

Interleukin-10: A Potential Prognostic Marker in Patients with Newly Diagnosed Multiple Myeloma

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Abstract

Background: Identification of high-risk patients with multiple myeloma (MM) is important for improving treatment outcomes. Efforts to identify significant prognostic markers are unremitting. Angiogenesis plays an important mechanism in the progression of MM. One of the mediators of this angiogenic process is interleukin-10 (IL-10).

Aim: To assess the role of IL-10 as a prognostic marker in MM.

Methods: This was a cross-sectional study that included 39 newly diagnosed patients with MM. Serum IL-10 level was measured using Magnetic Luminex® Assay multiplex. The relationship between IL-10 and tumor stage and other known prognostic markers in MM was studied.

Results: The median (interquartile range) value of IL-10 was 3 (2.9 – 3.2) pg/mL. Interleukin-10 level differed significantly according to the revised International Staging System stage of MM, being higher in higher stages. The median (interquartile range) IL-10 level was 2.89 (2.79 – 2.95) pg/mL in stage I, 3 (2.9 – 3.1) in stage II and 3.2 (3.1 – 3.66) in stage III ($p = 0.0009$). In addition, higher IL-10 significantly correlated with lower hemoglobin ($p = 0.002$), lower albumin ($p = 0.045$), higher creatinine ($p = 0.009$), higher β 2-microglobulin ($p = 0.002$), higher lactate dehydrogenase ($p = 0.0007$) and higher bone marrow plasma cell percentage ($p = 0.015$).

Conclusion: The results support a prognostic role of IL-10 in MM and its pathogenesis.

Keywords: Cytokines, Interleukin-10, Multiple myeloma, Prognosis., Tumor burden.

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Introduction

Multiple myeloma (MM) is a neoplasm of clonal plasma cells that originate from the post-germinal lymphoid B-cell lineage¹. It is the second most frequent hematological malignancy after lymphoma and remains largely incurable disease.

Multiple bone marrow microenvironmental changes are involved in the development and progression of MM, as the support provided by the immune microenvironment changes to myeloma cells is crucial for their survival²⁻⁴.

Interleukin-10 (IL-10) is an immune-regulatory cytokine produced by many cells including macrophages, T-lymphocytes, and natural killer

cells. Its role in cancer development is still controversial. It may promote tumor cell proliferation and metastasis via its immunosuppression functions⁵. Its anti-tumour effect may be due to the stimulation of natural killer and cytotoxic T-lymphocytes mediated killing of cancer cells⁶. Research is still required to evaluate the role of IL-10 in the tumorigenesis of MM. In addition, the prognostic role of IL-10 in MM has been suggested. A high level of IL-10 was found to correlate significantly with higher MM stage and β 2-microglobulin level⁷.

Our aim was to study the relationship between IL-10 level and other prognostic markers in MM.

Methods

This study was an observational cross-sectional study. It included 39 patients with newly diagnosed MM who presented to the Medical Oncology Department - South Egypt Cancer Institute and the Clinical Hematology Unit - Internal Medicine Department, Assiut University from July 2017 to July 2020.

All patients were proven to have MM according to the International Myeloma Working Group Criteria for the diagnosis of MM and Related Plasma Cell Disorders⁸.

All patients were diagnosed and evaluated at the outpatient clinic of the concerned department. They were subjected to full history taking, clinical examination and laboratory investigations. The laboratory investigations included complete blood picture (using Cell-Dyn Ruby, Abbott Diagnostics, USA), serum chemistry (creatinine, calcium, albumin, lactate dehydrogenase and β 2-microglobulin, using COBAS Integra 400 Plus, Roche, Switzerland), serum protein electrophoresis and immunofixation (using Pretty Interlab, Interlab, Italy) as well as bone marrow aspiration and trephine biopsies. Interphase fluorescence in situ hybridization (FISH) was performed to stratify the risk of the disease. The disease was staged according to the revised International Staging System (R-ISS).

