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VAD Chemotherapy versus Bortezomib Containing Regimens as Remission Induction For ASCT in Multiple Myeloma: A Single Center Experience

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ABSTRACT

Background: Complete response (CR) and very good partial response (VGPR) are targeted with pre-ASCT induction regimens in patients by diagnosed multiple myeloma (MM), who are candidates for ASCT. In this study, it was aimed to compare the response and survival evaluations of cases who underwent induction treatment by vincristine-doxorubicin-dexamethasone (VAD) protocol versus bortezomib containing regimens.

Materials and Methods: The data of 96 ASCT eligible patients, retrospectively analyzed. P value> 0.05 was considered statistically significant.

Results: While 66 cases had received bortezomib containing regimens as induction regimen, 30 cases had received VAD protocol. The total survival was 91.3 (st.s 6) months and 43 (st.s 7.9) months, respectively, when we compared the cases without ASCT and with ASCT (p = 0.001). The OS of patients who underwent ASCT after reaching at least VGPR was longer than the underwent ASCT without reaching VGPR (p=0.019). Post-ASCT PFS (p=0.717) and OS (p = 0.126) analyzes were performed in 74 cases undergoing ASCT treatment, there was no significant statistical difference when patients with treated by VAD protochol and treated by bortezomib containing regimens as pre-ASCT induction regimens was compared to each other.

Conclusion: Whatever the type of induction regimen is, the level of response achieved before ASCT is important. The survival of the myeloma patients are much more influenced with HDT-ASCT as well as post-transplantation strategies to keep the patients in remission. Even though it is outdated, we think that the VAD protocol may be an option in patients who are not responding with the new generation of agents in the following days.

Keywords: Multiple myeloma; VAD; Autologous stem cell transplantation; Bortezomib

INTRODUCTION

Multiple myeloma (MM) is a hematological neoplasm of origin from B cell in bone marrow. MM cases have a monoclonal protein (M-protein) in serum and urine as a results of an uncontrolled proliferation of plasma cells[1]. The most clinically findings of MM are characterized by hypercalcemia, renal failure, anemia and bone lesions. Approximately 1 to 2 percent of the all malignancy, and 15 percent of the hematologic neoplasms consist of MM cases[2]. İt's known that MM is not curable disease, and so the aim of the MM treatment is to be increasing the patient quality of life and disease free survival of MM cases[3].

According to patient's chronological age and patient's performance status, treatment approaches

in MM is differently. The initial estimation for choosing to treatment of MM is depending on eligiblity for high dose therapy (HDT) and autologous stem cell transplantation (ASCT) based on patient's age, performance status and comorbidities[4]. The complete response and very good partial response before ASCT are targeted by the induction chemotherapy protochols in the ASCT-candidates MM patients[5]. At the present time, the published data shows that tree-drug regimens including immunomodulatory drugs, proteasome inhibitors, alkylating agents and corticosteroids, are the mainstay of initial therapy for induction chemotherapy of pre-ASCT[3]. In recent years, the avaliable data showed that the overall survival time and patient's quality of life in MM cases is improved by usage the novel agents [6].

MM cases has been used as induction treatment by in VAD regimen (vincristine-doxorubicin-dexamethasone) in historically. Using the VAD regimen as induction chemotherapy in pre-ASCT period, it was compared with the older regimens including (Melphalan+ Prednison) and the data showed which VAD regimen was more potent and not disturbing the mobilization of stem cells [7]. A different report was showed that the the rate of complete response and overall survival were 27% and 84% by the induction chemotherapy as VAD regimen[8]. On the other hand, a published data showed that overall response rate by using bortezomibe containing regimens including bortezomibe with cyclophosphamide plus dexamethasone or lenalidomide plus dexamethasone was 63 % and 73% in pre ASCT period, respectively [9]. İn a nowadays, while the VAD regimen that it must be with hospitalization for administration, is not preferred, the bortezomibe containing regimen which are easier administration and improving response rates is preferred [9].

When we look at the litarature, although the VAD ptotokol as pre-ASCT induction therapy is outdated, we couldn't find enough the data that were compared with survival rate in post ASCT period of bortezomib-containing regimens and VAD protochol. Aim of this study is offering the data that it was compared with response rate and survival effect of VAD regimen and bortezomibe containing regimens as pre-ASCT induction chemotherapy, retrospectively.

