level was also detected in 20 healthy volunteers with mean age of 65.3±5.16 years, and the mean concentration was 0.34±0.15 ng/ml (range 0.1-0.6 ng/ml), significantly lower

Table 1. Clinical and Basic Demographic Characteristics of Patients

Variables	Patients (n=40)
Age	66.72±7.64
<65	17 (42.5%)
≥65	23 (57.5%)
Gender	
Male (n)	23 (57.5%)
Female (n)	17 (42.5%)
Stage	
I (n)	3 (7.5%)
II (n)	21 (52.5%)
III (n)	16 (40%)
Plasma cell (%)	63.5±10.81
B2M (mg/l)	5.55±2
M protein (g/dl)	7.02±2.08
Ig type	
IgG (n)	27 (67.5%)
IgA (n)	10 (25%)
Only light chain	3 (7.5%)
Light chain	
Kappa (n)	24 (60%)
Lambda (n)	15 (40%)
Kidney failure	
Yes (n)	17 (42.5%)
No (n)	23 (57.5%)
Osteolytic lesion	
Yes (n)	29 (72.5%)
No (n)	11 (27.5%)
Ca	10.31±0.75
Hb	8.35±0.8
ESR	104.5±13.14

than that of MM patients (P<0.0001; Figure 1).

A positive and significant correlation (p<0.0001) was observed between the IL-10 levels and disease stages. Serum IL-10 levels were increasing with advanced stages of disease (Table 2). Mean serum IL-10 levels in MM patients with stage III (2.83±0.66 ng/ml) were significantly higher than those of stage I (1.13±0.7 ng/ml; p=0.001) and

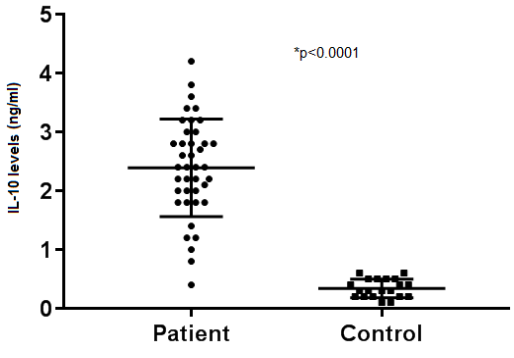

Figure 1. Serum IL-10 Levels in Controls and in Patients. Serum IL-10 concentrations were significantly higher in MM patients than in healthy volunteers (p<0.0001).

Table 2. Mean Values of Measured Parameters According to Disease Stage

Variables	Stage I	Stage II	Stage III	p-value
Age	64.66±14.04	66.14±8.11	67.87±5.94	0.71
Plasma cell (%)	50.0±10.0	61.42±10.01	68.75±9.21	0.007
B2M (mg/l)	2.8±0.4	4.31±0.64	7.7±1.13	<0.0001
M protein (g/dl)	7.1±1.85	6.46±1.86	7.74±2.28	0.185
IL-10 (ng/ml)	1.13±0.7	2.22±0.73	2.83±0.66	0.001
Ca	10.26±0.92	10.28±0.88	10.35±0.55	0.95
Hb	9.2±0.72	8.41±0.7	8.1±0.87	0.083
ESR	103.33±5.77	103.8±14.39	105.62±12.89	0.91

*p<0.05 is considered as significant

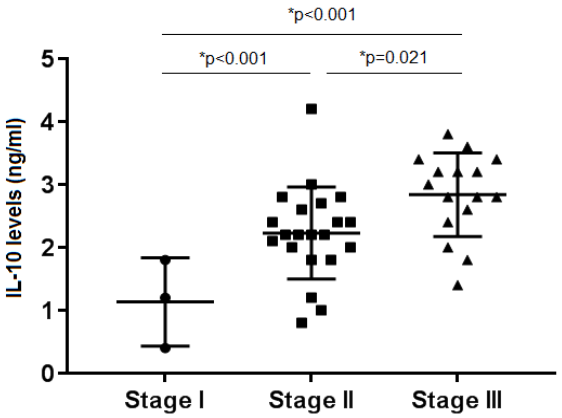

Figure 2. Mean of IL-10 in Different Stages. There is a significant difference in mean of IL-10 levels between disease stages.

