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Research Article

Serum Soluble Programme Death-1 and Programme Death-Ligand 1 Identify Multiple Myeloma Patients: Serum sPDL-1 May Be a Prognostic Marker

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Abstract

Objectives: Multiple myeloma (MM) is a plasma cell malignancy that still remains incurable. Programmed cell death(PD)-1 and programmed cell death ligand (PDL-1) pathway are immune checkpoint molecules. They play a role in the immune escape of tumor cells.

Methods: We measured serum soluble PD-1(sPD-1) and soluble PDL-1 (sPDL1) in 24 newly dignosed patients and 22 healthy controls (HC).

Results: We determined significantly increased serum sPDL-1 levels in MM patients when compared to HC. Moreover, sPDL-1 levels correlated positively with a p53 positive mutation status, elevated lactate dehydrogenase, C-reactive protein, calcium levels and poor performance status. A significant difference is detected between sPDL-1 level and PFS; but not OS. The sPDL-1 cut-off value for predicting survival outcomes was 1.03 ng/mL that was detected median value in MM patients. Patients with high serum sPDL-1 level were associated with a significantly decreased progression free survival ($p<0.045$).

Conclusion: We conclude that sPDL-1 level is a probable prognostic biomarker for a poor outcome in MM patients. PD-1/PDL-1 pathway blockage may be one of the new strategies for MM patients. However, there is still a need for future studies enrolling more patients in order to clarify the prognostic significance of PDL-1.

Keywords: Immune checkpoint, multiple myeloma, programmed cell death (pd)-1, programmed cell death ligand (pdl-1), survival outcomes

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Multiple myeloma (MM) is a malignant disease characterized by the clonal proliferation of plasma cells in bone marrow.[1] The treatment of MM has changed with the improvement of novel treatment modalities.[2, 3] Although there are various studies and treatment modalities in MM, unfortunately MM still remains incurable due to the character of disease as it relapses sooner or later. The tumor microenvironment is important in MM pathogenesis. Tumor microenvironmental changes that interact with myeloma cells support tumor growth, angiogenesis and drug resistance.[4, 5] PD-1 /PDL-1 pathway may play a role in tumor microenvironment in MM.

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It is suggested that there is a complex interaction between the tumor cells and immune system. T cells can hamper tumor devolepment or progression.[6, 7] On the other hand, tumor cells can oppose immune attack by down-regulating tumor-specific T cells and by expressing ligands that bind inhibitory receptors such as immune checkpoints. Tumors can result in deregulation of the immune-checkpoint proteins such as CTLA-4, programmed cell death (PD-1) and programmed cell death ligand (PDL-1) which causes an important mechanism of tumor immunoresistance.[6, 8]

PD-1, also known as CD279 is a co-inhibitory receptor that inhibits T-cell proliferation and activation. PD-1 is expressed on activated T cells ,B cells and myeloid lineage cells. PD-1 binds two ligands, PDL-1 (CD 274) and PDL-2 (CD 273). PDL-1 is expressed on regulatory T-cells (Tregs), B cells, activated CD4+ and CD8+ T cells, natural killer (NK) cells, dentritic cells and macrophages and up-regulated upon activation cytokines especially IFNγ.[6, 9-11]

PD1/PDL-1 pathway delivers a negative signal and inhibits the proliferation, survival and effector function including cytokine production of T-cells.

In physiological conditions, PD-1/PDL-1 signaling pathway are critical for maintaining self-tolerance and it protects against autoimmune diseases.[6, 7, 12] The expression of PD-1/PDL-1 on tumor cells and tumor microenvironment is increased in various hematological and solid malignancies.[9, 13-15] This increment causes T cell inhibition and tumor cells evade the immune system. In recent studies, it is shown that increased PDL-1 expression is associated with poor prognosis in various malignancies.[16-18] Thus; PD-1/PDL-1 pathway inhibitors can be used for the treatment of malignant tumors.

Studies revealed that the level of circulating soluble PDL-1(sPDL-1) is elevated and relevant to prognosis in cancer patients.[19, 20] PD-1 and/or PDL-1 is expressed on myeloma cells and/or in tumor microenvironment associated cells especially T-cells.[21, 22]

Until now, there is only one study in the literature demonstrating sPDL-1 level and their prognostic value in MM patients. There has been no data sPD-1 level in MM patients. We decided to conduct this study to investigate sPD-1 and sPDL-1 levels in MM patients and to elucidate their value in predicting survival outcomes.

