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Original Article

Retrospective Analysis of 345 Multiple Myeloma Cases: An Investigation from 2 Institutions

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Abstract

Background: Multiple myeloma (MM) accounts for a substantial mortality rate among hematological cancers. The prognosis of the disease has been noticeably changed during the past 2 decades. This study reports a retrospective analysis of 345 MM cases from 2 cancer centers.

Methods: Medical records of 345 MM cases were analyzed in retrospect. Diagnosis of MM was defined in presence of at least 10% plasma cells in bone marrow biopsy and one of the CRAB findings (hypercalcemia, renal failure, anemia and myeloma bone lesions). Survival analysis was performed using Kaplan-Meier method, and the effects of prognostic variables were assessed by Cox proportional hazards model.

Results: The mean age of the patients was 61.98 ± 11.44 years. Comparing to Mayo Clinic series, our patients were relatively younger and suffered from more advanced disease. By a median follow up time of 45 months, 1- and 5-year overall survival (OS) rates were 78.0% and 35.6%, respectively. Regarding first progression free survival (PFS1), similar rates of 57.7% and 17.0% were observed respectively. In multivariate analysis, hypercalcemia (corrected serum calcium >11 mg/dL), pancytopenia and elevated serum creatinine (Cr) (>2 mg/dL) were found to be independent prognostic factors affecting OS.

Conclusion: Presentation of MM in Iran which is a developing country, was significantly different from developed countries. This finding might be generalized to other developing countries as well. In addition, vincristine-adriamycin-dexamethasone (VAD) therapy was an inferior protocol compared to bortezomib as first and second lines. Furthermore, pancytopenia was observed in about 9% of the patients and was an independent prognosticator of the disease.

Keywords: Bortezomib, Multiple myeloma, Pancytopenia

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Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy. MM treatments have changed significantly in the last 2 decades and led to improved outcomes in terms of patients' survival.[1,2] Different chemotherapy protocols are being used in treatment of MM.[3] The spectrum ranges from older alkylating agents containing regimens to more potent and targeted therapies. Moreover, some patients have been treated with bone marrow transplantation as well, either autologous or allogeneic.[4] This study aimed to report the outcomes of 345 MM cases treated in our hematology/oncology centers in the past 2 decades.

Materials and Methods

Three hundred and forty-five newly diagnosed cases at 501 AJA and Arad hospitals were enrolled in this study. These cases were diagnosed with MM during September 1993 to August 2016. Diagnosis of MM was confirmed when at least 10% of bone marrow was occupied by plasma cells and one of the following abnormalities was seen: hypercalcemia, renal failure, anemia and presence of bone lesions. Pathology data and medical documents of patients were reviewed. First and second line chemotherapies, bone marrow transplantation, gender, age, blood urea nitrogen (BUN), creatinine (Cr), complete blood count (CBC), and presence of bone pain at time of diagnosis were studied. The patients were followed until death or their last contact with the hospital during the study period (September 1993 – April 2017). Parameters of interest in this study were overall and progression free survival (PFS) rates. Overall survival (OS) was defined as the time elapsed from the start of the first line treatment to death from any cause. First progression free survival (PFS1) was also defined as the time from the first line chemotherapy until relapse or death. Second PFS (PFS2) was another parameter that was calculated in this study and defined as the time from the start of second line therapy to second relapse or death. Besides, the presentation features of Iranian MM

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patients were compared to findings of a leading study from Mayo Clinic. Comparison of the medians was done by Wilcoxon signed rank test. The median follow up time was estimated by reverse Kaplan-Meier method. Log-rank test was used to compare survival curves, and the effect of possible prognostic variables was calculated by Cox proportional hazards model. Initially, univariate analysis was done and each variable with a P-value of less than 0.2 was selected for multivariate analysis. Finally *P* values of less than 0.05 in multivariate analysis were considered significant. The data were analyzed by SPSS software for windows version 23, and R software for Windows version 3.4.0 using survival package.

