Multiple Myeloma: an 11-year of Experience in South Egypt Cancer Institute

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Abstract

Background and objectives: Multiple myeloma (MM) is a malignant neoplasm of plasma cells accounting for approximately 10% of all hematologic cancers. The rates of MM vary among different populations and findings on racial differences in survival in MM have been inconclusive. Our aim is to investigate the demographic data with reviewing the different lines of treatment and to assess the outcome and survival of the patients treated from MM at a single institution over an 11-year period.

Methods: This retrospective study involved 70 patients with MM who were treated from January 1, 2008 to December 31, 2018 in the Medical Oncology Department at the South Egypt Cancer Institute (SECI).

Results: The median age of patients was 57 years. The most presenting symptoms were bone pain which occurred in 90% of patients followed by anemia, hypercalcemia and renal impairment which occurred in 64%, 27% and 21% of patients respectively. Patients who received bortezomib based regimens had higher median progression free survival (PFS) and overall survival (OS) compared with conventional treatment as the median PFS was 30 months (P=0.051) while OS was 37 months (P=0.011) in patients received bortezomib based regimens.

Conclusions: Multiple Myeloma in Egyptian patients is more common in younger age. Bortezomib based regimen gives survival outcome better than conventional treatment.

Key words: Multiple myeloma, bortezomib, survival

Introduction:

Multiple myeloma (MM) is a malignant neoplasm of plasma cells that accumulate in bone marrow leading to bone destruction and marrow failure [1]. It accounts for approximately 13% of all hematological malignancies and mainly affects the elderly population with a median age at diagnosis of about 65 years [2].

The diagnosis of MM requires the presence of one or more myeloma defining events (MDE) in addition to evidence of either 10% or more clonal plasma cells on bone marrow examination or a biopsy proven plasmacytoma. MDE consist of established CRAB (hypercalcemia, renal failure, anemia, or lytic bone lesions) features as well as three specific biomarkers: clonal bone marrow plasma cells ≥60%, serum free light chain (FLC) ratio ≥100 (provided involved FLC level is ≥100 mg/L), and more than one focal lesion on magnetic resonance imaging (MRI) [3].

Introduction of novel agents based treatment options improved outcome of patients both eligible and not eligible for high-dose chemotherapy- autologous stem cell transplantation [4-6]. Bortezomib, a first- class proteasome inhibitor, was approved by the Food and Drug Administration in 2003; since that time, further studies of bortezomib alone and as part of combinations regimens have shown the usefulness of this agent [7].

The rates of MM vary among different populations and findings on racial differences in survival in MM have been inconclusive [8]. So, we try to flash on the features and outcome of Egyptian patients with MM as well as the role of bortezomib in the treatment of MM through this retrospective study.

Patients and Methods:

Patients:

A total of 70 MM patients who had been treated during an 11-year period (from January 1, 2008 to December 31, 2018) at the Medical Oncology Department, South Egypt Cancer Institute (SECI). The study was conducted in accordance with the protocol approved by Ethical Committee rules at SECI. The International Myeloma Working Group (IMWG) criteria was used for the diagnosis of MM [9] and the Durie-Salmon staging system (SDS) for its staging [10].

The patients were analyzed with respect to the demographic profile, staging, treatment details and survival outcome. Response to treatment was assessed according IMWG uniform response criteria [11]. Cytogenetic analysis was not performed routinely in our institute.

Treatment:

In this study according to our local protocols during this period from January 1, 2008 to December 31, 2018, we used four regimens which are melphalan or cyclophosphamide based regimens, bortezomib-based regimens (bortezomib/ dexamethaasone , bortezomib / endoxan / dexamethasone , bortezomib / lenalidomide /dexamethasone), immunomodulatory drugs based regimens (thalidomide/ dexamethaasone, lenalidomide dexamethaasone) and VAD regimen (vincristin, doxorubicin, and dexamethasone).

Statistical analysis:

The data was recorded on a sheet form. These data were entered into the computer using SPSS program version (22). Kaplan-Meier test was performed to calculate overall and progression free survival for whole study group. OS was calculated from the date of diagnosis to date of death or date of lost follow up. PFS is defined as the time from treatment initiation until disease progression. PFS and OS were analyzed with the Kaplan-Meier method. A log-rank test was utilized to assess the differences between subgroups. $P < 0.05$ was considered to indicate a statistically significant difference.

Results:

The demographic data of the patients are shown in (Table 1) .The median age of patients with MM was 57 years (range 35 – 78). Forty eight patients were below or equal 60 years old (68.6%) while 22 patients were above 60 years old (31.4%). Of all patients 51.4% were males while females represented 48.6%. Baseline investigations revealed anemia (Hb <10gm/dl) in 64.3%, impaired renal function (serum Creatinine > 1.6mg/dl) in 21.4%, hypercalcemia (serum calcium >11mg) in 27.1% and lytic bony lesions in 90%. Regarding the SDS system of multiple myeloma, in our study 11 patients had stage I (15.7%), 26 patients (37.1%) had stage II while 33 patients (47.1%) had stage III.