Methods

Patients

Twenty-four new-diagnosed MM patients who were diagnosed and treated in our Hematology Department between June 2013 and April 2015 and 22 healthy controls (HC) were enrolled to this study. All the control subjects were matched with the population of the patients' group in terms of age and sex. The research protocol was approved by the Research Ethics Committee of Kocaeli University. From all participants, informed consent was obtained in writing, and all procedures were in accordance with the 1964 Helsinki Declaration. The patients were diagnosed MM according to the International Myeloma Working Group Criteria.[23] Data on sex, age, complete blood count and laboratory results including lactate dehydrogenase (LDH); C-reactive protein (CRP); albumin, creatinine (Cr) and calcium (Ca) were registered at the enrollement time of this study in MM patients and HC. Moreover, data about disease characteristics and treatment protocols of MM patients were also collected. Patients were categorized according to International Staging System (ISS).[24]

Five out of 24 patients couldn't have cytogenetic evaluation. The Multiple Myeloma fluorescence in situ hybridization (FISH) panel was studied from bone marrow samples of 19 patients. The Multiple Myeloma FISH panel included: TP53 locus-specific probe, to detect deletion of TP53 (17p13.1) and eletions of chromosome 13q (del13q) identified by interphase FISH.

Patients' performance status were classified according to Eastern Cooperative Oncology Group (ECOG) score. Albumin and B-2 microglobulin(B-2 M) levels' cut-off are designated as 3.5 according to ISS (3.5 gr/dL, 3.5 mg/L; respectively). LDH and CRP levels are designated normal or elevated according to our laboratory cut-off values (upper normal limit). The control group consisted of HC who were admitted to the internal medicine outpatient clinic but none of them had any hematological disease or any cancer. Blood samples were collected at the time of diagnosis from all MM patients, before the initiation of any treatment. Blood samples were collected from the patients, and the controls and the sera were stored at -80 ºC. Serum sPD-1 and sPDL-1 levels were measured using a commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kits (PDCD1 and PDCDL1, USCN Life Science, China, respectively) according to the manufacturer's instructions. The minimum detectable concentration of sPDL-1 and sPD-1 were 0.117 and 0.059 ng/mL, respectively. Each sample was measured in duplicate. The intra-assay and inter-assay variations were below 20%.

Treatment and Response Evaluation

According to our governments health insurance policy; the patients over 65years-old are treated with bortezomib-based regimens, in contrast to the patients below

65 years-old who are treated firstly with 2 cycles VAD (vincristine, adriamycin and dexamethasone) and then bortezomib-based regimens. Transplant eligible patients are treated with autologous hematopoetic stem cell transplantation after 4 or 6 cycles of treatment. Treatment responses were evaluated according to the International Myeloma Working Group (IMWG) criteria.[25] For this reason, 14 of 24 patients had to start 2 cycles of VAD in the first line therapy. Two patients could not receive bortezomib-based treatment. One of the patients who did not receive bortezomib died of myeloma complication during VAD chemotherapy. In the other patient, the patient's first-line treatment was completed with VAD because a dose of bortezomib resulted in heart failure. All the remaining 22 patients were received bortezomib 1.3 mg/m^2 1, 4, 8, 11 day, cyclophosphamide 500mg/weekly and dexamethasone 20 or 40 mg/1, 4, 8, 11.

Statistical Analysis

Statistical analyses were performed with SPSS version 21 (SPSS Inc, IBM, USA). The variables were not normally distributed, non-parametric methods were used for analyses. Median values of each parameters were reported with minimum-maximum values. The Kruskal-Wallis test was used for multi-group analyses. The Mann Whitney U test was utilized to compare non-parametric variables between the two groups. The correlation coefficients between different parameters was calculated by using the Spearman correlation. sPDL-1 cut-off value was determined as median sPDL-1 value in MM patients (1.03 ng/mL). Survival durations were calculated via the Kaplan-Meier method. The log-rank test was employed to compare cumulative survival in the patient groups. All statistical analysis were two sided and significance was defined as p<0.05.

Results

Patient Outcomes

A total of 24 patients (10 female, 14 male; median age 61 years) and 22 HC (10 female, 12 male; median age 58 years) were enrolled to this study; patients' and HC' clinical characteristics are shown in Table 1.