Results

Demographics and Basic Results

Two hundred and nineteen male and 126 female patients were included in the study. The mean age was 61.98 ± 11.44 years (range = 30–88 years). The mean ages of male and female patients were 62.45 ± 11.19 and 61.17 ± 11.86 years, respectively. The difference was not statistically significant (independent sample *t* test, $P = 0.32$). The most common presenting feature was bone pain in 73.8% of patients. The next common features were elevated erythrocyte sedimentation rate (ESR), anemia, elevated creatinine and elevated calcium. Characteristics of cases at baseline and their presenting features are summarized in Table 1.

Majority of cases were treated with chemotherapy alone. Chemotherapy was performed using different agents including vincristine-adriamycin-dexamethasone (VAD), mini-CHOP (cyclophosphamide-adriamycin-vincristine-dexamethasone), and bortezomib-containing regimens. One hundred and forty-six cases were treated with VAD, 120 cases with Bortezomib-based regimens, 58 cases with mini-CHOP and 20 cases with other types of chemotherapies in the first line. Twenty-four cases were treated with autologous stem cell transplantation (auto-SCT) as well. The mean time to transplant (TTT) was 22 months (range: 8–106 months).

In 265 cases, relapse (n = 186) or death before second line therapy (n = 79) occurred. One hundred and forty-five cases with relapse or refractory myeloma were treated in our center, including 67 patients treated with cyclophosphamide-containing regimens, 51 cases treated with bortezomib-based regimens, 17 cases treated with VAD, and 11 cases treated with other chemotherapy regimens. Data of first and second line treatments are demonstrated in Table 2.

Maintenance therapy by thalidomide, lenalidomide, or both performed in 79.6%, 3.9%, and 16.5% of the cases, respectively. For skeletal care, 82.4%, 6.0%, and 11.6% of the cases were treated with pamidronate, zoledronic acid or both, respectively.

Comparison of Presenting Features in Iranian MM Patients Versus Mayo Clinic Patients

Compared to the results from Mayo Clinic series,[5] it seems that Iranian patients with MM were younger, and suffered from more advanced disease. The median

Table 1. Baseline Characteristics of Patients

Baseline Characteristics		
Characteristic	**Mean ± SD**	**Range**
Gender	219M / 126F	N/A
Age	61.98 ± 11.44 years	30–88 years
WBC	(6.22 ± 2.89) × 10^3/μL	(0.6–19.5) ×10^3/μL
Hb	(9.70 ± 2.14) g/dL	(3.9–15.9) g/dL
Platelet	(195.01 ± 84.25) × 10^3/μL	(13.0–575.0) ×10^3/μL
Creatinine	(2.04 ± 2.56) mg/dL	(0.6–26.6) mg/dL
BUN	(28.63 ± 20.06) mg/dL	(8.0–148.0) mg/dL
Calcium	(9.72 ± 1.56) mg/dL	(6.20–18.0)
Corrected Calcium	(10.15 ± 1.55) mg/dL	(6.9–18.7) mg/dL
ESR	(97.38 ± 42.48) mm/h	(2–180) mm/h
BMPC%	40.11 ± 24.82	2.5–95.0
Albumin	(3.4 ± 0.7) g/dL	(1.3–5.6) g/dL
Presenting Characteristics		
Findings	**Prevalence (% Valid)**	
Bone pain	73.8%	
Anemia (Hb <10 mg/dL)	58.0%	
ESR >100 mm/h	59.3%	
Corrected Ca >11	20.1%	
Cr >2 mg/dL	22.1%	
Pancytopenia	8.9%	

Abbreviations: Hb, hemoglobin; WBC, white blood cell; BUN, blood urea nitrogen; ESR, erythrocyte sedimentation rate, Cr, creatinine; BMPC%, bone marrow plasma cell.