In the first line treatment, thirty three patients received melphalan or cyclophosphamide based regimens (47.1%) as bortezomib started to be available in our institute in late 2016, bortezomib based regimens were only given to 19 (27.1%) patients. Eleven (15.7%) patients received VAD regimen while 7 (10%) patients received immunomodulatory drugs based regimens like thalidomide or linalidomide. The median number of cycles was 5 (1-22) . Response to first line treatment was shown in (Table 2) where CR (26.3%) and PR (36.8%) were higher in patients who received bortezomib based regimens with significant p value (*P* value = 0.005).

As regarded second line treatment, Thirty three (47%) patients received second line therapy who either had progression of their disease or had toxicity during first line treatment. Bortezomib based regimens were given in 12 (36.4%) patients, Nine (27.3%) patients received melphalan or cyclophosphamide based regimens, Seven (21.2%) patients received VAD while thalidomide or linalidomide based regimens were used in 5 (15.2%) patients. In contrary to response to first line treatment there was no significant difference in response to different second line regimens (*P* value = 0.328) (table 3).

Patients who received bortezomib based regimens had higher median PFS which was 30 months followed by those who received VAD regimens which was 28 months. Those received alkylaying agent based regimen and immunomodulatory drugs based regimen had median PFS ,11 months, and 10 months respectively but PFS did not reach statistical significance in favor of the bortezomib arm (*P*=0.051) Figure (1).

Thirty one patients had in their treatment botezomib based regimen as first or second as it was not always available due to financial issue. We founded that those patients had median OS about 37 months compared to median 29 months in the other 39 patients who didn't receive bortezomib in their treatment and OS reach statistical significance in favor of the bortezomib arm (*P*=0.011) Figure (2).

Table (1): Distribution of the studied cases according to demographic and clinical data

Variable name	N = (70)	
	N	%
Age (years)		
Median age	57	
Range	35 – 78	
Age groups		
≤ 60	48	(68.6)
> 60	22	(31.4)
Sex		
Male	36	(51.4)
Female	34	(48.6)
Anemia	45	(64.3)
Renal impairment	15	(21.4)
Hyper-calcemia	19	(27.1)
Bone lesion	63	(90.0)
Duriesalmon		
I	11	(15.7)
II	26	(37.1)
III	33	(47.1)

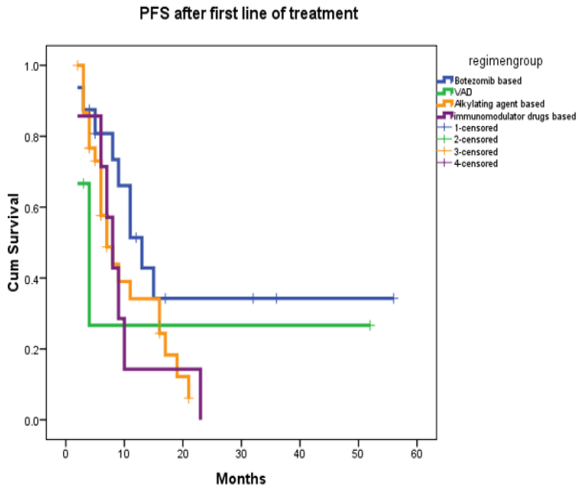

Figure 1: PFS in patients received botezomib based regimens

Table (2): Response to first line therapy

Regimen group	Response to the 1st line										p-value
	CR		PR		SD		Progression		Not done		
	N	%	N	%	N	%	N	%	N	%	
Bortezomib based	5	(26.3)	7	(36.8)	0	(0.0)	6	(31.6)	1	(5.3)	
VAD*	1	(9.1)	0	(0.0)	0	(0.0)	3	(27.3)	7	(63.6)	**0.005***
Melphalan or Cyclophosphamide based	4	(12.1)	13	(39.4)	3	(9.1)	11	(33.3)	2	(6.1)	
Thalidomide or Linalidomide based	0	(0.0)	3	(42.9)	1	(14.3)	2	(28.6)	1	(14.3)	

*** VAD** (vincristin, doxorubicin, and dexamethasone)

Table (3): Second line therapy and its response

Regimen group	Response to the 2nd line										p-value
	CR		PR		SD		Progression		Not done		
	N	%	N	%	N	%	N	%	N	%	
Bortezomib based	3	(25.0)	3	(25.0)	0	(0.0)	6	(50.0)	0	(0.0)	
VAD	0	(0.0)	1	(14.3)	0	(0.0)	4	(57.1)	2	(28.6)	0.328
Melphalan or Cyclophosphamide based	3	(33.3)	2	(22.2)	0	(0.0)	3	(33.3)	1	(11.1)	
Thalidomide or Linalidomide based	0	(0.0)	2	(40.0)	0	(0.0)	1	(20.0)	2	(40.0)	

