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Role of Suppressed Immunoglobulins in Outcome of Patients With Multiple Myeloma

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Abstract

Introduction: Multiple myeloma (MM) is typically presented with abundant monoclonal secretion of one type of immunoglobulin. The other classes of immunoglobulins, which are uninvolved and not secreted by malignant plasma cells, could be decreased. A number of previous studies reported the effect of suppression of uninvolved immunoglobulins on the outcome of patients with myeloma. However, its effect in regard to the type of treatment was not studied so far. The current study aimed at investigating the effect of uninvolved immunoglobulins suppression on the outcome of patients with myeloma in each individual type of treatment.

Methods: In the current retrospective study, 140 myeloma cases diagnosed from 1999 to 2016 were studied. Patients were divided into 2 groups according to the first-line chemotherapy: 58 cases treated with Velcade-based and 81 cases with other agents. In the 2 groups, the effects of immunoglobulin suppression as well as other prognostic parameters on overall survival (OS) and progression-free survival (PFS) were evaluated.

Results: The effect of immunoglobulin suppression on patients' outcome depended on the type of treatment. In the Velcade group, suppression of at least 2 classes of immunoglobulins was significantly related to poorer survival in terms of both OS and PFS. In the non-velcade group, suppression of immunoglobulins showed no significant relationship with OS or PFS.

Conclusions: For cases treated with Velcade, suppression of 2 types of immunoglobulins was related to poorer outcomes. Based on the results of the current study, it seemsed that immunoglobulin suppression was a predictive factor rather than a prognostic one. More studies with a larger sample size should be conducted to assess the outcome of patients treated with Velcade and severely suppressed immunoglobulins.

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INTRODUCTION

Multiple myeloma (MM) is the 2 most common hematologic cancer. In 2016, MM was responsible for about 30,300 of new cancer cases and 12,600 deaths in the United States [1]. MM is mostly present with monoclonal secretion of one type of immunoglobulins, which is usually IgG, IgA, or light chain. This immunoglobulin is referred to as 'involved' immunoglobulin, while the rest Igs are called 'uninvolved'. On one hand, the involved immunoglobulin produced by malignant plasma cells increases significantly in patients. and on the other hand, uninvolved immunoglobulins secreted by normal plasma cells are suppressed as a result of decrease of non-malignant plasma cells in about 90% of the cases [2]. The effect of suppression of uninvolved isotypes on the outcome of cases was previously studied and there was controversy in the results of the former works. In some studies, it was related to poorer outcome [3-5] and in others it did not affect patients' outcomes [6, 7]. However, in previous studies the effect of treatment type on

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the outcome of cases was not evaluated concurrently. The current study aimed at assessing 3 commonly analyzed immunoglobulins including IgG, IgA, and IgM to examine the effect of their suppressed values on the outcome of MM cases. Furthermore, this effect of each subgroup of the front-line therapy was studied separately.

METHODS

One hundred and forty patients with MM referred to 501 (AJA) and Arad hospitals, Tehran, Iran, from 1999 to 2016 were enrolled in the current retrospective study. Age, gender, creatinine (Cr), blood urea nitrogen (BUN), platelet, hemoglobin, and white blood cell (WBC) count of the cases at the time of diagnosis were extracted from medical records. First, immunoglobulin tests before starting the chemotherapy were studied to obtain the IgG, IgA and IgM levels in the patients. Uninvolved immunoglobulins of the cases were studied and suppressed immunoglobulin were defined as concentrations of lower than 700, 70, and 40 mg/dL for IgG, IgA and IgM, respectively [3, 5]. The studied patients were treated front-line with VAD (vincristine, adriamycin and dexamethasone) therapy (n = 61), Mini-CHOP (cyclophosphamide, vincristine, adriamycin and dexamethasone) therapy (n = 15), Velcade-based (n = 58), other chemotherapy (n = 5), and 1 case received supportive care only. To study the effect of prognostic factors on each type of therapy, cases were categorized into 2 groups: Velcade-based chemotherapy (n = 58), and non-velcade chemotherapies (n = 81). Overall survival (OS) was calculated as the time period from the start of the first-line treatment to death from any causes. Progression free survival (PFS) was considered as time elapsed from the first-line treatment to relapse or death [8]. The data were analyzed with SPSS version 23. Survival rates were calculated based on the Kaplan-meier estimate and compared by the log-rank test. Univariate and multivariate analyses were performed by the Cox proportional hazards model. Variables with P-values less than 0.1 in univariate were selected to enter a multivariate analysis. Finally, P-values less than 0.05 in multivariate were considered statistically significant. Written informed consent was obtained from all the participants in the study and the study protocol was approved by the Ethical Committee of AJA University of Medical Sciences, Tehran, Iran.

