Original Article

Outcome of Response of Multiple Myeloma to Induction Treatment in Kurdistan Region of Iraq

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Abstract

Background: Nowadays**,** the therapy of multiple myeloma (MM) has successful and hopeful outcomes. Worldwide, various treatment regimens are prescribed by clinical hematologists. **Objectives:** The objective was to evaluate response to induction treatment and survival of MM patients treated with various treatment regimens in the Kurdistan Region of Iraq (KRI). **Materials and Methods:** A total of 114 patients in the KRI were included in a retrospective study through the period of January 1, 2010, to September 31, 2019. The diagnosis of MM was confirmed using the International Myeloma Working Group (IMWG) guidelines. The treatment responses were assessed according to the IMWG response criteria. **Results:** Complete response among the MM patients was 35.7%, very good partial response (VGPR) was 28.7%, partial response reached 9.1%, and stable disease reached 16.5%. The Kaplan–Meier curve showed those with VGPR had better survival than the rest of the response categories. Meanwhile, there was a significant association between MM patients on bortezomib and dexamethasone treatment regimen and complete remission was noticed ($P = 0.02$). **Conclusions:** The combination therapy of bortezomib and dexamethasone is effective in achieving a better response to treatment and good survival than other therapy regimens.

Keywords: Bortezomib and dexamethasone, Kurdistan region of Iraq, multiple myeloma

Introduction

Multiple myeloma (MM) is a malignant proliferation of a single clone of plasma cells that produces monoclonal proteins. The plasma cell proliferation leads to extensive skeletal involvement, with osteolytic lesions, hypercalcemia, and anemia and/or soft-tissue plasmacytomas. Furthermore, the excessive production of nephrotoxic monoclonal immunoglobulin can result in renal failure and an increased risk of developing potentially life-threatening infections as a result of deficient functional immunoglobulins.[1-4]

The annual incidence of MM is about 4 / 100,000 population, which comprises about 1% of all malignant diseases and 15% of all hematological malignancies. MM is reported to affect less Asian populations and dark-skinned Americans are affected more than Whites with slightly higher male-to-female ratio. The age at diagnosis is around 65–70 years. About 15% and 2% of the patients are younger than 50 and 40 years, respectively.[5,6]

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Every case of myeloma is approached with a proper history, physical examination, and laboratory investigations (including complete blood count and differential count, blood urea nitrogen, serum creatinine, serum calcium, serum albumin, serum and urine protein electrophoresis and immunofixation, and measurements of serum immunoglobulin levels). Others such as bone marrow aspirate and biopsy including bone marrow immunohistochemistry and flowcytometry, radiological bone survey (X-ray, computed tomography [CT] scan, magnetic resonance imaging or positron emission tomography-CT scan),

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beta 2 microglobulin, C-reactive protein, lactic dehydrogenase and measurement of free monoclonal light chain are all crucial in confirming the pathology.[1,6,7]

The diagnosis of symptomatic MM is made by the presence of M protein in serum and/or urine electrophoresis, increased plasma cells in bone marrow (or plasmacytomas), and evidence of tissue damage and organ impairment. Staging of MM is done using the International Staging System (ISS) or the Revised ISS.

MM patients are planned to start treatment, according to whether he/she is a transplant eligible or not and this is mostly age dependent. The age of 65 years and less is transplant eligible and more than 65 years are not eligible in most centers.[8-10]

An important prognostic factor associated with improved survival in patients with newly diagnosed MM is the quality of response to first-line induction treatment especially the attainment of complete response (CR).[11-15] In order to help the clinical hematologists in our locality (Kurdistan Region of Iraq, KRI) to select the appropriate therapy modules for patients with MM, we implemented this study to evaluate the treatment response and survival of MM patients treated with different treatment regimens.

Materials and Methods

Study design and patients

The study design was a retrospective data review carried out on 114 patients with MM in KRI (including Erbil, Sulaymaniyah, and Duhok Cancer centers) through the period from January 1, 2010, to September 31, 2019.

Patients included in this study were diagnosed according to the International Myeloma Working Group (IMWG), and then they were selected to start induction treatment. We included those received induction while excluded others who could not enter induction treatment.