Serum samples were collected from patients before starting anti-myeloma therapy using a serum separator tube and stored at -20 °C for further evaluation. Serum concentration of IL-10 was evaluated according to the manufacturer's instructions using Magnetic Luminex® Assay multiplex kits (Human Premixed Multi-Analyte Kit, R&D Systems, Bio-Techne, Minneapolis, USA).

Statistical analysis

Continuous data were presented as mean and standard deviation (SD) or median and range, while categorical data as frequency and percentage. For abnormally-distributed quantitative data, comparison between two groups was done using Mann-Whitney and between more than two groups by Kruskal Wallis test. Correlations were assessed using the Spearman's rank correlation coefficient.

Data analysis was done using the IBM Statistical Package for Social Science (SPSS) for Windows, Version 21.0. (Armonk, NY: IBM Corp).

Ethical considerations

The study was approved by the Institutional Review Board of the South Egypt Cancer Institute, Assiut University (approval No: 380).

An informed written consent was taken from all patients and controls.

Results

The demographic and clinical characteristics of patients are summarized in Table 1. Two-thirds were males and their mean age was 58 (\pm 8.8) years.

Table 1: Demographic and clinical characteristics of 39 patients with multiple myeloma

Variable	Description	
Age (years)	Mean (SD)	58.3 (8.8)
Sex		
Male	n (%)	29 (74.4)
Female	n (%)	10 (25.6)
R-ISS stage		
I	n (%)	8 (20.5)
II	n (%)	17 (43.5)
III	n (%)	14 (36)
Bone marrow plasma cells (%)	Median (IQR)	30 (10-90)
Monoclonal protein type		
IgG	n (%)	38 (97.4)
IgA	n (%)	1 (2.6)
Light chain type		
Lambda	n (%)	30 (76.9)
Kappa	n (%)	9 (23.1)
Osteolytic lesion		
Yes	n (%)	35 (89.7)
No	n (%)	4 (10.3)
Calcium (mg/dL)	Mean (SD)	10.1 (1.3)
Hemoglobin (g/dL)	Mean (SD)	9.9 (2.5)
Albumin (gm/dL)	Median (IQR)	33.2 (16-45)
Creatinine (mg/dL)	Median (IQR)	1 (0.3-12.)
Lactate dehydrogenase (U/L)	Median (IQR)	350 (105-777)
β2-microglobulin (mg/l)	Median (IQR)	5 (1.2-15.6)
IL10 (pg/mL)	Median (IQR)	3 (2.9 – 3.2)

SD: Standard deviation; **IQR:** Interquartile range, **R-ISS:** Revised International Staging System

The correlation between IL-10 level and the studied variables is detailed in Table 2.

Table 2: Correlation between interleukin-10 level and the studied variables

Variable	Interleukin-10 (pg/mL) Median (IQR)	<i>p</i> value
Sex		
Male	3 (2.9 – 3.2)	0.447
Female	3 (2.9 – 3.1)	
R-ISS stage		
I	2.89 (2.79 – 2.95)	0.0009
II	3 (2.9 – 3.1)	
III	3.2 (3.1 – 3.66)	
Light chain type		
Lambda	3.1 (2.89 – 3.2)	0.136
Kappa	2.9 (2.9 – 3)	
Osteolytic lesion		
Yes	3 (2.89 – 3.2)	0.78
No	3.1 (2.95 – 3.15)	
Calcium (mg/dL)		
≤12	3 (2.89 – 3.2)	0.198
>12	3.2 (2.9 – 48.37)	
Hemoglobin (g/dL)		
>10	2.95 (2.88 – 3)	0.002
8.5 – 10	3.05 (2.95 – 3.25)	
<8.5	3.2 (3.08 – 5.84)	
Albumin (gm/dL)		
≥3.5	2.99 (2.88 – 3.08)	0.0449
<3.5	3.11 (2.95 – 3.3)	
Creatinine (mg/dL)		
<2	3 (2.88 – 3.1)	0.009
≥2	3.2 (3.03 – 3.6)	
β2-microglobulin (mg/l)		
<3.5	2.9 (2.86 – 3.03)	0.002
3.5-<5.5	3 (2.89 – 3.06)	
≥5.5	3.2 (3.1 – 3.66)	
	Spearman's rho	<i>p</i> value
Age (years)	0.1	0.544
Lactate dehydrogenase (U/L)	0.522	0.0007
Bone marrow plasma cells (%)	0.387	0.015