Table 2. First Line and Second Line Chemotherapy for All Cases

First line	Second Line for Each of First Line Treatments	Second Line for All First Line Treatments
VAD (n = 146, number of relapsed or refractory cases = 99)	Cyclophosphamide = 45 Bortezomib = 19 VAD = 6 Other chemotherapy or in other centers = 30	VAD = 17
Mini-CHOP: (n = 58, number of relapsed or refractory cases = 34)	Cyclophosphamide = 11 Bortezomib = 5 VAD = 5 Other chemotherapy or in other centers = 13	Cyclophosphamide = 67, mini-CHOP=13, cyclophosphamide-etoposide (alone or in combination) n=35, cyclophosphamide-vincristine, n=8, other combinations, n=11
Bortezomib-based: (n = 120, number of relapsed or refractory cases = 38)	Cyclophosphamide = 4 Bortezomib = 23 VAD = 4 Other chemotherapy or in other centers = 7	Bortezomib = 51
Others: (n = 20, number of relapsed or refractory cases = 13)	Cyclophosphamide = 7 Bortezomib = 4 VAD = 2 Other chemotherapy or in other centers = 0	Other chemotherapy or in other centers = 50

Abbreviations: VAD, vincristine-adriamycin-dexamethasone; CHOP, cyclophosphamide-adriamycin-vincristine-dexamethasone.

age, hemoglobin (Hb) and serum Cr in our study were 63 years, 9.5 g/dL and 1.4 mg/dL, respectively which were significantly different from 66 years, 10.9 g/dL and 1.2 mg/dL reported in Mayo Clinic study ($P < 0.001$ for all three items). Serum calcium concentration was not different between 2 groups ($P = 0.588$). In Mayo Clinic series, 73% of patients had Hb < 12 g/dL at the time of diagnosis, and during the disease course, the percentage reached 97%. In our patient series, the same condition (Hb < 12) observed in 85% of patients from the beginning.

Survival Analysis

The median follow up time was 45 months (95% CI: 37–51). Probability of OS at the end of 1, 2 and 5 years were 78.0% (95% CI: 73.1%–82.1%), 65.2% (95% CI: 59.6%–70.2%), and 35.6% (95% CI: 29.5%–41.7%), respectively. The median progression-free time was 17 months (95% CI: 14–19). The 1-, 2- and 5-year PFS1 rates were 57.7% (95% CI: 52.1%–62.9%), 35.6% (95% CI: 30.2%–41.1%), and 17.0% (95% CI: 12.5%–22.1%), respectively. The probability of OS was significantly different for BMT, Cr >2, corrected Ca>11, anemia, pancytopenia and age >65 years (Figure 1).

Differences for PFS1 were significant for gender, BMT, type of first line chemotherapy (VAD therapy was significantly inferior compared to bortezomib-based regimens), Cr >2, corrected Ca >11 and pancytopenia (Table 3).

Second PFS rates were 53.4% (95% CI: 44.7%–61.3%)