The majority of the patients (14 cases, 58.3%) were classified as ISS-3, and 4 and 6 patients (16.7% and 25%) were classified as ISS-1 and 2 at diagnosis, respectively.

Five out of 24 patients couldn't have cytogenetic evaluation. We couldn't determine treatment response in 2 patients who died due to complications of MM before the assessment of treatment response. Sixteen out of 22 patients (72.2%) were in complete remission or very good partial remission (CR/VGPR) after the completion of the first line treatment. Fifteen out of 24 (62.5%) received autologous stem cell transplantation (SCT) after achieving at least partial response after treatment. Twelve patients (50%) had relapsed during a median follow-up time of 32 months.

Serum sPD-L1 and serum sPD-1 Levels and Correlation with Cinical Features

The serum sPDL-1 level in MM patients was (1.03 ng/mL (range 0.55-2.75)) significantly higher than serum sPDL1 level (0.48 ng/mL; range: 0.19-0.68) in the HC (p=<0.001) (Fig. 1). However, the serum sPD-1 level of MM patients (0.18 ng/mL; range: 0.16-0.21) and HC (0.19 ng/mL; range: 0.16-0.28) was not significantly different (p=0.056).

Serum sPDL-1 level of patients with ECOG>2 and with p53 mutation were significantly increased when compared to patients with ECOG 0-2 and without p53 mutation (p<0.021; p<0.02 respectively). Additionally, serum sPDL-1 level was significantly elevated in the patients who have Ca>11 mg/dL and also who have CRP and LDH levels higher than normal (p<0.01; p<0.01 and p<0.01, respectively) (Table 2).

When serum sPD-1 levels are concerned, serum sPD-1 levels of patients with Cr>1.2 mg/dl, Ca>11mg/dl, and B2 M >3.5 were significantly elevated (p<0.02; p<0.03 and p<0.01, respectively) (Table 2).

There was a positive correlation between sPDL-1 level and Ca, LDH and CRP level in MM patients. Likewise, there was a positive correlation between sPD-1 level and B-2 M level,

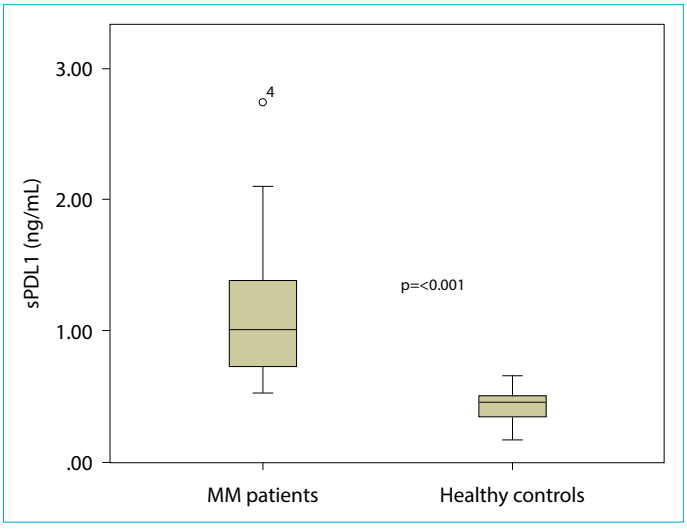

Figure 1. Serum sPDL-1 level in MM patients and healthy controls. The median serum sPDL-1 concentration in MM patients was 1.03 ng/mL (range 0.55-2.75) that was significantly higher than serum sPDL1-concentration (0.48 ng/mL; range: 0.19-0.68) in the healthy controls (p=<0.001).

