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Clinical Outcome of Patients with Newly Diagnosed Multiple Myeloma in Zagazig University Hospitals

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ABSTRACT

Background: Multiple myeloma (MM) is a clonal neoplastic plasma cell disorder. With availability of immunomodulators and bortezomib, better response rate and survival outcome have been achieved in newly diagnosed multiple myeloma (NDMM) patients.

Objective: To evaluate patients' response and outcomes to anti-myeloma treatment in a tertiary referral center.

Patients and Methods: From September 2020 to February 2022, at Zagazig University Hospitals, Hematology Unit of Internal Medicine Department, our prospective cohort study was conducted on 36 treatment-naïve patients with NDMM. All patients had received anti-myeloma agents and assessed for response and outcome.

Results: About the performance status (PS), one quarter of the cases had PS 0 (25%), and 55.6% of the cases were PS 1. Majority of cases responded to treatment (91.7%), while only three cases did not respond. Thirty-three cases showed no progression (91.7%) and three cases only showed progression (8.3%). Ten patients underwent autologous stem cell transplantation (ASCT). After a median follow-up period of 12 months (range 4-18 months); the OS rate was 76.8%, and PFS rate, was 90.7%.

Conclusion: This study highlights that by using proper anti-myeloma agents, a reasonable clinical outcome can be achieved in our tertiary center

Keywords: Anti-myeloma agents, Multiple Myeloma, Outcome.

INTRODUCTION

Dysfunction of the clonal plasma cells multiple myeloma is characterized by the clonal growth of plasma cells in the bone marrow and the presence of monoclonal proteins in the blood and urine [(1, 2)]. In terms of blood cancers, non-Hodgkin lymphoma and multiple myeloma are the most frequent [(3, 4)].

Inflammatory markers are of particular interest. Myeloma cell growth, survival, migration, and even treatment resistance may be directly influenced by the bone marrow microenvironment's condition, according to some researchers [(5, 6)].

Recently, an improvement of outcome of MM cases has been achieved by application of some novel agents together with autologous stem cell transplantation (ASCT), which considered now as a gold standard treatment method for MM patients without any organ failure [(7, 8)]. Some new treatment agents have been developed with changes in treatment strategies. So, evaluation of the benefits versus risks of each treatment decision is a must for selection of the most optimal approach for the patients. Bortezomib is a first-class proteasome inhibitor that is used in treatment of MM [(9, 10)].

We aimed to assess the patients' response and outcomes to anti-myeloma agents in a tertiary referral center.

PATIENTS AND METHODS

A prospective cohort study of 36 patients with NDMM was conducted from September 2020 to February 2022 at Zagazig University Hospitals in the Departments of Hematology and Clinical Pathology, Faculty of Medicine. There were 20 men and 16 women in the studied group.

Ethical consent:

Patients were made aware of the study's scope and goals, and they all signed informed permission forms before undergoing any testing, including a bone marrow aspiration. Patient information was protected and the study groups were not exposed to any danger or risk. In addition, Zagazig University Faculty of Medicine's Ethical Committee gave its clearance. The study was adhered to Helsinki Declaration of the World Medical Association as regard conducting human experiments.

Patient selection:

All newly diagnosed chemotherapy-naïve symptomatic MM patients, with good PS: 0-2, age: ≥18 years old, were eligible, While, Exclusion criteria included; patients with poor PS unfit, for proper treatment, HIV infection, or any other criteria do not fulfill inclusion criteria.

Patient assessment:

For accurate diagnosis and proper staging by ISS; all patients of the study were subjected to; full clinical assessment and laboratory investigations like serum protein electrophoresis, serum protein immunofixation, bone marrow aspiration and biopsy and immunostaining, conventional cytogenetics, B2 microglobulin, erythrocyte sedimentation rate and radiological studies including skeletal survey.