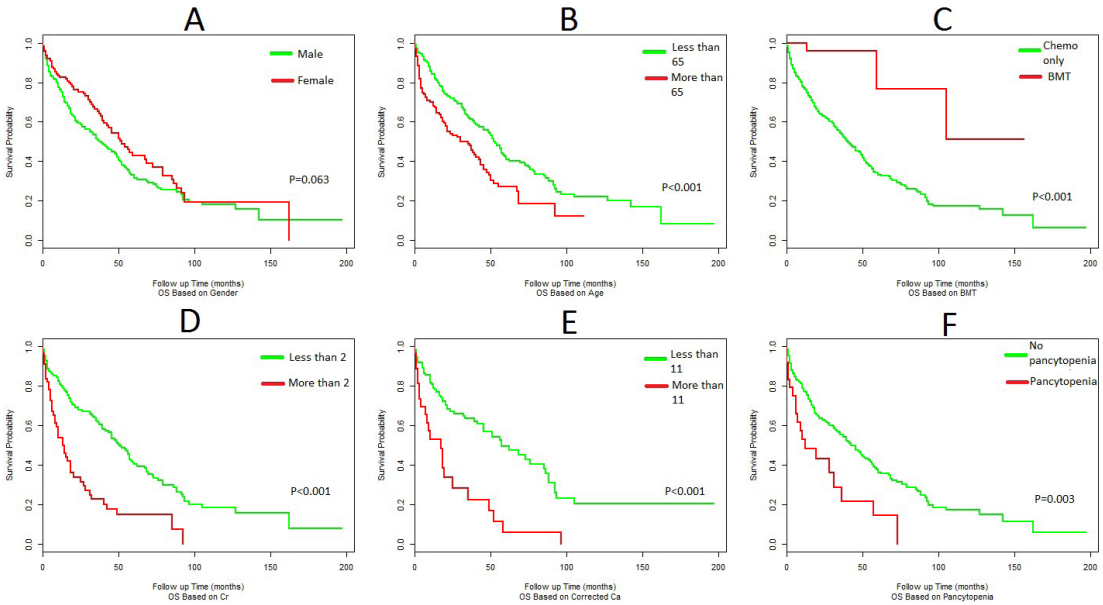

Figure 1. Differences in OS Curves Based on: (A) Gender, (B) Age, (C) BMT, (D) Serum Cr, (E) Corrected Ca, (F) Pancytopenia.

Table 3. Differences Among OS and First PFS of Patients in Different Subgroups

Covariate	Subgroups	2-year OS	*P*-Value	2-year PFS1	*P* Value
Gender	Male	59.3%	0.063	30.1%	0.032
	Female	75.2%		44.9%	
BMT	Yes	95.8%	<0.001	61.0%	0.019
	No	62.8%		33.7%	
First line chemotherapy	mini-CHOP	66.4%	0.920	34.7%	0.011
	Bortezomib based	64.5%		47.2%	
	VAD*	63.8%		25.56%	
Serum creatinine	>2 mg/dL	33.8%	<0.001	21.0%	<0.001
	≤2 mg/dL	67.8%		35.3%	
Corrected calcium	>11 mg/dL	33.6%	<0.001	23.7%	0.006
	≤11 mg/dL	67.0%		38.6%	
Anemia	Hb >10 g/dL	71.2%	0.002	36.6%	0.172
	Hb ≤10 g/dL	53.3%		30.1%	
Pancytopenia	Yes	43.0%	0.003	21.2%	0.004
	No	62.7%		34.1%	
Age	>65 years	54.1%	<0.001	33.2%	0.224
	≤65 years	72.1%		37.1%	
Albumin	>3.5 g/dL	69.1%	0.226	37.1%	0.583
	≤3.5 g/dL	55.6%		32.9%	

Abbreviations: VAD, vincristine, adriamycin and dexamethasone; OS, overall survival; BMT, bone marrow transplantation; mini-CHOP, cyclophosphamide-adriamycin-vincristine-dexamethasone; PFS1, first progression-free survival.

and 28.9% (95% CI: 21.4%-36.8%) at the end of 12 and 24 months, respectively. Subgroup analysis revealed a clinically important but statistically borderline difference for PFS2 among second line treatments. Two-year PFS2 rates were 20.6% (95% CI: 5.1%–43.3%), 27.8% (95% CI: 17.3%–39.3%) and 36.6% (95% CI: 23.0%–50.4%) for VAD, cyclophosphamide-containing and bortezomib-based groups, respectively ($P = 0.088$) (Figure 2).

In a 2 by 2 comparison, in both first and second lines of chemotherapy, bortezomib-based treatments resulted in best progression-free survival rates, and VAD therapies led to the worst PFS. The difference between VAD and bortezomib was statistically significant (Table 4).

Cox Proportional Hazards Model

Using univariate analysis on prognostic factors of OS, the following factors were selected to enter multivariate analysis: age, gender, serum creatinine, corrected calcium, anemia and pancytopenia. Three of them were statistically significant in multivariate analysis: pancytopenia (HR = 3.66, 95% CI: 1.73–7.73, $P < 0.001$), elevated serum Cr (HR = 2.32, 95% CI: 1.36–3.99, $P = 0.002$) and corrected Ca (HR = 2.59, 95% CI: 1.50–4.47, $P < 0.001$). Conducting a univariate analysis on factors affecting PFS1, the above 6 variables except age were significant and entered the multivariate analysis. Adjusted hazard ratios for significant findings after multivariate analysis were as follows: 3.13 (95% CI: 1.55–6.34, $P = 0.001$) for pancytopenia and 2.05 (95% CI: 1.24–3.40, $P = 0.005$) for elevated serum Cr. The detailed results of univariate and multivariate analysis are demonstrated in Table 5.