MATERIALS AND METHODS

Patients

The data of ninety six by ASCT eligible-MM cases who were followed-up in the Hematology Department of Ataturk Training and Research Hospital between 2008-2018 were retrospectively analyzed. Our study is a retrospective study, approval of local ethics committee and retrospective data screening was performed.All of cases was diagnosed by The İnternational Myeloma Working Group criteria for MM[1]. ASCT eligilibity in MM cases was determined by presence of age ≤70 years, ECOG (Eastern Cooperative Oncology Group) performans status ≤2, and New York Heart Association functional status ≤ 2, absent of cirrhosis of the liver. All of MM patient's biochemical parameters, beta 2 microglobulin, hemoglobin value, white blood cell count, platelet count, sedimentation, ISS stage, precense of extramedullary mass, presence of lytic bone lesions, presence of pathological fracture, range of plasma cell in bone marrow was recorded at the initial diagnosis time, at the second – fourth –sixth cycles of induction chemotherapy. Complete response, partial response, very good partial response and progressive disease, and relapse disease states were recorded in the pre-ASCT induction period. The time of overall survival, progression free survival were recorded in post-ASCT period and during the follow-up period in cases without ASCT treatment. This study has been designed in accordance with 2013 Brazil version of Helsinki Declaration and was approved by the local Ethics Committee.

Treatment Regimens

The bortezomibe containing regimens administrated as that it was used to every 21 days as 1,8,15,21 days by using 1,3 mg/m^2 bortezomibe, 1,8,15 days by using 300 mg/m^2 cyclophosphamide, and 1,8,15,21 days by using 40 mg dexamethasone. İn the first cycle, dexamethasone was administrated four days as 40 mg in 1,8 days. According to treatment response, bortezomib contained regimens was given 4 or 6 cycles as pre-ASCT induction chemotherapy.

The use of infusional VAD protochols was administered as usage of protochols that 0,4 mg vincristine and 9 mg/m^2 doxorubicin was given each day by continuous infusions four days, and 40 mg dexamethasone was given on days 1 to 4, 9 to 12, and 17 to 20 of each of every 28 days.
MM patients without ASCT treatment was administrated 6-8 cycle bortezomibe containing regimens or four cycle VAD protochols as first line therapy.

Stem Cell Harvest Procedure and ASCT
ASCT was performed by achieving after at least partial response. Treatment response was evaluated by determining plasma cell in bone marrow and monoclonal M protein in serum or urine and absence of plasmocytoma.
MM cases were prepared for ASCT with melphalan 200mg/m^2.

Evaluation response criteria to treatment
According to the IMWG response criteria, we determined the situation of complete response (CR), very good partial response (VGPR), partial response (PR), progressive disease (PD).
CR criteria is described by disappeared monoclonal M protein in serum and urine by immunofixation, and soft tissue plasmocytoma, <5% clonal plasma cells in bone marrow.
VGPR criteria is described by at least a 90% decreased of monoclonal M protein in urine and serum with or without presence monoclonal M protein in 24 hours urine and serum by immunofixation.
PR criteria is defined by ≥50% reduction of monoclonal M protein in serum and ≥90% reduction of monoclonal M protein in 24-hour urinary or to <200 mg/24 hour urinary monoclonal protein. In addition, soft tissue plasmocytoma at initial diagnosis have 50% reduction rate.
PD criteria was descirabed by >25% increase from lowest response value in the follow-up time:
Monoclonal M protein in serum (≥0.5 g/dL absolute increasing).
Monoclonal M protein in urine (≥200 mg/24 hours absolute increasing).
Plasma cell percentage in the bone marrow (≥10% absolute increasing).
And , ≥50 percent increase in the size or development of new bone lesions or soft tissue plasmacytomas.
Relapse was defined by the determining any clinical findings of MM including arising of serum creatinin ≥2 mg/dL, increasing serum calcium (>11.5 mg/dL), decreasing value of hemoglobin (≥2 g/dL), improving hyperviscosity by paraproteinemia in the serum.

Statistical analysis
Normality distributions of study groups were evaluated by the Kolmogorov-Smirnov test. The parametric values were given as mean ± SD, non-parametric values were given as median (Inter Quartile Range). Comparisons were done with Student's t-test in cases of normal distribution and with Mann-Whitney U test in cases of asymmetrical distribution. The Spearman and polyserial correlation coefficients were calculated to evaluate the relationship between the measurements. Kaplan-Meier's curves were used for overall survival analysis. $P < 0.05$ was considered statistically significant.

RESULTS
When the data of 96 cases who was candidate for autologous stem cell transplantation under the age of 70 years old were examined, it was observed that 66 cases received an induction regimen with bortezomib and 30 patients received an induction regimen with VAD (Table 1). İt was observed that autologous stem cell transplantation was performed in 74 cases, autologous stem cell transplantation was not performed in 22 cases.
It was compared patients treated by ASCT after induction chemotherapy and treated by only chemotherapy, we found that stage of ISS III (p=0.048), presence of high B_2 –microglobulin (≥ 5.5 mg/L) (p=0.028) was more frequently in patients with non undergoing ASCT, but at least VGPR before ASCT was more frequently in patients with undergoing ASCT (p=0.031).
Ten (45 %) of the 22 patients without autologous stem cell transplantation were lost during the induction regimen.We questioned the reasons for the non undergoing ASCT treatment in the remaining

12 patients, 6 (27.7 %) patients had comorbidity and 6 (27.7 %) patients did not accept with treated by ASCT. In these 12 cases non undergoing ASCT, 8 (66.6 %) cases had treated with VAD and 4 (33.3 %) had treated with bortezomib (p >0.05). The cases who did not undergo ASCT because of comorbidity were 3 of 4 cases using bortezomib in induction and 3 of 8 cases using VAD (p = 0.245).