*** VAD** (vincristin, doxorubicin, and dexamethasone)

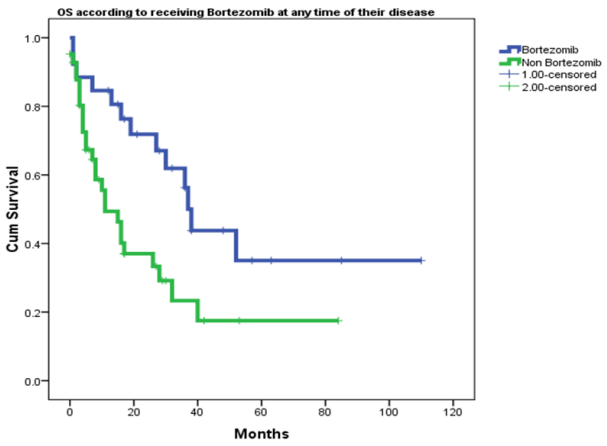

Figure 2: Overall survival in patients received botezomib based regimens

Discussion:

Multiple myeloma (MM) is a malignant neoplasm of plasma cells that accumulate in bone marrow leading to bone destruction and marrow failure [1]. In the current study we aimed at having a retrograde view of the MM disease to investigate the demographic data with reviewing the different lines of treatment and to assess the outcome and survival of the patients treated from MM at a single institution over an 11-year period.

The incidence of MM increases with age, and is most frequently observed in older adults, the median age at diagnosis was 65 years of age [2]. The median age of the Egyptian MM patients tend to be generally younger may be due to decreased life expectancy or different tumor biology. In our study, the median age was 57 years (range 35-78 years). Our data was similar to other Egyptian studies conducted by Bassiony et al where the median age of the patients was ±60 years (range, 48–70 years) [12] and by Abdel Karim et al where the mean age of the patients of 59 years, range (37-74 years) [13].

In the present study, 64.3% of patients presented with anemia, 21.4 % had renal impairment, 27.1 % had hypercalcemia and lytic bony lesions in 90%. About 48 % of patients presented in stage III.

Our results were close to the Egyptian study done by Abdel Karim et al. where bone ache was 75.8%, 69.4% of patients had anemia, renal impairment in 16.1% of patients, hypercalcemia in 12.9% of patients and 45.2% of patients had disease stage III. [13]. While in a study by Shin et al., they found that 29% of patients had anemia, 23%, had hypercalcemia and 13% had renal impairment [14].

As first line therapy, patients received bortezomib based combination therapy had better response in form of both CR and PR (63.1%) compared to other regimens used in treatment of MM , This results were similar to that reported by Jagannath et al., and Reeder et al., who reported CR and PR of about 60% and 70 % respectively [15-16].

Patients who received bortezomib based regimens had higher median PFS compared with other regimens but PFS did not reach statistical significance in favour of the bortezomib arm (p = 0.051) . Consistent with our results, Sonneveld et al. found a significantly longer PFS in patients allocated to bortezomib, doxorubicin, and dexamethasone than in patients allocated to vincristine, doxorubicin, and dexamethasone (p< 0.001) [17]. Also, Harousseau et al. compared a bortezomib–dexamethasone combination with a vincristine–doxorubicin–dexamethasone combination, but PFS did not reach statistical significance in favour of the bortezomib arm (p = 0.057) [18].

Thirty one patients had in their treatment botezomib based regimen as first or second line. We founded that those patients had median OS about 37 months compared to median 29 months in the other 39 patients who didn't receive bortezomib in their treatment and OS reach statistical significance in favor of the bortezomib arm (P=0.011).

In previously untreated MM, among studies of patients who were not candidates for transplant, the vista trial reported a statistically significant difference in OS when bortezomib was compared with a non-bortezomib-containing regimen (hr: 0.65; p < 0.001) [19-20-21]. In the studies of transplant patients, Sonneveld et al. demonstrated a statistically significant difference in OS (hr: 0.77; 95% ci: 0.60 to 1.00; p = 0.049 [17]. Also in relapsed and refractory MM, Bortezomib in combination with pegylated liposomal doxorubicin was found to significantly improve OS (65% vs. 76%, p = 0.03) [22]. Bortezomib monotherapy improved OS significantly more than did dexamethasone (hr: 0.77, p = 0.003; and hr: 0.67, p = 0.47) [23].

The drawbacks of this study are relatively small sample size, cytogenetic analysis was not performed routinely, a lot of financial obstacles affected type and availability of myeloma treatment at the time period of this study and a retrospective nature of the study.