Assumptions of proportional hazards model were

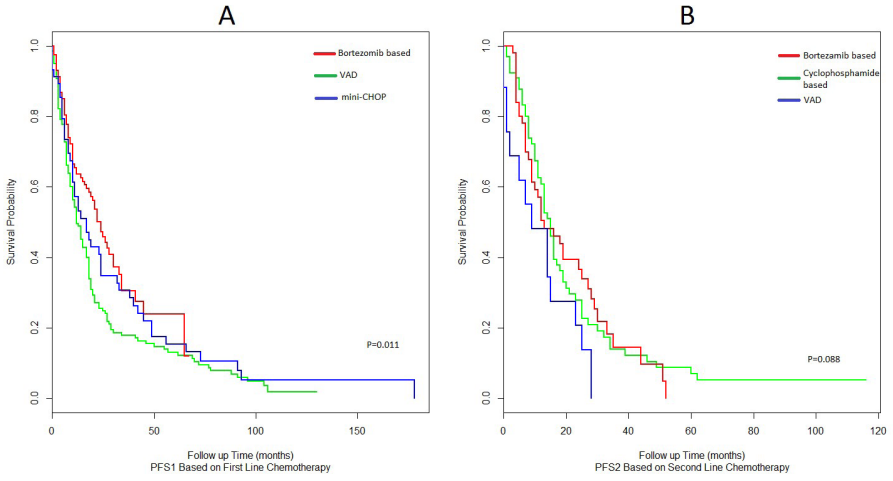

Figure 2. (A) PFS1 Curves Categorized by First Line of Chemotherapy. (B) Second PFS Based on Second Line of Treatment.

Table 4. Comparing First and Second Line Treatments in a 2 by 2 Manner on PFS1 and PFS2

First or Second Line Chemotherapies	PFS1		PFS2	
	2-Year Probability	*P*	2-Year Probability	*P*
VAD	25.6%	0.002	20.6%	0.027
Bortezomib	47.2%		36.6%	
VAD	25.6%	0.261	20.6%	0.058
Cyclophosphamide containing (mini-CHOP in first line)	34.7%		27.8%	
Bortezomib	47.2%	0.339	36.6%	0.892
Cyclophosphamide containing (mini-CHOP in first line)	34.7%		27.8%	

Abbreviations: VAD, vincristine, adriamycin and dexamethasone; PFS1, first progression-free survival; PFS2, second progression-free survival, mini-CHOP, cyclophosphamide-adriamycin-vincristine-dexamethasone.

Table 5. Results of Univariate and Multivariate Analysis of Prognostic Factors on OS and PFS1

Covariate	OS				PFS1			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (>65 years)	1.71 (1.28–2.28)	<0.001	1.47 (0.92–2.36)	0.110	1.17 (0.91–1.51)	0.226	N/A	N/A
Gender (F/M)	0.76 (0.57–1.02)	0.063	1.10 (0.68–1.78)	0.693	0.76 (0.56–0.98)	0.033	0.90 (0.59–1.38)	0.624
Serum Cr > 2 mg/dL	2.60 (1.83–3.71)	<0.001	2.32 (1.36–3.99)	0.002	1.88 (1.35–2.61)	<0.001	2.05 (1.24–3.40)	0.005
Corrected Ca >11 mg/dL	2.90 (1.76–4.78)	<0.001	2.59 (1.50–4.47)	<0.001	1.91 (1.19–3.07)	0.007	1.60 (0.95–2.71)	0.078
Anemia (Hb <10 g/dL)	1.63 (1.19–2.23)	0.002	0.71 (0.44–1.15)	0.167	1.22 (0.92–1.61)	0.171	0.82 (0.54–1.27)	0.377
Pancytopenia	2.10 (1.28–3.44)	0.003	3.66 (1.73–7.73)	<0.001	1.97 (1.24–3.15)	0.005	3.13 (1.55–6.34)	0.001
Serum albumin <3.5 g/dL	1.28 (0.86–1.91)	0.225	N/A	N/A	1.11 (0.77–1.60)	0.583	N/A	N/A