of stage II (2.22±0.73 ng/ml; p=0.034) patients (Figure 2). Similarly, the highest plasma cells were recorded for MM stage III patients (68.75±9.21%), differing significantly from those of stage I patients (50.0±10.0%; p=0.011). Also, a trend was found for higher percentage of plasma cells in patients with stage III compared with stage II (61.42±10.01%; p=0.07). B2M value in stage III patients (7.7±1.13mg/l) was significantly higher than those with

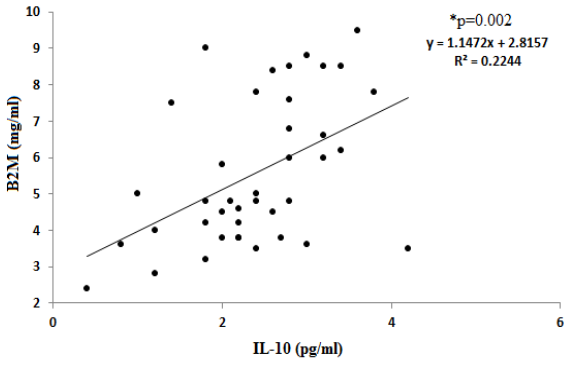

Figure 3. A Positive and Significant Correlation (p=0.002) was Found between the IL-10 and B2M Levels

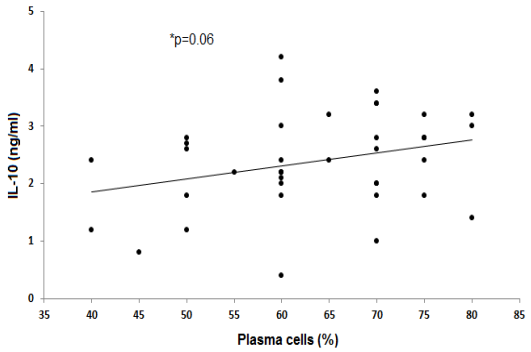

Figure 4. A Trend for Positive Correlation (p=0.06) was Found between the IL-10 Levels and Plasma Cells

stage II (4.31±0.64 mg/l; p<0.0001) and stage I (2.8±0.4 mg/l; p<0.0001). Although M protein levels in stage III patients (7.74±2.28 g/dl) were also elevated in comparison with stages I (6.46±1.86 g/dl) and II (7.1±1.85 g/dl), the difference did not reach statistical significance (Table 2). We didn't find significant difference in mean of Ca, Hb and ESR between Stages I, II and III.

We have also analyzed the correlation between IL-10 levels with osteolytic lesions and kidney failure, as well as other markers of tumor burden (M-protein levels, B2M, plasma cell numbers, and etc.). We found that there is a positive and significant correlation (p=0.002) between IL-10 levels and B2M (Figure 3). A trend (p=0.06) for positive correlation was observed between IL-10 levels and plasma cells (Figure 4). However, we didn't observe any significant correlation between IL-10 concentration with other parameters such as M protein, Ca, Hb and ESR levels.

Discussion

Multiple myeloma is a monoclonal B lineage malignancy which engage bone marrow by repositioning of immunoglobulin (Ig) heavy chain switched and malignant plasma cells which produce Ig (Kyle et al., 2008). Recent investigations have demonstrated that MM progression is caused by several mechanisms and various mediators. Among them, inflammatory cells, especially macrophages, play a critical role in tumor growth, angiogenesis and disease progression (Coussens et al., 2002).