A sample of 176 patients with MM was selected after eligibility for inclusion and exclusion criteria, only 114 patients were enrolled in the study.

The data were collected from the three governorates (Erbil, Sulaymaniyah, and Duhok) Cancer Centers. The questionnaire designed and included the required information as residency, age, gender, presenting features (fatigue, anemia, bone pain, pathological fracture, serum creatinine, hypercalcemia, and finally infectious states such as pneumonia, urinary tract infection, and Herpes Zoster) that are well demonstrated in Tables 1 and 2. Other valuable information included were the treatment regimens used such as VTD (bortezomib, thalidomide, and dexamethasone), VRD (bortezomib, lenalidomide, and dexamethasone), VMP (bortezomib, melphalan, and dexamethasone), VD (bortezomib and dexamethasone), MPT (melphalan, prednisolone, and thalidomide), MP (melphalan and prednisolone), VCD (bortezomib, cyclophosphamide, and dexamethasone), and RD (lenalidomide and dexamethasone). Also, treatment responses according to IMWG assessed by the senior clinical hematologists; CR, very good partial response (VGPR), PR (partial response), SD (stable disease), and the survival of MM patients (in months) after completing treatment regimen. All the required laboratory tools to diagnose the disease were carried out at our cancer center laboratories of KRI.

Table 1: Demographic and clinical characteristics of patients under study (n=114)

Variable	Frequency (%)
Governorate	
Sulaymaniyah	48 (42.1)
Hawler	47 (41.2)
Duhok	19 (16.7)
Age (years)	
<65	73 (64.03)
≥65	41 (35.96)
Gender	
Male	65 (57.02)
Female	49 (42.98)
Presenting features	
Fatigue	
Yes	78 (68.4)
No	36 (31.6)
Anemia	
Yes	50 (43.9)
No	64 (56.1)
Bone pain	
Yes	89 (78.0)
No	25 (22.0)
Pathological fracture	
Yes	25 (22.0)
No	89 (78.0)
Renal involvement	
Yes	20 (17.54)
No	94 (82.46)
Hypercalcemia	
Yes	8 (7.0)
No	106 (93.0)
Infective event	
Yes	4 (3.5)
No	110 (96.5)

Statistical analysis

Statistical analysis was carried out using SPSS version 22 (SPSS, IBM Company, Chicago, IL 60606, USA). Chi-square test and Fisher's exact test was applied for analyzing the data. Kaplan–Meier curve was used to assess the survival of MM patients. The level of significance (P value) was regarded as statistically significant if it was 0.05 or less.

Ethical consideration

Ethical considerations considered in concordance with the Helsinki Declaration with approval of the study from Ethical Committee of Kurdistan Board for Medical Specialties and Cancer Centers.

Table 2: Patterns of response of multiple myeloma cases in relation to induction regimens, disease stage at diagnosis, age at presentation, gender, serum creatinine, pathological fractures and serum calcium, hemoglobin, and serum protein electrophoresis at diagnosis (*n*=114)