Abbreviations: OS, overall survival; PFS1, first progression-free survival; Hb, hemoglobin; Cr, creatinine.

met and no evidence were found to contradict them (Schoenfeld's global test, $P = 0.703$). Furthermore, residual plots were used to graphically assess each covariate and individual tests were all non-significant ($P = 0.103$, 0.99, 0.919, 0.467, 0.840, and 0.537 for age, gender, creatinine, corrected serum calcium, anemia and pancytopenia, respectively).

Discussion

In this study, bone pain and anemia were the most commonly observed features in our patients. Elevated creatinine and calcium were observed in about 20% of the cases at the time of diagnosis. Comparing to the results from Mayo Clinic series, patients in our study suffered from more advanced disease at a younger age.[5] MM arises from a prior monoclonal gammopathy of undetermined significance (MGUS).[6] Therefore, since the life expectancy in Iran is lower than developed countries,[7] it may be hypothesized that Iranian patients with MGUS do not survive enough to develop overt MM. Additionally, more advanced forms of the disease at the time of manifestation, could be, to some extent, due to the not well organized referral system in Iran. Other possible reasons could be genetic and socioeconomic differences.

Pancytopenia was seen in 8.9% of the cases. Pancytopenia is not a common feature in myeloma cases,[8] and according to our analysis, it is related to poorer outcomes. To the best of our knowledge, its adverse effect on MM prognosis has not been reported in the literature.

As expected, in our cases, elevated creatinine and calcium had a negative impact on OS. Furthermore, males had a slightly worse prognosis than females. This finding is similar to the results of previous studies[9-11] and in contrast to the findings of Boyd et al.[12] It should be mentioned that in latter study, cases with Cr >5.65 mg/dL were excluded,[12,13] so their inclusion criteria could lead to a selection bias. Overall, survival is higher for females with MM.

In this study, different chemotherapy regimens were compared to each other. Based on the PFS1 data in first line therapy, mini-CHOP did not differ significantly from Bortezomib and VAD, but Bortezomib was superior compared to VAD. However, the OS of these 3 types of chemotherapy did not vary noticeably. The majority of cases, who received VAD therapy in the first line, were treated by cyclophosphamide- or bortezomib- based combinations in the subsequent lines. Therefore, lower efficacy of VAD could be compensated in the following lines of therapy.

Similar to the first line therapy, bortezomib was also significantly superior to VAD in the second line, according to PFS2 analysis. Therefore, based on PFS1 and PFS2, it can be concluded that VAD was less effective, and its acceptable OS was probably due to the

efficacy of bortezomib or cyclophosphamide in the next lines of therapy.

VAD was once a choice for MM treatment in many centers in 1990s. Later in 2005, a study raised serious doubts about its value for MM treatment.[14] Therefore, a disagreement took place among experts about whether VAD should be completely discarded from MM therapies or not.[15,16]

SCT is proven to be an effective treatment in order to increase relatively long-term survivals in MM patients.[17,18] Although our study revealed better outcomes for SCT, the sample was not symmetrically distributed between 2 groups (SCT vs. chemotherapy). Also the mean TTT was 22 months which means cases of early mortality were analyzed in the chemotherapy group. Hence, a powerful and methodical interpretation could not be made.

Lack of myeloma staging for the disease was a major limitation of this study. Of our patients, 24 cases received SCT. Comparing to developed countries, this number of cases is quite low. Fortunately, in recent years, number of cases who underwent SCT is increasing.

In conclusion, it seems that Iranian MM patients suffered from more progressive disease at the time of diagnosis. Additionally, based on current data, VAD was not an effective treatment in first and second lines of chemotherapy. Although Bortezomib had better PFS1 and PFS2, there was no statistical significant difference between bortezomib and mini-CHOP, and Bortezomib and cyclophosphamide in first and second lines of therapy, respectively.

Authors' Contribution
All authors contributed equally.

Conflict of Interest Disclosures
The authors have no conflicts of interest.

