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Superiority of CyBorD Over VAD is More Evident in First than in Second Line Treatment of Multiple Myeloma

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Abstract

Introduction: In the era of novel anti-myeloma agents and monoclonal antibodies (daratumumab) and due to their high cost, earlier low cost regimens (VAD or CyBorD) may be used.

Objective: to compare outcome of treatment of CyBorD versus VAD regimens in multiple myeloma.

Methods: This cohort study included 89 MM patients treated at National Cancer Institute (NCI), Cairo, Egypt from January 2011 to December 2015. All patients were evaluated clinically and laboratory for different responses with either lines of treatment (VAD *vs.* CyBorD), and correlated with different survival parameters; Progression Free Survival (PFS), Disease Free (DFS), and Overall Survival (OS), and clinico-pathologic factors.

Results: The median age of patients was 54 years (32-76), with male predominance (male to female ratio 1.87:1). The most common presenting symptoms were bony pains (44.9%) followed by bony masses (22.5%), fractures (16.9%), pallor (7.9%), neurological symptoms (5.6%) and finally oliguria (2.2%). CyBorD have better overall response rate (≥ PR) (p=0.031), PFS (p=0.004) and DFS (p=0.013) as 1st line treatment compared to VAD regimen. Also in previously treated patients CyBorD showed better PFS (p=0.039) compared to VAD regimen.

There was a significant relation between age (p=0.001 & <0.001) and ASCT (p=0.001 & 0.034) with PFS and OS respectively.

Conclusion: CyBorD have significant better overall response treatment (≥ PR), PFS and DFS in 1st line treatment compared to VAD regimen. While in previously treated patients only PFS benefit for CyBorD over VAD regimen was obtained. Age and ASCT had significant effect on PFS and OS.

Keywords: Multiple myeloma; CyBorD; VAD regimen

Abbreviation

PFS: Progression Free Survival; OS: Overall Survival; VGPR: Very Good Partial Response; PR: Partial Responses

Introduction

Multiple myeloma is a malignant neoplasm of monoclonal population of terminally differentiated, immunoglobulin-producing plasma cells that accumulate in bone marrow, leading to bone destruction and marrow failure [1]. In Egypt, MM represented 0.53% of cancers in males and 0.34% of cancers in females at 4-year period from (2008-2011) with peak age of diagnosis from 60 to 65 years in males and from 70 to 75 years for females [2]. VAD regimen had been used for about 2 decades as the standard induction therapy for MM patients [3]. Later on, Cyclophosphamide combined with Dexamethasone, or Betamethasone (CyBet), replaced VAD as the standard induction regimen with less toxicity and same outcome [4]. Bortezomib, a proteasome inhibitor with antimyeloma activity was approved in 2003, had overcome resistance to chemotherapy associated with certain cytogenetic abnormalities [5,6]. Bortezomib in combination with Cyclophosphamide and Dexamethasone (CyBorD) have proven efficacy with ORR of 88%, ≥ VGPR of 61%, CR/nCR of 39% of newly diagnosed MM patients and replaced VAD as the standard induction protocol [7].

In this cohort study, we evaluated the outcome of CyBorD versus VAD regimen and its relation to different prognostic factors.

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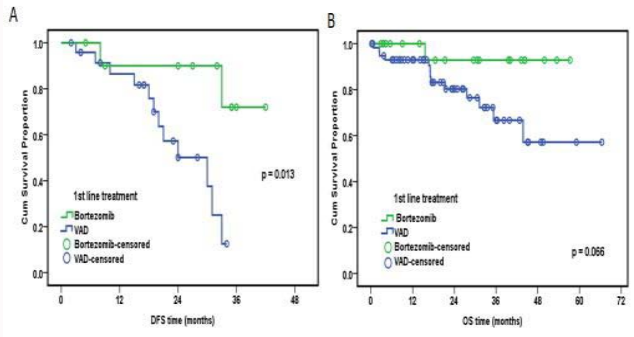

Figure 1: DFS and OS according to 1st line.