Variable	Patterns of response				Total, *n* (%)	*P*
	CR, *n* (%)	PR, *n* (%)	SD, *n* (%)	VGPR, *n* (%)		
Regimens						
MP	0	1 (33.3)	2 (66.7)	0	3 (100.0)	0.02 (S)
MPT	1 (25.0)	1 (25.0)	2 (50.0)	0	4 (100.0)	
RD	0	1 (100)	0	0	1 (100.0)	
VCD	1 (33.3)	0	2 (66.7)	0	3 (100.0)	
VD	4 (80.0)	0	0	1 (20.0)	5 (100.0)	
VMP	3 (50.0)	1 (16.7)	2 (33.3)	0	6 (100.0)	
VRD	13 (38.2)	10 (29.4)	2 (5.9)	9 (26.5)	34 (100.0)	
VTD	18 (31.0)	8 (13.8)	9 (15.5)	23 (39.7)	58 (100.0)	
Disease stage ISS						
I	6 (23.1)	0	7 (26.9)	13 (50.0)	26 (100.0)	0.01 (S)
II	21 (40.4)	11 (21.2)	7 (13.5)	13 (25.0)	52 (100.0)	
III	13 (36.1)	11 (30.6)	5 (13.9)	7 (19.4)	36 (100.0)	
Age groups (years)						
<65	30 (41.1)	13 (17.8)	12 (16.4)	18 (24.7)	73 (100.0)	0.31 (NS)
≥65	10 (24.4)	9 (22.0)	7 (17.1)	15 (36.6)	41 (100.0)	
Serum creatinine (mg/dL)						
≤2	33 (35.1)	20 (21.2)	15 (15.9)	26 (27.6)	94 (100.0)	0.67 (NS)
>2	7 (35.0)	2 (10.0)	4 (20.0)	7 (35.0)	20 (100.0)	
HGB (g/dL)						
<10	16 (32)	12 (24.0)	10 (20)	12 (24)	50 (100.0)	0.46 (NS)
≥10	24 (37.5)	10 (15.6)	9 (14.0)	21 (32.8)	64 (100.0)	
SPE						
<3	19 (32.2)	10 (16.9)	10 (16.9)	20 (33.9)	59 (100.0)	0.64 (NS)
≥3	21 (38.1)	12 (21.8)	9 (16.3)	13 (23.6)	55 (100.0)	
Gender						
Male	20 (30.7)	16 (24.6)	11 (16.9)	18 (27.6)	65 (100.0)	0.38 (NS)
Female	20 (40.8)	6 (12.2)	8 (16.3)	15 (30.6)	49 (100.0)	
Hypercalcemia						
≤11	39 (36.7)	20 (18.8)	17 (16)	30 (28.3)	106 (100.0)	0.58 (NS)
>11	1 (12.5)	2 (25.0)	2 (25.0)	3 (37.5)	8 (100.0)	
Pathological fracture						
Absent	32 (35.9)	18 (20.2)	10 (11.2)	29 (32.5)	89 (100.0)	0.03 (S)
Present	8 (32.0)	4 (16.0)	9 (36.0)	4 (16.0)	25 (100.0)	
Total	40 (35.7)	22 (19.1)	19 (16.5)	33 (28.7)	114 (100.0)	

S: Significant, NS: Not significant, SPE: Serum protein electrophoresis, HGB: Hemoglobin, MP: Melphalan and prednisolone, MPT: Melphalan, prednisolone and thalidomide, RD: Lenalidomide and dexamethasone, VCD: Bortezomib, cyclophosphamide and dexamethasone, VD: Bortezomib and dexamethasone, VMP: Bortezomib, melphalan and dexamethasone, VRD: Bortezomib, lenalidomide and dexamethasone, VTD: Bortezomib, thalidomide and dexamethasone, ISS: International staging system, CR: Complete response, PR: Partial response, SD: Stable disease, VGPR: Very good PR

Results

This study included 114 MM patients. The proportion of patients was as follows Sulaymaniyah (42.1%), Erbil (41.2%), and Duhok (16.7%). Nearly 2/3rd (64.03%) of patients were <65 years, the rest (35.96%) were 65 years and more. The male to female ratio was 1.3:1 [Table 1].

Common presenting clinical features among MM patients were bone pain (78%), fatigue (68.4%), anemia (43.9%), pathological fracture (22%), renal involvement (17.5%), hypercalcemia (7%), and infective events (3.5%) [Table 1].

Treatment regimens used for patients were commonly VTD (in 58 cases), VRD (in 34 cases), VMP (in 6 cases), VD (in 5 cases), MPT (in 4 cases), MP (in 3 cases, VCD (in 3 cases), and RD (in 1 case), as shown in Figure 1.

CR to the induction treatment recorded at 35.7% of the MM patients, VGPR among 28.7%, PR among 19.1% and SD among 16.5% [Figure 2].

Kaplan–Meier curve showed that our MM patients with VGPR had better survival than other patients with other responses as shown in Figure 3. The Kaplan–Meier curve showed that MM patients had a good 5-year survival

response and a cumulative rate of 5-year survival was 75% [Figure 4].

A significant association between MM patients on the VD treatment regimen and CR was observed, while PR and SD were significantly higher among patients on the MP treatment regimen ($P = 0.02$). Furthermore, a significant association was observed between lower stage MM disease (using ISS stage) and VGPR to treatment ($P = 0.01$) [Table 2].