RESULTS

Basic Characteristics

Patients' demographic and clinical data are summarized in Table 1. One hundred and forty cases, 82 (58.57%) males and 58 (41.43%) females, were enrolled in the current study. The mean age of the patients was 62 ± 12 years. The obtained results showed that 0, 1, 2, and 3 types of immunoglobulins were suppressed in 38 (27.1%), 38 (27.1%), 56 (40.0%), and 8 (5.7%) cases, respectively.

The Cox Proportional Hazards Model

The univariate and multivariate Cox analyses of prognostic parameters on OS are shown in Table 2. In all cases, among the analyzed parameters, only Cr > 2 mg/dL was detected significantly in the multivariate analysis; the hazard ratio was 2.407 (95% CI: 1.248-4.646, P = 0.009).

Table 1: Demographic and Clinical Features of the Patients

Parameter	Mean ± SD (Number of the Cases)	Range
Age, year	61.81 ± 11.75 (140)	30-85
Albumin (g/dL)	3.42 ± 0.68 (121)	1.6-5.6
BMPC%	35.5 ± 23.7 (108)	2.5-95
Creatinine (mg/dL)	1.82 ± 1.67 (130)	0.7-12.5
WBC	6.2 ± 2.8 (132)	0.7-15.3
Hemoglobin	9.7 ± 2.2 (131)	3.9-15.3
Platelet	189 ± 78 (131)	13-461
Calcium (mg/dL)	9.7 ± 1.5 (108)	6.2-18
ESR	96 ± 42 (114)	2-180

BMPC, bone marrow plasma cell; WBC, white blood cell; ESR, erythrocyte sedimentation rate

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Table 2: Univariate and Multivariate Analyses for Prognostic Factors on Overall Survival in the Study Cases

Parameter	Univariate		Multivariate	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Age > 65 years	2.048 (1.304-3.215)	0.002	1.266 (0.686-2.334)	0.451
Albumin < 3.5 (g/dL)	1.399 (0.869-2.251)	0.167		
BMPC > 40%	0.914 (0.525-1.593)	0.752		
Cr > 2 (mg/dL)	3.023 (1.82-5.023)	< 0.001	2.407 (1.248-4.646)	0.009
Hemoglobin < 10 (g/dL)	1.498 (0.951-2.360)	0.081	0.972 (0.560-1.686)	0.920
Platelet < 150 ($\times 10^9$/L)	1.541 (0.960-2.473)	0.073	1.494 (0.824-2.771)	0.186
Ca > 10.5 (mg/dL)	2.523 (1.348-4.724)	0.004	1.741 (0.850-3.566)	0.129
Suppression of 1 or More Immunoglobulins	1.222 (0.746-2.004)	0.426		
Suppression of 2 or More Immunoglobulins	1.580 (0.975-2.561)	0.063	1.327 (0.721-2.445)	0.363

BMPC, bone marrow plasma cell; Cr, creatinine; Ca, calcium

Table 3: Multivariate Analysis of Prognostic Parameters of the Overall Survival and Progression-free Survival in Velcade-based Cases

Parameters	OS		PFS	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Age > 65 years	2.851 (0.905-8.982)	0.074	N/A	N/A
Ca > 10.5 (mg/dL)	1.298 (0.250-6.739)	0.756	2.562 (0.671-9.787)	0.169
Cr > 2 (mg/dL)	4.611 (1.535-13.845)	0.006	3.184 (1.226-8.270)	0.017
Suppression of 2 or More Immunoglobulins	5.610 (1.509-20.852)	0.010	2.855 (1.093-7.454)	0.032

OS, overall survival; PFS, progression-free survival; Ca, calcium; Cr, creatinine

Table 4: Multivariate Analysis of Prognostic Factors of the Overall Survival in the Non-velcade Cases

Parameters	Hazard Ratio	Confidence Interval (95%)	P Value
Age > 65 years	1.141	0.563-2.314	0.715
Cr > 2 (mg/dL)	2.042	0.952-4.377	0.067
Ca > 10.5 (mg/dL)	2.131	0.969-4.684	0.060

Ca, calcium; Cr, creatinine

The univariate analysis was performed for each subgroup of the therapy. In cases treated with Velcade-based chemotherapy, univariate analysis revealed that agess > 65 years, elevated serum Cr serum Ca, and suppression of 2 types of immunoglobulin could be related to poorer OS. Multivariate analysis of these 4 parameters was performed and Cr and suppression of 2 immunoglobulin remained significant (Table 3).