Table 1. Characteristics of MM patients and healthy controls

	MM	HC	p
N	24	22	
Age, median(range)	61 (44-77)	58 (40-74)	0.08
Gender (%)			
Female	10 (41.7)	10 (45.5%)	0.79
Male	14 (58.3)	12 (54.5%)	
Type			
IgG kappa	9 (37.5)		
IgG lambda	3 (12.5)		
IgA kappa	4 (16.7)		
Kappa	4 (16.7)		
Lambda	4 (16.7)		
ECOG PS score			
0-2	15 (62.5)		
>2	9 (37.5)		
ISS			
1	4 (16.7)		
2	6 (25)		
3	14 (58.3)		
Hb (g/dl), median (range)	9.5 (7.33-15.4)	14.1 (12.5-15.1)	0.001
WBC (x106/L), median (range)	6205 (3200-18800)	6700 (5040-9800)	0.55
Lymphocyte (x106/L), median (range)	2095 (990-5030)	2340 (1180-4400)	0.56
PLT (x109/L), median (range)	214 (107-394)	240 (171-362)	0.72
Creatinine (mg/dL), median (range)	0.95 (0.48-8.48)	0.8 (0.59-0.97)	0.006
Calcium (mg/dL), median (range)	9.75 (8.5-13)	9.2 (8.9-9.9)	0.017
Albumin (gr/dL), median (range)	3.15 (2-4.5)	4.38 (3.9-4.8)	0.001
B-2 M median (mg/L) media (range)	8.4 (1.9-25.3)		
CRP (mg/dL), median (range)	0.92 (0-7.55)	0.15 (0.02-1)	0.001
LDH (U/L) median (range)	173 (73-520)	184 (125-222)	0.55
ESR	43 (10-126)	10 (2-22)	0.001
Bone Lesion (%)			
Lytic	14 (58.3)		
Plasmocytoma	6 (25)		
No bone lesion	4 (16.7)		
Response to 1st line therapy			
CR	2 (8.3)		
VGPR	14 (58.3)		
PR	5 (20.8)		
PD	1 (4.2)		
NA	2 (8.3)		
HSCT			
Yes	15 (62.5)		
No	9 (37.5)		
Relapse Patients	12 (50)		
After HSCT	7 (58.4)		
After conventional therapy	5 (41.6)		

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group performance status; ISS: International Staging System ; Hb: Hemoglobin; WBC: White blood count; PLT: Platelet; B-2 M: Beta-2 microglobulin; CRP: C-reactive protein; LDH: lactate dehydrogenase; ESR: erythrocyte sedimentation rate; CR: complete remission; VGPR: very good partial remission; PR: partial remission; PD: progressive disease; NA: not applicable ; HSCT: hematopoetic stem cell transplantation.

Table 2. sPD-1and sPDL-1 levels of patients grouped with different characteristics