No significant association was observed between different response criteria and age of the patient ($P = 0.31$), serum creatinine ($P = 0.67$), hemoglobin ($P = 0.46$), serum protein electrophoresis ($P = 0.64$), serum calcium ($P = 0.58$), and gender of the patients ($P = 0.38$). The pathological fractures were significantly higher among MM patients with standard treatment ($P = 0.03$) [Table 2].

Discussion

Previously, the MM had an average survival of 3 years but with the advancement in diagnosis and combination therapies, almost 60%–70% of the patients will obtain a CR with the survival of more than 10 years for patient's age within the fifth decade.[16]

The present study showed that CR was achieved in 35.7% of the patients, VGPR by 28.7% and SD by 16.5%. These findings are better than the results of the Terzi *et al*.[17] study in Turkey, which reported that CR was achieved by 27.6% of MM patients after first-line induction treatment. This difference might be due to difference in the treatment regimens and other risk factors such as age between two studies.

In the present study, there was a significant association between MM patients on the VD treatment regimen and CR, while PR and SD were significantly higher among patients on the MP treatment regimen ($P = 0.02$). These findings are similar to other studies done, such as that by Bassiony *et al*.[18] study in Egypt and Driscoll *et al*.[19] study in the USA, they stated that combination therapy of VD for MM is effective in achieving a significant response to treatment. A previous study in France revealed that the therapy regimen of VD was effective and well tolerated in the treatment of newly diagnosed MM.[20] Another study in the USA by Kapoor *et al*.,[21] reported that Bortezomib combination therapy is effective in targeting proteasome and a high response to treatment with better survival. Jagannath *et al*.[22] found that adding VD regimen for MM leads to higher

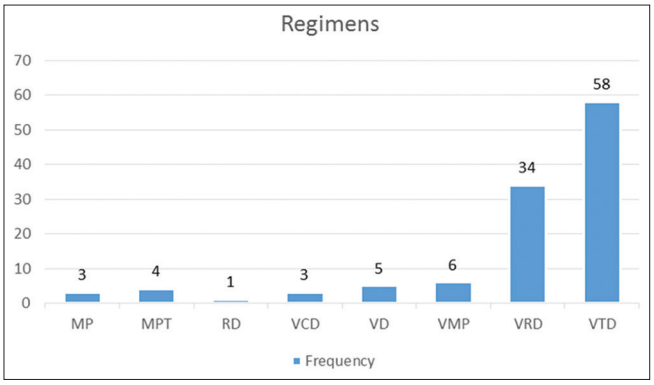

Figure 1: Regimens used in the first induction ($n = 114$)

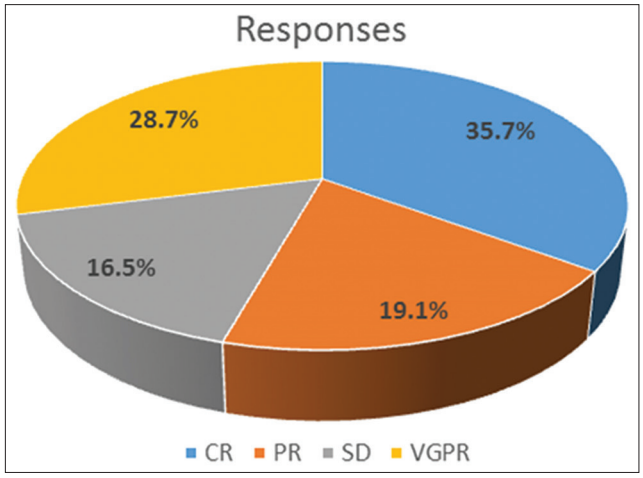

Figure 2: Patterns of response after the first induction ($n = 114$)