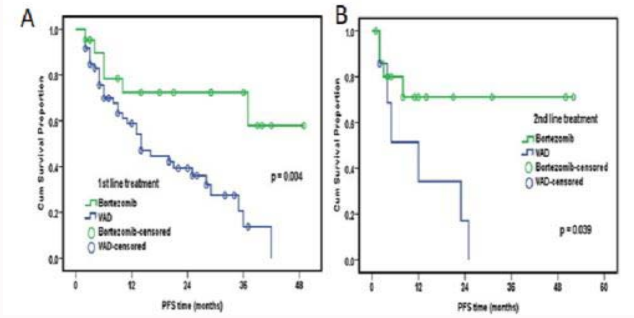

Figure 2: PFS according to chemotherapy in 1st (A) or 2nd line (B).

Patients and Methods

This cohort study included all (89) newly diagnosed multiple myeloma patients treated in the Medical Oncology department of National Cancer Institute (NCI), Cairo University, Egypt from beginning of 2011 to the end of 2015. Either VAD or CyBorD were the 1st line induction in 81 patients and the 2nd line in 23 patients (either relapsed or progressed). Patients were subjected to full history taking, clinical examination, for bony pains, masses, pathological fractures, neurological manifestations, and laboratory assessment including serum protein electrophoresis, serum and urine immunofixation, to detect the type of M proteins, Hemoglobin and platelet level, Serum calcium level, Serum albumin level, B_2-microglobulin level, C-reaction protein, Serum LDH, Serum creatinine level bone marrow aspiration for detecting the Percentage of plasma cells in BM, immunophenotyping, and cytogenetics, assessment of response to treatment according to International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma; Complete Response (CR) was demarcated by the loss of M protein in serum and urine as well as the loss of any soft tissue plasmacytomas and bone marrow plasma cells <5%; PR was definite by 50% drop of serum M proteins and urine M protein <200 mg/24 hr. While, Very Good Partial Response (VGPR) include the criteria for Partial Response (PR) and also M proteins were detected only by immunofixation and not on electrophoresis or serum M protein reduction ≥ 90% and urine M protein <100 mg/24 hr [8]. VAD consists of Vincristine 0.4 mg/day continuous IV infusion over 4 days, Doxorubicin 9 mg/m^2/day continuous IV infusion over 4 days and Dexamethasone 40 mg daily PO for 4 days and repeat cycle every 28 days for 4-6 cycles. CyBorD consists of 4-weekly cycles of bortezomib 1.3 mg/m^2 SC or IV, cyclophosphamide 300 mg/m^2 and dexamethasone 40 mg on days 1, 8, 15 and 22.

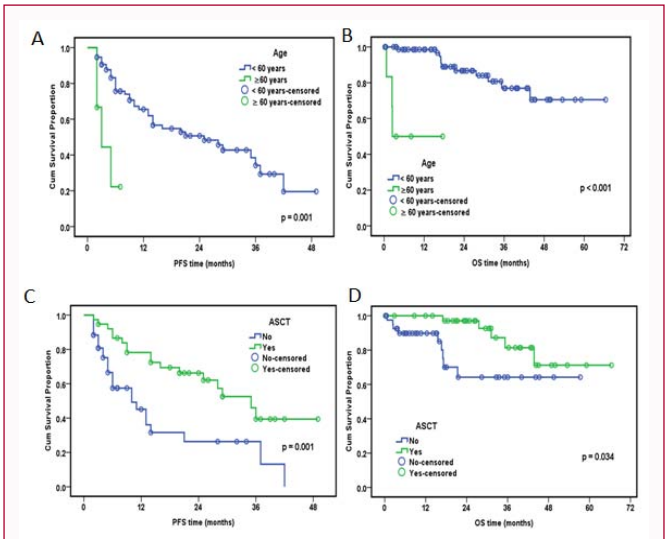

Figure 3: PFS and OS according to age (A&B) and ASCT (C&D).