Among Velcade-based cases, the univariate analysis of PFS showed significance for suppression of 2 or more immunoglobulins, Ca > 10.5 mg/dL, and Cr > 2 mg/dL. Similar to OS, in multivariate analysis of PFS, the elevated serum Cr and suppression of 2 or more immunoglobulins remained significant (Table 3). In cases treated with other agents, the non-velcade group, univariate analysis showed that age > 65 years, Ca > 10.5 mg/dL, and Cr > 2 mg/dL were related to higher risk. None of them remained significant in the multivariate analysis (Table 4). No parameter was significant in the univariate analysis for PFS in this group.

Survival Analysis

The mean OS was 46 months in all cases. Overall survival rates at the end of 1st, 2nd, 3rd, and 5th year of diagnosis were 73%, 63%, 57%, and 37%, respectively. Mean OS for 0, 1, 2, and 3 decreased types of immunoglobulin were 53, 57, 37, 31 months, respectively (log-rank test, P = 0.087). Figure 1 shows that the mean OS for at least 2 types of immunoglobulin suppression was lower compared with those of one class or no suppression (37 vs. 57 months, P = 0.058). However, this difference was not statistically significant in the current sample size.

Comparison of Velcade-based regimens (mean OS = 45.7 months) with other agents (mean OS = 45.6 months) showed no significant difference (P = 0.75). In the Velcade subgroup, 2 immunoglobulins suppression (mean OS=39 months) led to inferior survival compared with other cases (mean OS = N/A, P = 0.003) (Figure 2).

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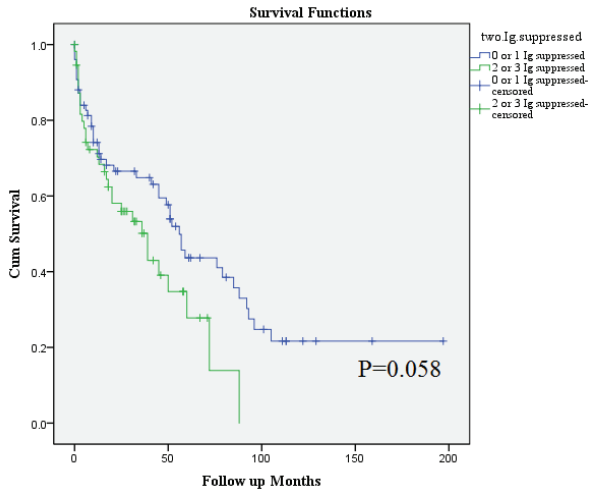

Figure 1: Overall Survival in Patients With Suppression of at Least 2 Immunoglobulins and Other Cases

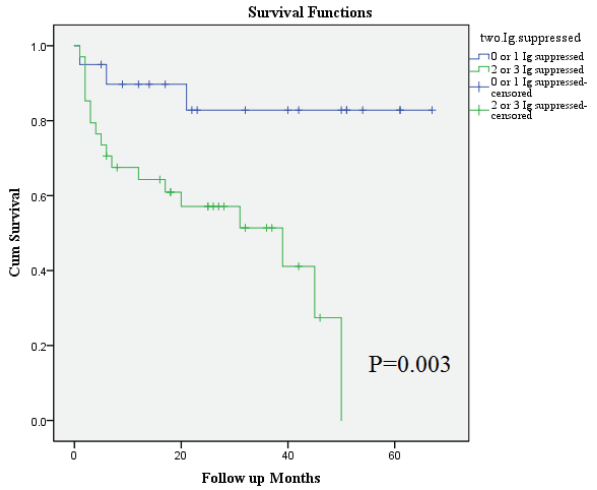

Figure 2: Comparison of Overall Survival in Velcade Subgroup Based on Immunoglobulins Suppression