Characteristics	n (%)	sPDL-1 (ng/mL) Median (min-max)	p	sPD-1 (ng/mL) Median (min-max)	p
Gender					
Female	10 (41.7)	1.11 (0.59-2.11)	0.84	0.18 (0.16-0.19)	0.97
Male	14 (58.3)	0.89 (0.55-2.75)		0.18 (0.16-0.21)	
ECOG PS score					
0-2	15 (62.5)	0.83 (0.55-1.67)	**0.021**	0.17 (0.16-0.19)	0.06
>2	9 (37.5)	1.13 (0.83-2.75)		0.18 (0.16-0.21)	
Light Chain					
kappa	17 (70.8)	1.08 (0.55-2.11)	0.85	0.18 (0.16-0.21)	0.95
lambda	7 (29.1)	0.98 (0.69-2.75)		0.18 (0.17-0.18)	
Chain Type					
Heavy+Light	16 (66.6)	0.98 (0.55-2.11)	0.49	0.17 (0.16-0.19)	**0.02**
Only Light	8 (33.4)	1.05 (0.74-2.75)		0.18 (0.18-0.21)	
Creatinine(mg/dL)					
<1.2	14 (58.3)	0.86 (0.55-2.11)	0.108	0.17 (0.16-0.19)	**0.02**
≥1.2	10 (41.7)	1.18 (0.75-2.75)		0.18 (0.17-0.21)	
Calcium(mg/dL)					
<11	17 (70.8)	0.88 (0.55-1.78)	**0.01**	0.17 (0.16-0.19)	**0.03**
≥11	7 (29.1)	1.31 (0.83-2.75)		0.18 (0.18-0.21)	
Albumin(gr/dL)					
<3.5	13 (54.1)	1.23 (0.55-2.75)	0.08	0.18 (0.16-0.21)	0.16
≥3.5	11 (45.9)	0.83 (0.59-1.78)		0.17 (0.16-0.19)	
B-2 M(mg/dL)					
<3.5	5 (20.9)	0.88 (0.59-1.78)	0.48	0.16 (0.16-0.18)	**0.01**
≥3.5	19 (79.1)	1.08 (0.55-2.75)		0.18 (0.17-0.21)	
CRP					
Normal	9 (37.5)	0.75 (0.55-2.11)	**0.01**	0.17 (0.16-0.19)	0.21
Elevated	15 (62.5)	1.23 (0.69-2.75)		0.18 (0.16-0.21)	
LDH(U/L)					
Normal	15 (62.5)	0.83 (0.55-1.78)	**0.01**	0.17 (0.16-0.21)	0.41
Elevated	9 (37.5)	1.24 (0.83-2.75)		0.18 (0.16-0.19)	
Bone lesion					
Yes	20 (83.3)	0.64(0.59-1.48)	0.11	0.18 (0.16-0.21)	0.57
No	4 (16.7)	1.1 (0.55-2.75)		0.17 (0.17-0.19)	
P53 mutation					
Yes	4 (28.6)	1.71 (0.98-2.75)	**0.02**	0.17 (0.16-0.19)	0.46
No	15 (71.4)	0.83 (0.55-1.78)		0.18 (0.18-0.18)	
13q mutation					
Yes	3 (15.8)	0.89 (0.55-2.75)	0.55	0.18 (0.16-0.19)	0.63
No	16 (84.2)	1.13 (0.74-2.11)		0.18 (0.16-0.18)	
ISS					
ISS 1-2	10 (41.6)	0.59 (0.59-2.11)	0.88	0.17 (0.16-0.19)	**0.01**
ISS 3	14 (58.4)	1.03 (0.55-2.75)		0.18 (0.17-0.21)	
1st line therapy response					
CR, VGPR	16 (72.2)	0.99 (0.55-1.78)	0.54	0.18 (0.16-0.19)	0.69
PR, PD	6 (27.8)	1.05 (0.59-2.75)		0.18 (0.17-0.21)	
Relapse					
Yes	12 (50)	1.03 (0.55-2.75)	0.79	0.18 (0.16-0.19)	0.21
No	12 (50)	1.01 (0.59-2.11)		0.18 (0.16-0.21)	
Survival					
Yes	14 (58.3)	0.89 (0.55-1.78)	0.19	0.17 (0.16-0.19)	0.056
No	10 (41.7)	1.1 (0.74-2.75)		0.18 (0.17-0.21)	

Abbreviations: sPD-1: soluble programmed death cell-1; sPDL-1: soluble programmed death cell ligand-1; ECOG PS: Eastern Cooperative Oncology Group performance status; B-2 M: Beta-2 microglobulin; CRP: C-reactive protein; LDH: lactate dehydrogenase; ISS: International Staging System ; CR: complete remission; VGPR: very good partial remission; PR: partial remission; PD: progressive disease.

Table 3. Correlation of sPD-L1 and sPDL-1 level with clinicopathological features in MM patients

	Serum sPDL-1 p	Serum sPD-1 p
Age	0.84	0.543
Leukocyte	0.38	0.835
Lymphocyte	0.53	0.192
HB	0.35	0.195
HTC	0.44	0.170
PLT	0.46	0.901
Cr	0.29	0.157
Ca	**0.01 (R:0.490)**	0.161
Albumin	0.11	**0.03 (R:-435)**
B2-M	0.75	**0.01 (R:474)**
CRP	**0.03 (R:480)**	0.105
LDH	**0.001 (R:684)**	0.95
ESR	0.171	0.135
Kappa light chain	0.344	0.895
Lambda light chain	0.598	0.586
BM plasma cell (%)	0.559	**0.04 (R:0.413)**

bone marrow plasma cell percentage. There was a negative correlation between sPD-1 level and albumin level (Table 3). Furthermore, we detected a positive correlation between sPDL-1 levels and age only in HC.

Survival Analysis

We used median sPDL-1 value in MM patients to determine a cut-off value for serum sPDL-1 level; the cut-off value was 1,03 ng/mL. The median follow-up time was 32 months (range 2–51 months). Twelve patients relapsed at a median of 32 months (range 2-51 months) and 9 patients died at a median of 33 months (range 2–52 months).