Table 1: Clinico-pathologic features.

		Number (89)	Percent
Age	Median (range)	54 (32 to 76)years	
	<60 years	80	89.90%
	≥ 60 years	9	10.10%
Sex	Male	58	65.20%
	Female	31	34.80%
Clinical Presentation	Bony pains	40	44.9
	Bony masses	20	22.5
	Fracture	15	16.9
	Neurological symptoms	7	7.9
	Fatigue	5	5.6
	Oliguria	2	2.2
LDH	Normal	27	30.3
	High	18	20.2
Cytogenetics	Available	7	7.9
Albumin	Median (range) mg/dl	3.5(1.8 to 4.8)	
B_2 Microglobulin	Median (range) mg/dl	5 (1.9 to 36)	
Creatinine	Median (range) mg/dl	1(0.4 to 8.7)	
DSS	IA	3	3.4
	IIA	7	7.9
	IIB	1	1.1
	IIIA	64	71.9
	IIIB	14	15.7
ISS	I	12	13.5
	II	37	41.6
	III	40	44.9

Statistical Methods

Data was analyzed using SPSSwin version 21 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test or (Fisher's exact test) was used to examine the relation between qualitative variables. Kaplan-

Table 2: Relation of clinico-pathologic factors and line of treatment.

Investigation	Total number (81)		VAD (60)		CyBorD (21)		P value
	No	%	No	%	No	%	
Age							
<60 years	75	93	55	91.7	20	95	1
≥ 60 years	6	7.4	5	8.3	1	4.8	
Sex							
Male	52	64	35	58.3	17	81	0.063
Female	29	36	25	41.7	4	19	
Clinical picture							
Bony pains	40	49	27	45	13	62	0.182
Bony Masses	16	20	11	18.3	5	24	0.587
Fracture	14	17	12	20	2	9.5	0.274
Pallor	6	7.4	6	10	0	0	0.331
Weakness	3	3.7	2	3.3	1	4.8	*
Oliguria	2	2.5	2	3.3	0	0	*
B_2 microglobulin							
≤ 3.5mg/l	18	22	14	23.3	4	19	0.684
>3.5mg/l	63	78	46	76.7	17	81	
Creatinine							
≤ 1.5mg/dl	59	73	45	75	14	67	0.46
>1.5mg/dl	22	27	15	25	7	33	
LDH Normal	26	32	21	35	5	24	0.440
High	17	21	12	20	5	24	
Albumin							
<3gm/dl	15	19	10	16.7	5	24	0.468
≥ 3gm/dl	66	82	50	83.3	16	76	
DSS							
I and II	11	14	10	16.7	1	4.8	0.171
III	70	86	50	83.3	1	4.8	
ISS I	12	15	10	16.7	2	9.5	
II	35	43	24	40	11	52	0.552
III	34	42	26	43.3	8	38	

Table 3: Relation between different responses and 1st line treatment.

Response	Total Number (81)		VAD -60		CyBorD -21		P value
	NO	%	No	%	No	%	
CR	36	44.4	25	42	11	52	0.176
VGPR	7	8.6	5	8.3	2	9.5	
PR	11	13.6	6	10	5	24	
MR	5	6.2	4	6.7	1	4.8	
NR	11	13.6	9	15	2	9.5	
No assessment	11	13.6	11	18	0	0	
CR	36	44.4	25	42	11	52	0.395S
No CR	45	55.6	35	58	10	48	
≥ VGPR	43	53.1	30	50	13	62	0.347
<VGPR	38	46.9	30	50	8	38	
CR+VGPR+PR	54	66.7	36	60	18	86	0.031
NO CR+VGPR+PR	27	33.3	24	40	3	14	

Table 4: PFS and DFS according to chemotherapy received.