Treatment:

All patients have been treated by combination regimens of immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs), including VCD (Velcade 1.3 mg/m^2 day 1,4,8,11, cyclophosphamide 300 mg/m^2/week and

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dexamethasone 40 mg/week) or VRD (Velcade 1.3 mg/m^2 day 1,4,8,11, lenalidomide 25 mg/day and dexamethasone 40 mg/week) or VDT (Velcade 1.3 mg/m^2 day 1,4,8,11, thalidomide 100 mg/day and dexamethasone 40 mg/week) or CRD (Cyclophosphamide 300 mg/m^2/week, lenalidomide 25 mg/day and dexamethasone 40 mg/week) or CDT (Cyclophosphamide 300 mg/m^2/week, thalidomide 100 mg/day and dexamethasone 40 mg/week).

Follow up:

Follow up was done for the patients after receiving their treatment for at least 18 months regarding response and survival analysis.

Statistical analysis

The data were analyzed using SPSS version 24. The data were represented by numbers and percentages, or by the mean, standard deviation, and median. Kaplan and Meier method was used for estimating survival. The time from the time of diagnosis to the time of death, the last follow-up visit, or the end of the research was used to compute overall survival (OS). PFS (progression-free survival) was computed from the start of treatment to the date of verified illness progression, relapse, or the study's conclusion. Deaths that weren't caused by cancer were censored for the PFS.

RESULTS

Clinical character and outcome of the study population:

Table 1 shows the basal clinical characteristics and outcome of the studied patients. Mean age was 55.5 years. Regarding Eastern Cooperative Oncology Group (ECOG) performance status (PS), ECOG PS 1 was the most common. As regards stage of the disease according to International Staging System (ISS), 38.9% of the patients were presented with stage II. 100% of the cases in this study were presented with anemic manifestations at diagnosis. 80.6% of the cases were presented with B- symptoms. While, 22 (61.6%) of the patients suffered from bony pain. Renal impairment was identified in 50% of cases. While, 47.2% of the cases were represented with neurological defects.

The majority of cases responded to treatment (91.7%). Thirty-three cases showed no progression (91.7%).

Bortezomib-based medication was administered in 55.6% of cases, while conventional chemotherapy was applied on 44.4% of cases. Regarding the treatment by combination regimens of immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs), VCD was applied to 41.7%. Ten patients underwent ASCT, while the majority did not undergo bone marrow transplantation (BMT) (72.2%). After a median follow-up period of 12 months (range 4-18 months); 80.6% of cases survived, while 19.4% died (Table 1).

Table (1): Baseline characteristics and outcome of all NDMM patients

Parameter		Total N=36	
Age		55.5 (40-75)	
Sex	Female	16	44.4%
	Male	20	55.6%
PS	0	9	25.0%
	1	20	55.6%
	2	7	19.4%
Smoking		16	44.4%
Anemic Symptom		36	100.0 %
Bony Pain		22	61.1%
B Symptoms		29	80.6%
Renal Impairment		18	50.0%
Neurological deficits		17	47.2%
DM		12	33.3%
HTN		14	38.9%
International Staging System (ISS)	1	11	30.6%
	2	14	38.9%
	3	11	30.6%
Response to treatment	No	3	8.3%
	Yes	33	91.7%
Progression	No	33	91.7%
	Yes	3	8.3%
Treatment protocol	Bortezomib-based	20	55.6%
	Conventional agents	16	44.4%
Protocol type	CRD	2	5.6%
	CTD	14	38.9%
	VCD	15	41.7%
	VRD	3	8.3%
	VTD	2	5.6%
ASCT		10	27.8%
Death	No	29	80.6%
	Yes	7	19.4%

Laboratory findings of the patients:

Regarding laboratory characteristics of the patients, hypercellular BM was represented in 69.4% of cases. Most of the patients (77.8%) were presented with immunoglobulin IgG. Kappa and lambda light chain (LC) were represented in 77.8% and 22.2% of patients, respectively.