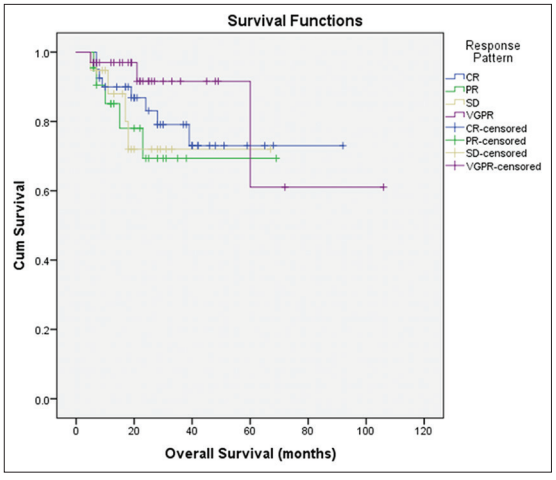

Figure 3: Survival outcome in relation to the patterns of response

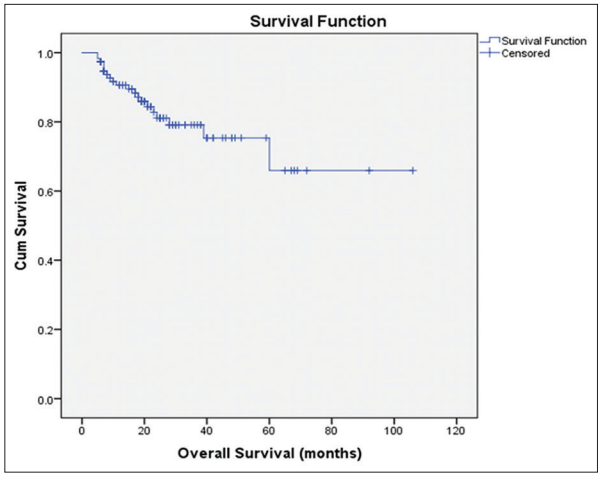

Figure 4: General survival outcome of multiple myeloma

treatment response more than using bortezomib alone with less adverse effects. Regarding patients with VGPR, Petrucci *et al*.[23] study in Italy, found that weekly infusion of bortezomib and low-dose melphalan and dexamethasone lead to a high response to treatment among elderly patients with relapsed/refractory.

In the current study, patients with lower MM ISS stage had significantly VGPR to treatment ($P = 0.01$). This finding coincides with the results of Tan *et al*.[24] study in Singapore, which found that advancing age, high ISS, and adverse cytogenetics are independent risk factors on achieving a high rate of VGPR.

Our study also showed that patients with VGPR had better survival than other regimens. This finding is consistent with the results of Tandon *et al*.[25] study in the USA and Harousseau *et al*.[26] study in France.

Generally, our study reported a good prognosis for MM patients with a 75% cumulative rate for 5 years of survival. These findings are better than the results of Yassin study in Erbil, which found that the median survival of patients with MM after adding thalidomide was 34 months.[27] Additionally, our study survival is better than the results of Hameed *et al*.[28] study in Pakistan which found that the cumulative survival of MM patients at 36 months was 85%. This might be due to more nonbortezomib containing regimens in both other studies particularly in the second study that reaches 90% of the cases.

In the present study, a higher proportion of MM patients are those with younger than 65 years. This finding is close to the results of Zweegman *et al*.[29] study in Netherlands. Our study reported the predominance of the male gender. Similarly, Boyd *et al*.[30] study in the UK found gender differences in the prevalence of MM in favor of male predominance also. Bone pain was a common complaint among studied patients. This finding is consistent with the results of Yassin study in Erbil.[31] However, the current study revealed no significant differences between patients with different responses to treatment regarding the age of patients, serum creatinine, hemoglobin, serum protein electrophoresis, and gender. These findings resemble the results of Mohammed's study in Iraq[32] and Liu *et al*.[33] study in Taiwan. Inconsistently, other literatures such as Najjar and Al Tameemi study in Iraq[34] and Lu *et al*.[35] study in China reported the effect of age, gender, serum creatinine, hemoglobin, and serum protein electrophoresis on treatment outcome of MM. This inconsistency might be attributed to differences in treatment protocols used or discrepancies in disease epidemiology between different studies. The present study found that pathological fractures were significantly higher among MM patients with standard treatment ($P = 0.03$). Consistently, Collins' study in Ireland[36] reported that healing of pathological fractures is correlated significantly with the treatment response of MM.

Conclusions

This study concluded that combination therapy of VD is effective in achieving a better response of treatment and good survival than other therapy regimens. MM patients with VGPR are related to lower ISS stages and better survival.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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