	Number	Events	1Y-PFS	2Y-PFS	3Y-PFS	P value
Whole group	89	50	59.70%	44.10%	28.20%	
1st Line treatment	81	42	62.50%	48.30%	32.60%	0.004
VAD`	60	36	58.80%	39.30%	13.70%	
Bortezomib-based	21	6	72.40%	72.40%	72.40%	
2nd Line treatment	23	10	58.10%	46.50%	34.90%	0.039
VAD	7	6	34.30%	17.10%	0.00%	
Bortezomib-based	16	4	71.10%	71.10%	71.10%	
	Number	**Events**	**1Y-DFS**	**2Y-DFS**	**3Y-DFS**	**P value**
1st Line treatment	36	14	87.50%	64.20%	36.70%	0.013
VAD	25	12	86.50%	50.10%	12.50%	
Bortezomib-based	11	2	90.00%	90.00%	72.00%	
2nd Line treatment	10	4	64.00%	48.00%	48.00%	*
VAD	1	1	0.00%	0.00%	0.00%	
Bortezomib-based	9	3	77.80%	58.30%	58.30%	

Meier method calculated all survival estimates. Other predictor and prognostic variables were related to survival using log rank test. P value was set significant at 0.05 levels.

Results

VAD or CyBorD were used as induction regimen for 81 newly diagnosed patients with MM and as 2nd line chemotherapy for 23 patients (either relapsed or progressed).

Demographic Distribution

The median age was 54 years (32-76) with a mean of 51.1 +/- 7.4 years and male predominance (male to female ratio of 1.87:1). The main presenting symptoms were bony pains in 40 patients (44.9%), bony masses in 20 patients (22.5%) bony fractures in 15 patients (16.9%), fatigue in 7 patients (7.9%), neurological symptoms in 5 patients (5.6%), and finally oliguria in 2 patients (2.2%). According to International Staging System (ISS), stage III (44.9%), followed by stage II (41.6%). While, according to Salmon Durie System (DSS) 87.6% were stage III and 9% were stage II (Table 1). Cytogenetic analysis were done only for 7 patients (7.9%) [5 patients have normal karyotype, 1 patient has t (4:14) and 1 patient 17p del]. None of the different clinico-pathologic features have significant relation to any of the two cohorts of first line treatment either CyBorD or VAD regimens (Table 2).

Response and Survival

There were no significant relation between different responses and types of treatment except for the higher Overall response rate (CR+VGPR+PR) with CyBorD than VAD regimen (p 0.031) in 1st line (Table 3). Forty six patients underwent Autologous Stem Cell Transplantation (ASCT), 38 following 1st line treatment [26 patients after VAD regimen while 12 patients after CyBorD], and 8 patients following 2nd line treatment with CyBorD. Following ASCT, 25/46 patients (54.3%) received maintenance therapy with either thalidomide (15) or lenalidomide (10) while, 21/46 patients (45.7%) did not receive maintenance. At a median follow up of 22 months,

Table 5: PFS and OS according to different prognostic factors.