The WBC count was 8 X 10/L, while, mean HB and platelet count were 8.6 g/dl and 184 X10/L, respectively. While, B2 microglobulin mean level was 3.35 mg/dl. The mean percentage of plasma cells in bone marrow (BM) was 20%. As regards immunophenotypic characterization of the patients, mean level of CD138 was 45%. While, CD38 mean value was 33% (Table 2).

Table (2): Laboratory and radiographic data

Parameter		Total N=36	
CBC	WBC (10^9/L)	8 ± 2.1	
	Hb (g/dl)	8.6 ± 1.14	
	PLT (10^9/L)	184 ± 4.12	
LFTs	T. Bil (mg/dl)	0.6 ± 0.11	
	PTN (g/dl)	9 ± 1.81	
	Alb (g/dl)	3 ± 0.41	
	ALT (U/L)	15.1 ± 3.12	
	AST (U/L)	15.5 ± 3.31	
KFTs	BUN (mg/dl)	24.5 ± 5.21	
	Cr. (mg/dl)	1.4 ± 0.43	
Electrolytes	Ca (mg/dl)	9 ± 1.71	
	Uric A (mg/dl)	7 ± 0.71	
LDH (225) U/L		220 ± 45.21	
Inflammatory Markers	B2 Microglobulin (mg/L)	3.35 ± 0.61	
	ESR 1 (mm/hr)	110 ± 23.38	
	CRP (mg/L)	7 ± 1.51	
SPEP	alpha-1	0.3 ± 0.04	
	alpha-2	0.7 ± 0.05	
	beta-1	0.3 ±0.01	
	beta-2	0.3 ± 0.02	
	Gamma	3.5 ± 1.02	
LC	k	28	77.8%
	L	8	22.2%
BM Cellularity	Hypercellular	25	69.4%
	Normocellular	11	30.6%
Plasma Cells%		0.2 ± 0.03	
M-protein	IgA	8	22.2%
	IgG	28	77.8%
FCM	CD 138	0.45 ± 0.01	
	CD 38	0.33 ± 0.02	
Bony lesion		4	11.1%

OS and PFS rate:
The OS rate was 76.8%, and PFS rate, was 90.7% (Table 3 and Figure 1, 2).

Table (3): The 1.5-year OS and PFS rate of the studied group

	Total N	N of Events	Censored N (%)	Survival Rate %	Survival Time, Months	
					Mean 95% CI	Median
OS	36	7	29 (80.6%)	76.8	16.2 15.0-17.4	NR
PFS	36	3	33 (91.7%)	90.7%	11.5 10.9-12.2	NR

