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

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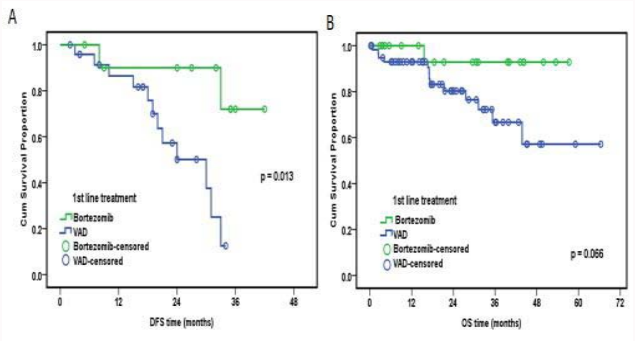


**Figure 1:** DFS and OS according to 1st line.

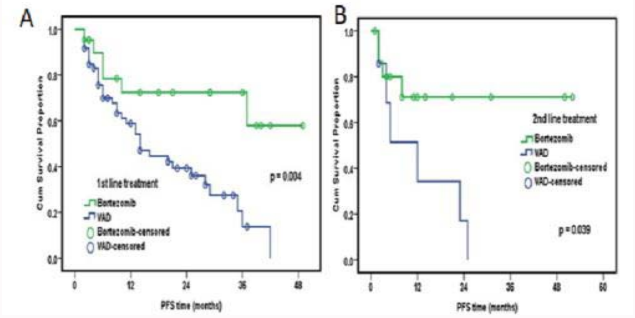


**Figure 2:** PFS according to chemotherapy in 1st (A) or 2nd line (B).

## Patients and Methods

This retrospective 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.

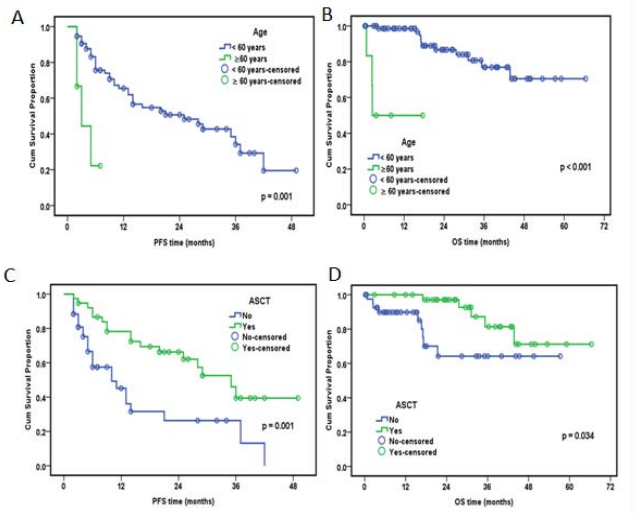


**Figure 3:** PFS and OS according to age (A&B) and ASCT (C&D).

**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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