Whole group	No-81	1-Y OS (%)	2-Y OS (%)	3-Y OS (%)	P value	1-Y PFS (%)	2-Y PFS (%)	3-Y PFS (%)	P value
Age									
<60 years	75	98.6	86.7	76.9	<0.001				0.001
≥ 60 years	6	50	-	-		65.5	50.7	34.20%	
Sex									
Male	52	96.1	84.1	74.9	0.872	59.5	48.4	31.9	0.741
Female	29	92.6	82.8	74.6		66.8	48.1	32.1	
Clinical Presentation									
Bony pains	40	94.6	78.8	67.1	0.471	68.4	57.4	34.6	0.486
Bony masses	16	93.8	85.2	85.2	0.954	59.6	51.1	51.1	0.498
Fracture	14	100	90.9	75.8	0.601	62.3	42.7	-	0.476
Weakness	6	100	-	-	*	50	50	50	*
Pallor	3	100	100	-	0.364	44.4	-	-	0.052
Oliguria	2	50	-	-	*	50	-	-	*
Creatinine									
≤ 1.5mg/dl	59	94.8	83.2	72.5	0.731	60.7	45.1	31.9	0.241
>1.5mg/dl	22	95	85.5	85.5		70.4	61.6	61.6	
Albumin									
< 3gm/dl	15	92.6	85.7	68.6	0.879	45	45	45	0.167
≥ 3gm/dl	66	93.7	85.3	73.9		66.4	50.2	32.2	
LDH	**43**								
Normal	26	96	86.4	78.5	0.451	63	48.5	24.9	0.817
High	17	100	100	100		50.2	43	32.3	
B_2-microglobulin									
≤ 3.5 mg/l	18	94.4	94.4	94.4	0.091	70.8	49.6	33.1	0.658
> 3.5mg/l	63	94.9	79.8	66.4		60	48.4	31.8	
ISS I	12	100	100	100	0.134	63.6	42.4	42.4	0.95
II	35	94.1	89.6	70.5		72.3	56	22.3	
III	34	93.4	71	71		52	43.2	36	
Durie Salmon Staging									
I and II	11	90.9	90.9	72.7	0.901	61.4	36.8	36.8	0.464
III	70	95.4	82.3	73.9		62.6	50.3	32.6	
ASCT									
No	43	89.8	64.2	64.2	0.034	45.2	26.3	13.2	0.001
Yes	38	100	97.1	81.4		78.2	66.3	39.4	

14/36 patients (38.9%) who achieved CR to 1st line treatment (VAD and CyBorD) relapsed. Also, after median follow up 23 months 4/10 patients (40%) who achieved CR to 2nd line treatment (VAD and CyBorD) relapsed. Median DFS was 33 months in 1st line treatment, and 18 months in 2nd line treatment. CyBorD resulted in better DFS than VAD in 1st line treatment (p=0.013) as shown in (Table 4 and Figure 1). Median PFS of the whole group (89 patients) was 16 months. CyBorD had better PFS than VAD regimen in 1st line treatment (p=0.004) with median PFS of 21 months, and in 2nd line treatment (p=0.039) with median PFS of 23 months (Table 4 and Figure 2). At a median follow up of 20.8 (0.2 to 66.4) months for the whole group of patients (89), the cumulative overall survival at 1 year was 92.4%, at 2 years was 82.4 %, at 3 years was 73.9% and at end of the study was 51.5%. In 81 patients who received 1st line treatment (CyBorD or VAD), the cumulative overall survival at 1year was 94.8%, at 2 years was 83.6%, at 3 years was 74.1% and by the end of study was 68%. No significant relation between chemotherapy (CyBorD or VAD) and OS in 1st or subsequent lines as shown (Figure 1).

Age and ASCT had significant impact on PFS (p=0.001 for both) and OS (p<0.001 and 0.034 respectively), while the rest of clinico-pathologic factors (sex, clinical presentation, B_2 microglobulin, albumin, creatinine, LDH, ISS and Durie Salmon staging) had no significant effect on either PFS or OS as shown in (Table 5 and Figure 3).

Discussion

Multiple myeloma results from plasma cells associated with abnormal monoclonal immunoglobulin production and bony lesions. MM represents 1.8% of all cancers and about 17% of haematological

malignancies in USA [9]. The incidence of multiple myeloma increases with age, most frequently older adults. The median age was 54 years (32-76) with a mean of 51.1 +/- 7.4 years that was similar to the mean age of 58.5 years range (27 to 80 years) mentioned by El Husseiny et al., 2014 [10]. As reported from other Arabic regions, The median ages in Saudi Arabian and Moroccan studies were 56 years, 59 years , respectively [11,12]. The median age in UK was 72 years [13]. The younger age at diagnosis is an important point for further investigations regarding possible genetic abnormalities, environmental and other causative factors. Multiple myeloma is more frequent in males than in females (approximately1.4:1) [9], as well as at certain Arabic regions e.g. Moracoo [12]. In our study, males were 65.2% of the patients and females were 34.8% with male to female ratio (1.87:1).