CI: Confidence Interval

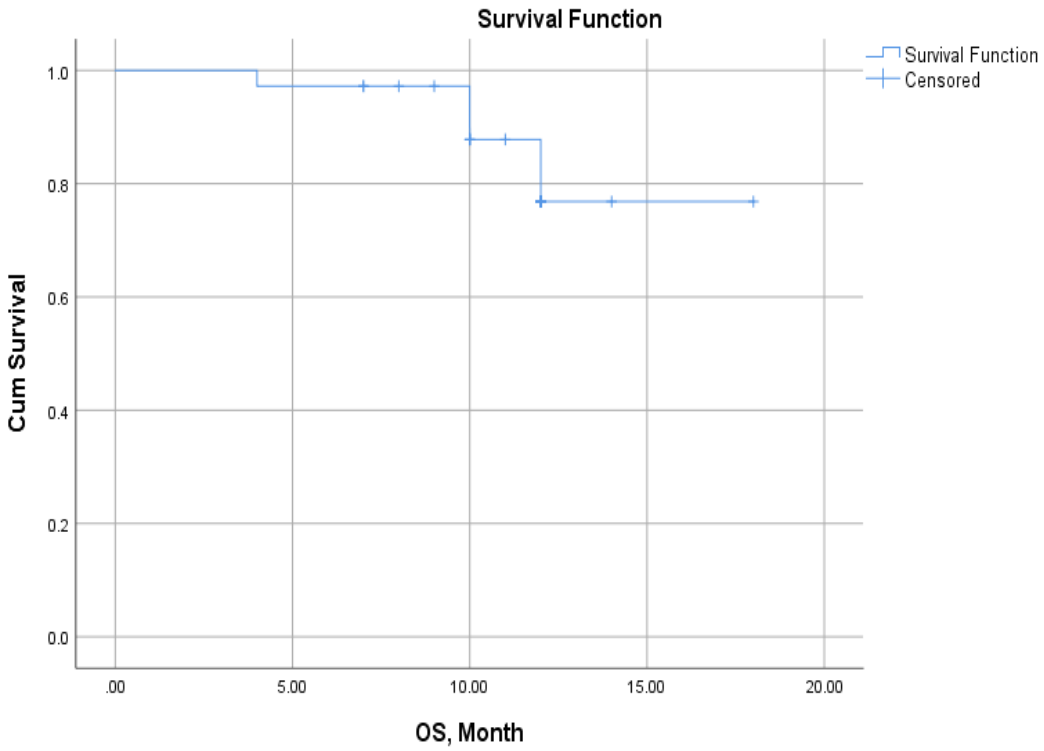

Figure (1): The 1.5-year overall survival rate for all patients

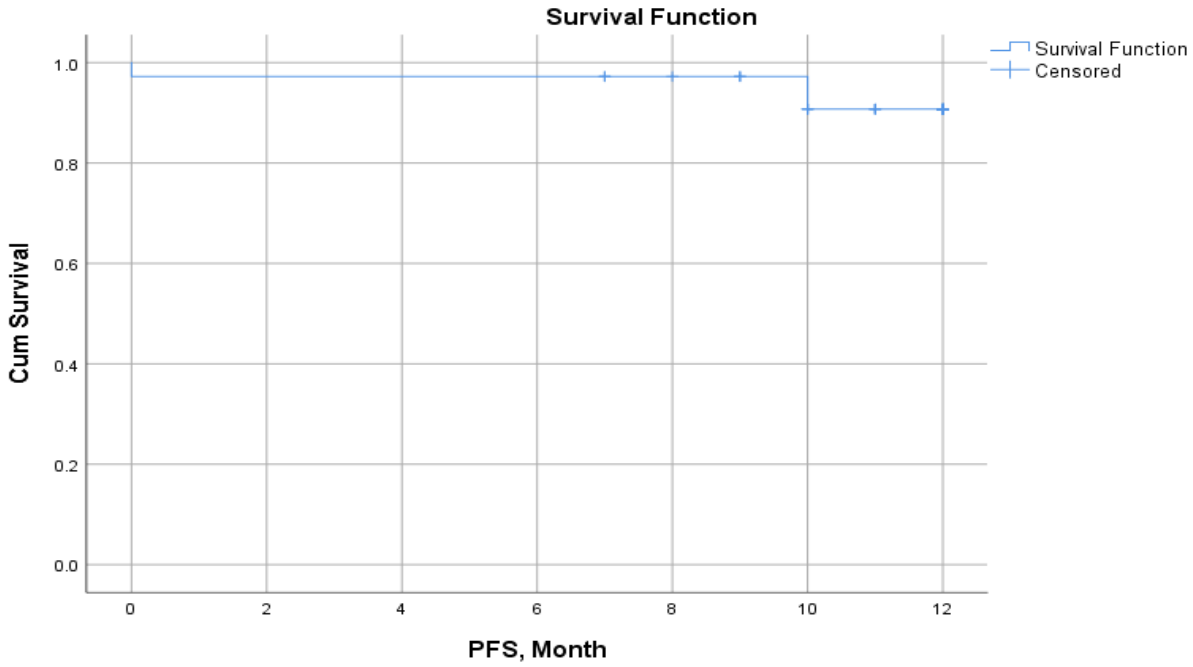

Figure (2): The 1.5-year progression-free survival rate for all patients

DISCUSSION

Multiple myeloma patients have seen a dramatic improvement in their prognosis over the past two decades, thanks to the utilization of autologous hematopoietic stem cell transplantation, as well as new immunomodulatory medicines and proteasome inhibitors. The current 5-year survival rate is 48.5%, and the median overall survival (OS) is above 6 years, according to the most recent data available. Unfortunately, MM is still seen as a terminal illness [11, 12].Regarding the demographic data, our current study was conducted on 36 patients with multiple myeloma, with mean age of 55.5 years ranging between 40-75 years. The gender ratio of cases was roughly equal with males representing 55.6%, and females representing 44.4%. About the PS, one quarter of the cases were PS 0 (25%), 55.6% of the cases were PS 1, and 19.4% of cases were PS 2. Concerning smoking, 44.4% of cases were smokers, while 55.6% were non-smokers. According to **Wongrakpanich *et al.*** [13] there were 50.6

percent males and 49.4 percent females in a study of 161 people with MM. The patients' ages ranged from 41 to 91 years at the time of diagnosis, with the median being 69. There were a preponderance of patients who were of African-American descent (82.7 percent).

All the cases in this study were diagnosed with anemic symptoms. Twenty-two patients suffered from bony pain. 80.6% of cases were with B symptoms. Regarding the renal impairment there was a 1:1 ratio of patients with/without renal impairment. The results reported 47.2% of cases diagnosed with neurological defects. One third of patients were diabetic. Fourteen cases were hypertensive. Regarding the severity staging of multiple myeloma, 30.6% represented ISS (I and III), and 38.9% represented ISS (II). The majority of cases responded treatment (91.7%), while only three cases did not respond. Thirty-three cases showed no progression (91.7%) and three cases only showed progression (8.3%). In the study of **Kelkitli *et al.