The 3- year progression free survival (PFS) of patients with high sPDL-1 level (>1.03 ng/mL) was significantly decreased in comparison to patients with low sPDL-1 level (<1.03 ng/mL) (19% vs 63%, p=0.045) (Fig. 2). Although, the 3-year OS of patients with high sPDL-1 level (>1.03 ng/mL) was also less than patients with low sPDL-1 level (<1.03 ng/mL), it was not statistically significant (53% vs 70%, p=0.179) (Fig. 3).

Discussion

In this study, we found that while serum sPDL-1 levels were higher in MM patients compared to HC, sPD1 levels were not significantly different between MM patients and HC. There was no correlation between sPD-1 level and treatment response, relapse and survival. However, when sPDL-1 levels are concerned, while no relation between sPDL-1 level and treatment response or overall survival was detected, high sPDL-1 levels were related to decreased progression-free survival (p=0.045).

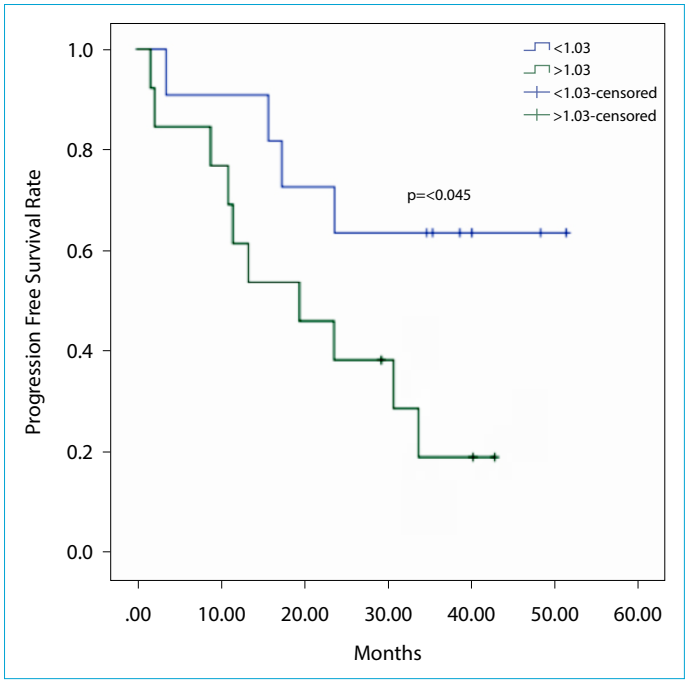

Figure 2. PFS analysis in MM patients. Serum high PDL-1 level >1.03 ng/mL was associated with shorter PFS (p=0.045).

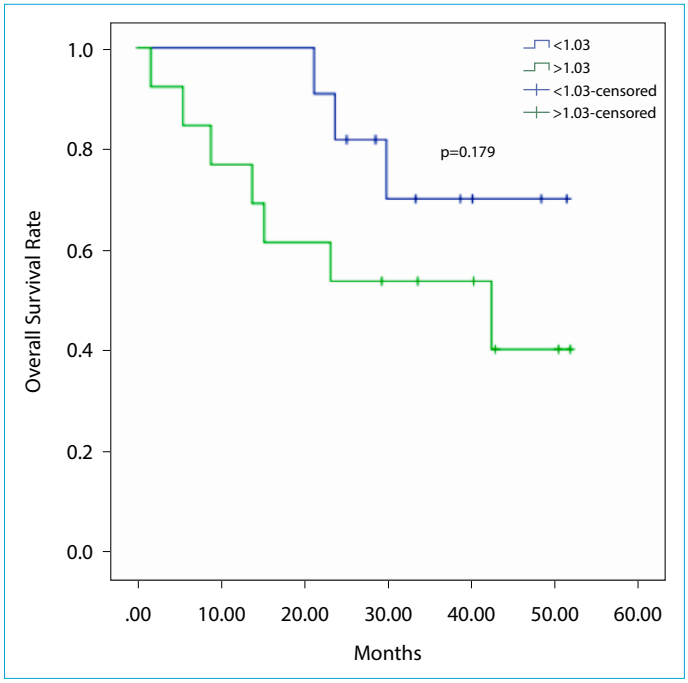

Figure 3. Survival analysis in MM patients. Serum high PDL-1 level >1.03 ng/mL was associated with shorter OS (p=0.179).