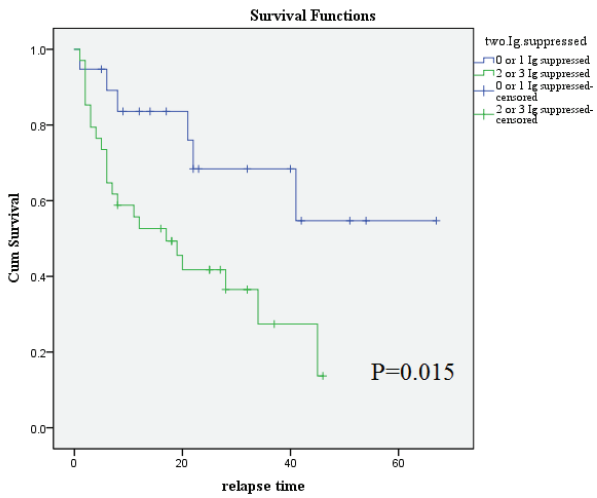

Figure 3: Comparison of Progression-free Survival in the Velcade Subgroup Based on Immunoglobulins Suppression

As mentioned before, univariate and multivariate analyses confirmed that suppression of at least 2 immunoglobulins was significantly related to poorer survival in the Velcade-based receiving subgroup. For cases with suppression of no or one immunoglobulin, Velcade was superior (mean OS = N/A vs. 51 months, P = 0.022). In cases with 2 or 3 immunoglobulin suppressions, there was no significant difference between Velcade (mean OS = 37 months) and other agents (mean OS = 39 months, P = 0.387). In the Velcade subgroup, a significant difference was observed in PFS between suppression of at least 2 immunoglobulins (mean PFS = 18 months) and other cases (mean PFS = N/A, P = 0.015) (Figure 3).

DISCUSSION

The current study aimed examining the effect of suppression of uninvolved immunoglobulins on the outcome of cases with MM. Limited studies previously examined the effect of immunoglobulins suppression on patients' outcome and as mentioned before, there were biases on the results of their works. Based on the studies by Kastritis et al, [3] and Harutyunyan et al. [4], immunoglobulin suppression was associated with poorer survival. In the study by Sari et al. [5], suppression of uninvolved immunoglobulins was related to lower survival, although the findings were not statistically significant. Another similar study conducted by Pruzanski et al. [9] showed that the degree of suppression of uninvolved immunoglobulins was related to worsened prognostic factors, but its effect on survival was not assessed. In contrast to the abovementioned papers, 2 studies [6, 7] reported that the suppression of other isotypes (e g, IgA, or IgM for IgG-kappa myeloma) could not affect patients' outcome. Nonetheless, the level of uninvolved pair of monoclonal immunoglobulins (e g, IgG-lambda for IgG-kappa myeloma) was related to poorer survival. However, none of these papers explicitly reported the effect of immunoglobulins suppression in each treatment subgroup. Results of the current study showed that the effect of immunoglobulins suppression on prognosis in patients with MM was influenced by the treatment type, and a significant effect was only detected for suppression of at least 2 immunoglobulins in the Velcade subgroup. In the current study, suppression of immunoglobulins did not show any significant impact in multivariate analysis of all cases. Although among all cases, suppression of 2 or more immunoglobulins was related to shorter survival, the hazard was not statistically significant. Results of the current showed that among cases with less than 2 types of immunoglobulin suppression, Velcade-based treatment was superior, but in patients with suppression of 2 or 3 immunoglobulin classes, there was no superiority of Velcade to other agents. Therefore, based on the current study data, Velcade advantage to other therapies could be eliminated

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in cases with severe immunoglobulins suppression. According to these results, it is proposed that severe immunoglobulins suppression is a predictive factor for efficacy of Velcade treatment. As mentioned earlier, in the current study patients, among cases treated with Velcade, suppression of 2 or 3 immunoglobulins was significantly related to inferior outcomes. A possible explanation for this result could be the of Velcade mechanism of action. Cases with 2 types of immunoglobulin suppressions showed severely lower levels of normal immunoglobulins. As Velcade was more effective on cells with a higher secretory level [10, 11], in patients with severe immunoglobulins suppression, the level of uninvolved immunoglobulins could be worsened as a result of Velcade chemotherapy. In conclusion, in the Velcade-based chemotherapy, suppression of 2 or 3 immunoglobulins was related to significant shorter overall and progression free survivals. More studies should be conducted to assess the effect of severe reduction of uninvolved immunoglobulins in cases treated with Velcade-based chemotherapy.

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CONFLICT OF INTEREST

The authors declared conflict of interests.

ETHICS APPROVAL

The study was approved by the Ethical Committee of AJA University of Medical Sciences (AJAUMS).

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