High-dose therapy with ASCT after 4-6 cycles of induction chemotherapy is the standard care for newly diagnosed MM patients who are candidates for ASCT since it provides a survival advantage over chemotherapy alone [14,15]. The current study evaluated the efficacy of CyBorD *vs.* VAD as an induction treatment or 2nd line treatment for MM. There was no significant increase in complete response rate or high quality response (≥ VGPR) after bortezomib treatment in newly diagnosed patients when compared to VAD. While, there was a significant rise in the overall response rate (≥ PR) (p=0.031). In the Phase III HOVON-65/GMMG-HD4 Trial, bortezomib-based regimen as induction treatment showed better CR+nCR than VAD [6], also in the IFM 2005/01 trial, bortezomib/dexamethasone resulted in better ORR, CR/nCR, and VGPR than VAD [16], unlike Korean and Swedish retrospective studies which showed significant increase in high quality response (≥ VGPR) only [17,18].

In our study, there was no significant relation between ISS and response to 1st line treatment unlike the Egyptian retrospective study in 2014 which showed a significant association [19].

The HOVON-65/GMMG-HD4 Trial showed Overall Survival (OS), Progression Free Survival (PFS) benefit for bortezomib-based regimen [6]. In the current study, there was only a trend towards better OS (p=0.06), but a significant DFS (p=0.013) and PFS (p=0.004) benefit for CyBorD over VAD as 1st line treatment which is consistent with results of the Swedish retrospective study in 2012, PFS was better with bortezomib [18].

In our study CyBorD had only a PFS advantage over VAD in 2nd line sitting, but no significant difference in complete response, VGPR, Overall Response Rate (ORR), or OS between CyBorD and VAD regimens, which is consistent with results from other studies utilizing bortezomib containing regimens in relapsed or progressed MM despite being not CyBorD and not versus VAD [20,21]. Bortezomib combination has better outcome than bortezomib alone in relapsed/progressed myeloma [22]. To our knowledge, there is no direct comparison between bortezomib containing regimens and VAD in 2nd line treatment of MM (relapsed/progressed), so this is the first study to do that and although its small sample size, it may give an idea about the importance of giving potent drugs in first rather than 2nd or subsequent lines of therapy.

In our study, there was a significant association between ASCT (p=0.001 and 0.034), age (p=0.001 and <0.001) with PFS and OS respectively, while other prognostic factors including (sex, clinical presentation, albumin, LDH, creatinine, B_2 microglobulin, ISS, Durie Salmon Staging) showed no statically significant association, whereas in a previous Egyptian retrospective study, there was a significant association between ISS, creatinine and PFS. Also, there was a significant association between different prognostic factors (sex, B_2 microgloulin, creatinine, albumin, LDH and ISS) and OS [19]. In the Japanese retrospective study, there was a significant relation of age, ASCT and albumin to PFS; also, there was a significant relation between age, ASCT, LDH and creatinine with OS [23]. In the Chinese retrospective study in 2017, there was a significant relation between B_2 microglobulin and PFS, and a significant relation between albumin, B_2 microglobulin and OS [24].

Conclusion

In the era of novel antimyeloma agents and monoclonal antibodies (daratumumab) and due to their high cost earlier low cost regimens (VAD or CyBorD) may be used. CyBorD have significant better overall response treatment (≥ PR), PFS and DFS in 1st line treatment compared to VAD regimen. While in previously treated patients only PFS benefit for CyBorD over VAD regimen was obtained. Age and ASCT had significant effect on PFS and OS.

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