IL-10 is an inflammatory mediator generated by monocytes, macrophages, T cells, B cells, natural killer (NK) cells and mast cells (Benjamin et al., 1994, Moore et al., 1993), which can augment proliferation of B cells and affect their differentiation into plasma cells (Lauta 2003, Otsuki et al., 2002). In our study, a significant correlation was seen between IL-10 and percentage of plasma cells in MM patients. Our data support the idea that IL-10 induces proliferations of these cells into plasma cells. Previous studies have supported the impact of IL-10 in different hematological malignancies such as Hodgkin lymphoma and non-Hodgkin lymphoma (Gupta et al., 2012, Visco et al., 2004). It is also implicated in pathogenesis of other malignant B-cell neoplasms such as chronic lymphocytic leukemia (CLL) and diffuse large B-cell lymphoma (DLBL) (Alexandrakis et al., 2015). Furthermore, higher IL-10 levels were reported to be associated significantly with shorter survival rate among patients with DLBL (Gupta et al., 2012). More recently studies have reported that IL-10 acts as a growth factor for MM cells and elevated serum levels of IL-10 can be associated with advanced stage (Alexandrakis et al., 2013, Kovacs 2010).

Although several studies considered relationship between IL-10 and MM progression, the prognostic role of IL-10 in MM still remains unclear. In the current study, we reported serum levels of IL-10 were significantly higher among Iranian MM patients compared with healthy controls. In addition, IL-10 concentrations increased significantly with clinicopathological characteristics like advanced stages of disease. Our results are consistent with a study by Wang et al., (2016), in which serum IL-10 levels in MM patients were higher than healthy controls. Furthermore, they suggested that increased IL-10 levels correlated significantly with worse clinic-pathological features. In another study by Alexandrakis et al., (2015), they reported higher IL-10 concentration in serum of patients with MM compared with controls. Similarly, Pappa et al., (2007) stated elevated amounts of IL-10 correlated positively with advanced stages of MM. Data from our study and pervious research confirmed the idea that serum IL-10 concentration is closely related to higher stages of MM, pointing a significant role for IL-10 in the pathogenesis and progression of this malignancy.

Macrophages have important biological functions namely an important role in neovascularization process, tumor growth and metastasis (Hao et al., 2012). Different molecules act as chemo-attractants for macrophages in microenvironments such as IL-4, IL-13, transforming growth factor beta (TGF-β) and IL-10. A potential role for IL-10 in inducing and development of MM was first indicated that IL-10 stimulated proliferation of cytokine dependent cell lines and freshly explanted myeloma cells among patients with active MM by the Janus-Kinase/ signal transducer and activator of transcription pathway as well as the mitogen-activated protein (MAP) kinase and phosphatidylinositol 3-kinase /AKT pathways in the absence of IL-6 (Lu et al., 1995, Manier et al., 2012, Palumbo et al., 2011).

In this study, correlations between IL-10 levels with renal failure and osteolytic lesions were not showed to be considerable. However, we confirmed significant correlations between elevated IL-10 levels and β2-microglobulin concentrations. This finding was in line with Brenning et al., (1986) study where pre-treatment serum β2-microglobulin found to be a valuable marker for predicting survival among patients with MM. Furthermore, Ortega et al., (1992) indicated β2-microglobulin as one of the main independent prognostic factors in MM. Therefore, we recommend evaluation of serum IL-10 among patients with MM in order to determine severity of the disease as it serves as a non-invasive diagnostic tool. However, further studies would be needed to support prognostic significance of IL-10 among MM patients. A limitation of this study was that we did not evaluate serum levels of IL-10 after

treatment of MM patients. Further study with larger sample size from different parts of Iran is valuable.

In conclusion, it was the first investigation in Iran which provided this evidence that patients with advanced stages of MM had higher levels of IL-10. Thus, IL-10 levels can be easily evaluated in MM patients and could serve as a remarkable prognostic factor. We recommend measurement of serum IL-10 as a non-invasive diagnostic tool for predicting stage of MM and its clinical management. Further genomics and epigenetics studies are necessary to consider gene expression of IL-10 and mutations among MM patients.

Funding

This work was supported by a grant provided from the Mazandaran University of medical sciences, Sari, Iran (2015-2016)

Conflict of interests

There is no conflict of interests. All the authors have read and approved the final version of the manuscript.

Acknowledgements

The authors would like to acknowledge Tooba Clinic and Imam Hospital at the Mazandaran University of Medical Sciences for samples collection and technical supports.

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