PROGNOSTIC VALUE OF INFLAMMATORY FACTORS IN EXTRAMEDULLARY MULTIPLE MYELOMA

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INTRODUCTION

The improvement in survival statistics of multiple myeloma might be associated with an increasing incidence of extramedullary disease (EMD), which remains a major clinical challenge. There is no consensus on the management of the disease, and its pathobiology is not fully understood. High-risk cytogenetic abnormalities, an inflammatory microenvironment in the bone marrow (Fig.1.), increased migration, and downregulation of adhesion molecules all lead to increased epithelial-mesenchymal transition (EMT), resulting in disease progression and tumor dissemination. Certain cytokines are known to be poor prognostic markers in myeloma. Our research group found that decreased PACAP levels also indicate poor prognosis (Fig.2.), but the relationship of EMD and various factors remains unknown.

AIM

The aim of our studies was to investigate inflammatory factors (IFN-γ, IL-1β, IL-2, IL-3, IL-6, IL-8, IL-9, IL-10, IL-17A, MCP-1, MIP-1α, TGF-α, TNF-α) and particularly PACAP (Fig.3.) in blood samples from MM patients (n=73) with (n=25) or without (n=48) EMD to determine the prognostic role of these factors.

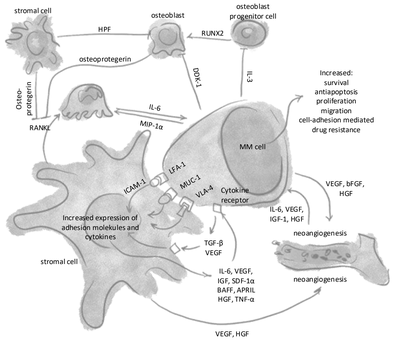


Figure 1. The bone marrow microenvironment in multiple myeloma

METHOD

The study was performed at the Divison of Hematology, 1st Department of Internal Medicine, University of Pécs. Patients were followed from July 2019 to January 2024. The cohort was population-based. Exclusion criteria included acute infectious diseases. The study had two main outcomes during follow-up: progression and death from the disease. Factors were measured with ELISA and Luminex. The measurements were performed at the Department of Anatomy and the Department of Pharmacology and Pharmacotherapy of the University of Pécs. Statistical analysis was performed using independent sample t-test, Mann-Whitney test, and Spearman correlation analysis.

RESULTS

Our preliminary results showed that patients with EMD had higher levels of IFN-γ,IL-8,IL-10,MCP-1 and PACAP, while TGF-α was found to be lower compared to patients without EMD (Fig.4.). PACAP and IFN-γ showed a positive correlation with progression-free survival; whereas a negative correlation was detected for IL-6,-9,-10,MCP-1 and MIP-1α. IFN-γ showed a positive correlation with overall survival, while IL-9 and -10 showed a negative correlation (Fig.5.).

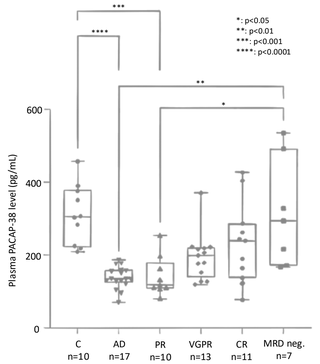


Figure 2. The plasma PACAP-38 levels in relation to the depth of therapeutic response. AD: active disease, PR: partial response, VGPR: very good partial response, CR: complete response, MRD neg: measurable residual disease negativity.

	General function and role in multiple myeloma
IFN-γ	Proinflammatory, increased
IL-2	Proinflammatory, receptor elevation is poor prognostic factor
IL-3	Proinflammatory, osteoblast inhibition, tumor cell growth
IL-6	Proinflammatory, elevated , proliferation, adhesion, tumorgenesis
IL-8	Proinflammatory, osteoclastogenesis, angiogenesis, survival
IL-9	Anti-inflammatory, increased
IL-10	Anti-inflammatory, increased, tumorgenesis, angiogenesis
IL-17A	Proinflammatory, proliferation, migration, survival
MCP-1	Proinflammatory, angiogenesis, homing, migration
MIP-1α	Proinflammatory, proliferation, osteoclastogenesis, increased
PACAP	Anti-inflammatory, decrease is poor prognostic factor
TGF- α	Pro- and anti-inflammatory, elevation is poor prognostic factor
TNF- α	Proinflammatory, tumorgenesis, migration, proliferation

Figure 3. General function and role of the inflammatory factors

	Elevated in EMD	Decreased in EMD
IFN-γ	Elevated, p=0.035	-
IL-2	-	-
IL-3	-	-
IL-6	-	-
IL-8	Elevated, p=0.048	-
IL-9	-	-
IL-10	-	-
IL-17A	-	-
MCP-1	Elevated, p=0.038	-
MIP-1α	-	-
PACAP	Elevated, n=0.043	-
TGF- α	-	Decreased, p=0.036
TNF- α	-	-

Figure 4. Elevation and decrease the inflammatory factors in EMD

	Overall survival (OS)	Progression-free survival (PFS)
IFN-γ	**p=0.03, r=0.76, n=12**	**p=0.04, r=0.64, n=12**
IL-2	p=0.33, r=-1.00, n=6	p=0.99, r=-0.50, n=6
IL-3	p=0.99, r=-0.50, n=5	p=0.33, r=-1.00, n=5
IL-6	p=0.85, r=0.05, n=17	**p=0.03, r=-0.61, n=17**
IL-8	p=0.73, r=-0.21, n=6	p=0.99, r=0.03, n=6
IL-9	**p=0.04, r=-0.60, n=10**	**p=0.01, r=-0.74, n=10**
IL-10	**p=0.03, r=-0.56, n=12**	**p=0.04, r=-0.58, n=12**
IL-17A	p=0.91, r=0.05, n=7	p=0.89, r=0.06, n=7
MCP-1	p=0.38, r=-0.46, n=6	**p=0.03, r=-0.77, n=6**
MIP-1α	p=0.92, r=0.04, n=11	**p=0.02, r=-0.70, n=11**
PACAP	p=0.68, r=-0.12, n=13	**p=0.04, r=0.57, n=13**
TGF-α	p=0.63, r=-0.36, n=10	p=0.38, r=-0.52, n=10
TNF-α	p=0.37, r=0.28, n=10	p=0.70, r=-0.14, n=10

Figure 5. Correlation between different factors and survival.

CONCLUSIONS

In conclusion, several inflammatory factors are thought to play a role in MM tumor dissemination and they have prognostic significance. Thus, the incorporation of these inflammatory markers into prognostic nomograms should be considered.

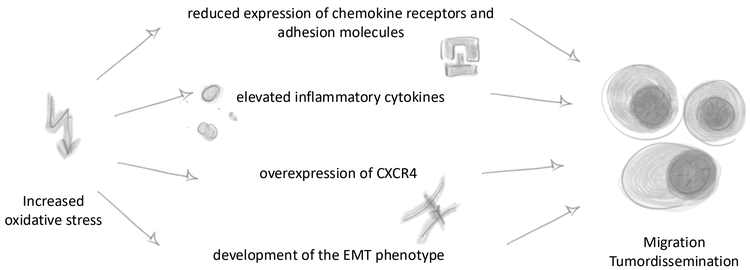


Figure 6. The role of the oxidative stress in tumordissemination

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