Recently, it is found that PD-1 or/and PDL-1 expression is increased on both the tumor cells and tumor- infiltrating T-cells (TILs) localized in tumor microenvironment in the hematologic malignancies. For this reason, the treatment strategies targeting PD-1/PDL-1 pathway blockage (anti-

PD1 or anti-PDL-1 monoclonal antibody) can enhance the anti-tumor immune response by proliferating TILs in the tumour microenvironment.[8, 14]

There are several studies showing that PDL-1 expression is increased in the plasma cells of MM patients by flow cytometry in contrast to plasma cells of HC' showing no expression of PDL-1.[21, 22, 26] Sponaas et al.[27] found that PDL-1 expression is increased on plasma cells and DCs in the MM patients.

Immunomodulatory drug lenalidomide targets the multiple myeloma cell directly, but also causes modulation of the tumor microenvironment and by this way it leads to induction of immune responses against myeloma cells. Several studies have reported that PDL-1 expression is decreased on multiple myeloma cells after lenalidomide incubation. [26, 28] With regard to these aforementioned data, it can be suggested that the PD-1/PDL-1 pathway is a potential therapeutic target in patients with MM.

Beside expression on cells, PD-1 and PDL-1 is also present in soluble forms. It is suggested that the soluble form of PDL-1 originates from the cleavage of membrane PDL-1 (mPDL-1) and thus sPDL-1 have the similar features with mPDL-1. sPDL-1 can bind PD-1 receptor similar to mPDL-1and may play a substantial role in the PD-1/PDL-1 pathway.[19, 29]

There are only a few studies demonstrating sPDL-1 and sPD-1 levels in hematological diseases. sPD-1 is studied especially on autoimmune and rheumatologic patients groups.[12, 30]

In this study, we found that sPD-1 level was not different in MM patients when compared to HC. It is known that Cr >1.2 mg/dl, Ca >11mg/dl, and B2 M >3.5 are associated with high tumor burden and poor survival outcomes in MM patients. In our study, sPD-1 levels of patients with Cr >1.2 mg/dl, Ca >11mg/dl, and B2 M >3.5 were significantly elevated. Additionally, a positive correlation was detected between sPD-1 level and B-2 M level, bone marrow plasma cell percentage. There was a negative correlation between sPD-1 level and albumin level. These outcomes revealed sPD-1 level may be associated with high tumor burden and agressive disease in MM. However, no significant relation could be detected between sPD-1 level and OS, PFS, treatment response. We think that this could be due to the small number of patients enrolled to this study.

sPDL-1 levels of healthy donors were investigated in a study, revealing a positive correlation between sPDL-1 and age. In the present study, we confirmed this result and demonstrated that sPDL-1 levels increase with age in HC in contrast to MM patients.[29]

There are only a small number of studies demonstrating sPDL-1 level in hematological malignancies. There is a study investigating sPDL-1 level in plasma of DLBCL patients and it revealed that patients with elevated sPD-L1 showed a poorer prognosis with a 3-year OS of 76% versus 89% (p=<0.001).[20]

There is just one another study investigating sPDL-1 levels in MM patients.[31] In this study, Wang et al described that sPDL-1 level in MM patients was higher than HC similar to our study. They also determined that there was a significant correlation between sPDL-1 level and disease progression but, there was no significant correlation between sPDL-1 level and ISS, LDH level, renal function, or treatment response. In the present study, we found that MM patients with elevated levels of Ca, CRP, LDH and those with positive p53 mutation have high sPDL-1 level. It is known that positivity p53 mutation (deletion of the 17p chrosomal region) is related to a poor outcome in MM.[32] These results showed that elevated sPDL-1 level is associated with agressive disease in MM patients. In the study conducted by Wang et al., high sPDL-1 level was found to be an independent prognostic factor for lower PFS, but not OS . Similar to this study, we found that MM patients who have high sPDL-1 level had lower PFS, but not OS. But we did not detect difference in terms of treatment response or OS.

Conclusion

We found that elevated sPD-1 and sPDL-1 levels is associated with aggressive disease characteristics and moreover MM patients with elevated sPDL-1 levels have low PFS. Moreover, serum sPDL-1 of MM patients have significantly increased sPDL-1 levels in comparison to HC and can be a potential diagnostic and prognostic tool in the future. PD-1/PDL-1 pathway may play a role in MM pathogenesis; in that case a new treatment strategy against PD-1/PDL-1 pathway may be concerned. Studies enrolling higher numbers of patients are needed.

Disclosures

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