IQR: Interquartile range, **R-ISS:** Revised International Staging System

The following variables significantly correlated with higher IL-10 level: higher R-ISS stage, lower hemoglobin level, lower albumin level, higher

creatinine level, higher β2-microglobulin level, higher lactate dehydrogenase level, and higher percentage of plasma cells in the bone marrow. Although IL-10 level was higher in patients with osteolytic lesions and a calcium level above 12 mg/dL, this was not statistically significant.

Discussion

The interaction of plasma cells with bone marrow microenvironment mediates myeloma disease progression⁹. Multiple myeloma remains largely an incurable disease despite the development of many therapeutic agents, such as bortezomib and lenalidomide. Failure to cure is multifactorial and can be attributed to the underlying genetic aberrations and to the surrounding microenvironment¹⁰.

Accurate identification of high-risk patients and risk stratification are very important in improving outcomes of MM patients. A large number of prognostic markers have been described, but none of them completely explains the heterogeneity seen in this tumor¹¹.

Interleukin-10 is an anti-inflammatory cytokine that plays a crucial role in the immune suppressive microenvironment in MM¹². It is involved in the terminal differentiation of B-cells into plasma cells and enhances its proliferation. Furthermore, it seems to enhance the proliferation of MM cells¹³.

Previous studies showed that IL-10 level is higher in patients with MM when compared with controls without MM^{12, 14, 15}. Wang et al¹² found that IL-10 serum concentration in their studied MM patients was much higher than in normal controls. Also, Alexandrakis et al¹⁴ reported that serum level of IL-10 was significantly higher in newly diagnosed MM patients compared to healthy controls and its level was significantly related to high ISS stage. A similar finding was reported by Aref et al¹⁵.

Our study showed a significantly higher serum levels of IL-10 in MM patients with advanced ISS stages and this falls in line with previous studies¹⁴.

In addition to the strong association between IL-10 level and stage found in this study, IL-10 level positively correlated with other individual prognostic markers of MM, such as serum β2-microglobulin and bone marrow plasma cells percentage. This is in agreement with Shekarriz et al¹¹ who demonstrated that there was a significant correlation between elevated IL-10 levels and serum β2-microglobulin concentration and a trend for a positive correlation between the IL-10 level and

bone marrow plasma cells percentage. Wang et al ¹² also found that the serum level of IL-10 was significantly higher in patients with higher bone marrow plasma cells percentage, as well as those with elevated serum β 2-microglobulin and lactate dehydrogenase levels. Similarly, Gu et al ¹⁶ reported that serum IL-10 level showed significant positive correlations with lactate dehydrogenase and serum β 2-microglobulin concentrations. This further confirms the possible prognostic role of IL-10 in MM.

In addition to IL-10, the prognostic role of other cytokines, like IL-6 and IL-17A, in MM has been recently suggested ¹⁶. More research is needed to confirm the prognostic value of IL-10 and other cytokines and to study the value of incorporating them into the current staging systems.

Conclusion

The results of this study confirm the association between higher IL-10 level and advanced stage and other prognostic markers in patients with MM. The incorporation of IL-10 in risk stratification of MM may be considered. Further studies with larger sample and outcome evaluation are needed to validate its prognostic role.

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Authors' contribution

Conception or design: DAM, SMK, RB; Acquisition, analysis or interpretation of data: DAM, SMK, MGME, RB; Drafting the manuscript: DAM, SMK, MRA, RB; Revising the manuscript: MGME; Approval of the manuscript version to be published: All authors; Agreement to be accountable for all aspects of the work: All authors.

Conflict of interest

The authors declare that they have no conflict of interest to disclose.

Data availability

Deidentified individual participant data used to produce the results of this study are available from the corresponding author (SMK) upon request.

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Study registration

None.

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