Conclusion:

Multiple Myeloma in Egyptian patients is more common in younger age and mostly diagnosed at advanced stage. Bortezomib based regimen gives a response rate and survival outcome better than conventional treatment. So, Bortezomib based regimen should be received whenever possible in developing countries.

Abbreviations

CRAB	Hypercalcemia, renal failure, anemia, or lytic bone lesions
FLC	Free light chain
IMWG	International Myeloma Working Group
MDE	Myeloma defining events
MM	Multiple myeloma
MRI	Magnetic resonance imaging
OS	Overall survival
PFS	Progression free survival
SDS	Durie-Salmon staging system
SECI	South Egypt Cancer Institute
VAD	Vincristin, doxorubicin, and Dexamethasone

Conflicts of interest:

There are no conflicts of interest.

Authors' contributions

This work was carried out in collaboration among all authors. Authors Refaat A and Ibraheem A designed the study, performed the statistical analysis, and wrote the protocol. Author Gneady A collected the patients' data. Authors Refaat A did the literature searches and wrote the final draft.

References:

[1] Siegel RL, Miller KD, Jemal A .Cancer statistics, 2017. CA: a cancer J Clin 2017 ; 67:7–30.

[2] Palumbo A, Anderson K. Multiple myeloma. N Engl J Med 2011; 364:1046–1060.

[3] Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group Updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014.;15:e538-e548.

[4] Kumar SK, DispenzieriA, LacyMQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia 2014; 28(5):28:1122–1128.

[5] Pulte D, Gondos A, Brenner H. Improvement in survival of older adults with multiple myeloma: results of an updated period analysis of SEER data. Oncologist 2011; 16:1600–1603.

[6] Gay F, Oliva S, Petrucci MT, Conticello C, et al. Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma: a randomised, multicentre, phase 3 trial. Lancet Oncol 2015; 16:1617–1629.

[7] Anuj M, Girindra R, Paulette M, et al. New cancers after autotransplants for multiple myeloma. Biol Blood Marrow Transplant 2015; 21:738–745.

[8] Derman BA, Jasielec J, Langerman SS et al. Racial differences in treatment and outcomes in multiple myeloma: a multiple myeloma research foundation analysis. Blood Cancer J. Aug 2020; 10(8): 80.

[9] Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014.; 15(12): e538-548.

[10] Rajkumar SV, Kyle RA. Multiple myeloma: diagnosis and treatment. Mayo Clin Proc 2005.;80(10):1371–82.

[11] Kumar S, Paiva B, Anderson KC et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. The Lancet Oncology 2016; 17(8): 328-346.

[12] Bassiony ES, Barakat AF, Ghannam AA, et al. Bortezomib in multiple myeloma: Treatment response and survival outcome. Tanta Medical Journal 2017; 45(3):129

[13] Abdel Karim, K., Mostafa, M.Y., Elghoniemy, et al. Multiple Myeloma: A Retrospective Analysis of the Patients Treated at Ain Shams University Clinical Oncology Department with a Review of the Literature. The Egyptian Journal of Hospital Medicine 2018; 31(6182),1-5.

[14] Shin J, Koh Y, Youk J et al. Clinicopathological characteristics of extremely young Korean multiple myeloma patients: therapeutic implications. The Korean journal of internal medicine 2017; 32(4): 722-730.

[15] Jagannath S, Durie BG, Wolf J et al. Bortezomib therapy alone and in combination with dexamethasone for previously untreated symptomatic multiple myeloma. Br J Haematol 2005; 129:776–783.

[16] Reeder CB, Reece DE, Kukreti V, et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. Leukemia 2009; 23(7):1337-41.

[17] Sonneveld P, Schmidt–Wolf IG, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. J Clin Oncol 2012; 30:2946–55.

[18] Harousseau JL, Attal M, Avet–Loiseau H, et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the ifm 2005-01 phase III trial. J Clin Oncol 2010; 28:4621–9.

[19] San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 2008; 359:906–17.

[20] Moreau P, Hulin C, Marit G, et al. Stem cell collection in patients with de novo multiple myeloma treated with the combination of bortezomib and dexamethasone before autologous stem cell transplantation according to IFM 2005-01 trial. Leukemia 2010; 24:1233–5.

[21] Moreau P, Attal M, Pegourie B, et al. Achievement of VGPR to induction therapy is an important prognostic factor for longer PFS in the IFM 2005-01 trial. Blood 2011; 117:3041–4.

[22] Orlowski RZ, Nagler A, Sonneveld P, et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. J Clin Oncol 2007; 25:3892–901.

[23] Richardson PG, Sonneveld P, Schuster M, et al. Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the apex trial. Blood 2007; 110:3557–60.