* [14],** there were 151 individuals with multiple myeloma included in the study, and 83 (55 percent) of those patients were men and 68 (45 percent) were women. The average patient was 63 years old, with a range of 35 to 89 years. The IgG type of monoclonal protein was the most commonly found in the patients (58.6 percent). Patients with renal insufficiency (29%) and ISS stage III (74%) were also included in the study. Six patients died from pneumonia, six from heart failure, four from neutropenic fever, two from cerebral bleeding, two from cardiac tamponade, and two from pulmonary emboli during follow-up, totaling fifty-eight (38%). Bortezomib-based medication was administered in 55.6% of cases, while conventional chemotherapy was applied on 44.4% of cases. Regarding the treatment by combination regimens of immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs), VCD was applied to 41.7%, CTD (38.9%), VRD (8.3%), and both CRD and VTD (5.6%). Ten patients underwent bone marrow transplantation (BMT), while the majority did not undergo BMT (72.2%). During the 18 months follow-up period, 80.6% of cases survived, while 19.4% died **[14].**

Kelkitli *et al.*[14] also found that, regarding the treatment of multiple myeloma, 102 cases had vincristine, doxorubicin, dexamethasone (VAD), melphalan, prednisone, thalidomide (MPT), bortezomib, melphalan, prednisone (VMP), ASCT, and melphalan, prednisone (MP). Twenty-five cases showed hypercellular bone marrow (69.4%), and eleven cases showed normocellular bone marrow (30.6%). Regarding the immunoglobulins, IgG was evaluated in 77.8% of cases, while IgA was assessed in 22.2%. About the plasma cell low-chain (LC), 28 cases were kappa (77.8%), and eight cases were lambda (22.2%). four cases showed bony lesion. In terms of ISS staging, patients had been diagnosed with stage I (29.0%), stage II (37.7%), or stage III (21.0%) MM. The most common paraprotein type was IgG (50.9%), followed by IgA (16.8%), lambda light chain (5.6%), and kappa light chain (9.3%).

CONCLUSION

Despite the prospective design of the study, the limitation of the study sample size and relatively short follow-up; this study highlights that by using proper anti-myeloma agents, a reasonable clinical outcome can be achieved.

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Conflict of interest: Nil.

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