Ethical Statement
Written informed consent was obtained from all participants and the study protocol was approved by ethical committee of AJA University of Medical Sciences.

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References
1. Anderson KC. Progress and Paradigms in Multiple Myeloma. Clin Cancer Res. 2016;22(22):5419-27. doi: 10.1158/1078-0432.ccr-16-0625.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66(1):7-30. doi: 10.3322/caac.21332.
3. Kumar SK, Rajkumar V, Kyle RA, van Duin M, Sonneveld P, Mateos MV, et al. Multiple myeloma. Nat Rev Dis Primers. 2017;3:17046. doi: 10.1038/nrdp.2017.46.
4. Hari P. Recent advances in understanding multiple myeloma. Hematol Oncol Stem Cell Ther. 2017;10(4):267-71. doi: 10.1016/j.hemonc.2017.05.005.
5. Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc. 2003;78(1):21-33. doi: 10.4065/78.1.21.
6. Landgren O, Kyle RA, Pfeiffer RM, Katzmann JA, Caporaso NE, Hayes RB, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. Blood. 2009;113(22):5412-7. doi: 10.1182/blood-2008-12-194241.
7. Murray CJ, Barber RM, Foreman KJ, Abbasoglu Ozgoren A, Abd-Allah F, Abera SF, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: quantifying the epidemiological transition. Lancet. 2015;386(10009):2145-91. doi: 10.1016/s0140-6736(15)61340-x.
8. Sridevi HB, Rai S, Suresh PK, Somesh MS, Minal J. Pancytopenia in Multiple Myeloma- An Enigma: Our Experience from Tertiary Care Hospital. J Clin Diagn Res. 2015;9(11):Ec04-6. doi: 10.7860/jcdr/2015/12788.6718.
9. Coleman MP, Gatta G, Verdecchia A, Esteve J, Sant M, Storm H, et al. EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century. Ann Oncol. 2003;14 Suppl 5:v128-49.
10. Kristinsson SY, Landgren O, Dickman PW, Derolf AR, Bjorkholm M. Patterns of survival in multiple myeloma: a population-based study of patients diagnosed in Sweden from 1973 to 2003. J Clin Oncol. 2007;25(15):1993-9. doi: 10.1200/jco.2006.09.0100.
11. Turesson I, Velez R, Kristinsson SY, Landgren O. Patterns of improved survival in patients with multiple myeloma in the twenty-first century: a population-based study. J Clin Oncol. 2010;28(5):830-4. doi: 10.1200/jco.2009.25.4177.
12. Boyd KD, Ross FM, Chiecchio L, Dagrada G, Konn ZJ, Tapper WJ, et al. Gender disparities in the tumor genetics and clinical outcome of multiple myeloma. Cancer Epidemiol Biomarkers Prev. 2011;20(8):1703-7. doi: 10.1158/1055-9965.epi-11-0157.
13. Morgan GJ, Davies FE, Gregory WM, Cocks K, Bell SE, Szubert AJ, et al. First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial. Lancet. 2010;376(9757):1989-99. doi: 10.1016/s0140-6736(10)62051-x.
14. Cavo M, Zamagni E, Tosi P, Tacchetti P, Cellini C, Cangini D, et al. Superiority of thalidomide and dexamethasone over vincristine-doxorubicindexamethasone (VAD) as primary therapy in preparation for autologous transplantation for multiple myeloma. Blood. 2005;106(1):35-9. doi: 10.1182/blood-2005-02-0522.
15. Lane SW, Gill D, Mollee PN, Rajkumar SV. Role of VAD in the initial treatment of multiple myeloma. Blood. 2005;106(10):3674; author reply -5. doi: 10.1182/blood-2005-07-2610.
16. Rajkumar SV. Multiple myeloma: the death of VAD as initial therapy. Blood. 2005;106(1):2-3. doi: 10.1182/blood-2005-04-1451.
17. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. N Engl J Med. 1996;335(2):91-7. doi: 10.1056/nejm199607113350204.
18. Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med. 2003;348(19):1875-83. doi: 10.1056/NEJMoa022340.