The patients who was administered induction chemotherapy by bortezomibe containing regimens and by VAD protocol was compared with each other, according to the presence of achieving at least PR in the second month during the pre-ASCT period, the presence of achieving PR / CR and VGPR rates before the pre-transplant period, No statistically significant difference was found between the two groups of patient and it was showed at Table 2.

When 22 patients of non undergoing ASCT were excluded from statistically analyze, the response rates (at least PR, CR, VGPR in pre ASCT period and relapses in post ASCT period) were compared to treatment with Bortezomibe containing regimens and VAD protocols in induction cycle for patients undergoing ASCT. The response and relaps rates of Bortezomib containing regimens and VAD protocol were not different for undergoing ASCT patients, and it was showed in Table 3.

When we performed survival analysis of our cases, the overall survival was 91.3 (±6 months) months in undergoing ASCT patients and 43 (±9 months) months in non undergoing ASCT patients, OS of undergoing ASCT patients was more longer and it was statistically significantly (p=0.001). İt was shown in Figure 1.

In cases who VAD protocol was applied as induction regimen, patients who received bortezomib-containing chemotherapy as induction regimen were compared according to their OS, and, the mean OS of the cases receiving VAD protocol was found to be 87.4 (± 6.5) months and the mean OS of the cases receiving bortezomib-containing chemotherapy was 81.5 (± 9.3) months (p = 0.854). Figure 2 shows that the comparisions of overall survival according to induction therapy including bortezomib containin regimens and VAD therapy.

The OS analysis of 74 cases with autologous transplantation was evaluated 59.4 (± 14.8) months for bortezomibe containing regimen patients and 77.3 (± 5.4) months for VAD protocol patients respectively (p = 0.126). İt was shown in the Figure 3. The progression free survival for 74 patients by ASCT treatment, it was 82.5 (±15) months for patients with bortezomib containing regimens as induction treatment and it was 79.8 (±7.3) months for patients with VAD protochols as induction treatment (p=0.717). The total survival of patients who underwent ASCT after reaching at least VGPR was longer than that of stem cell transplantation without reaching VGPR (p=0.019). İt was showed in Figure 4. The OS of patients who underwent ASCT after reaching at least VGPR was 87.6 ± 7.9 months and, the OS of patients who underwent ASCT after without reaching at least VGPR was 49.5 ± 9.45 months.

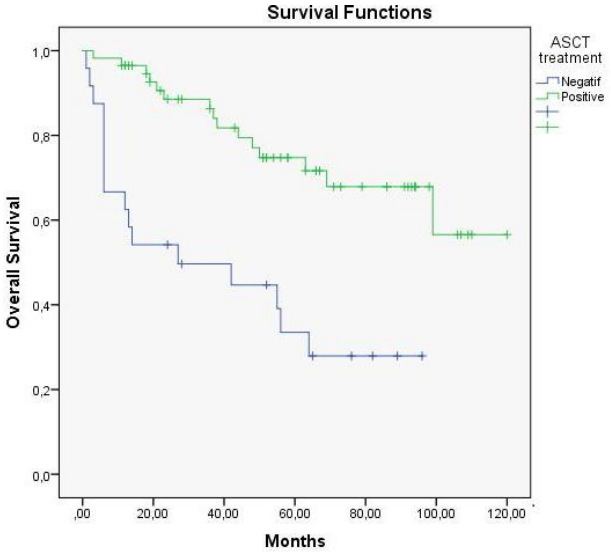

Figure 1: Comparisons of overall survival undergoing ASCT treatment and Non ASCT treatment for multiple myeloma patients

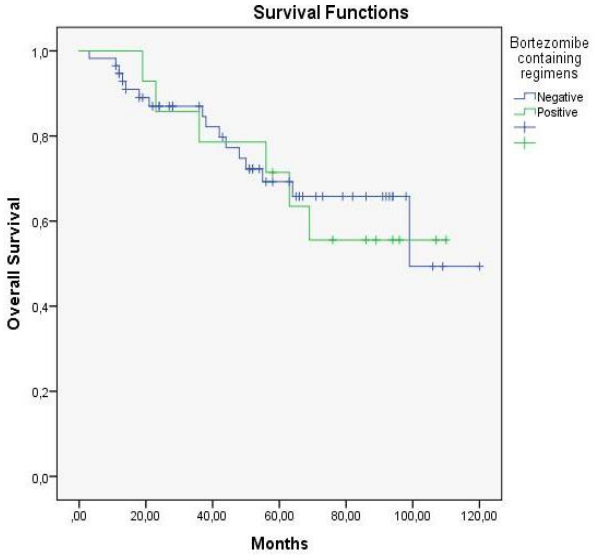

Figure 2: The comparisions of overall survival according to treated with bortezomib containin regimens and VAD protochol as induction therapy

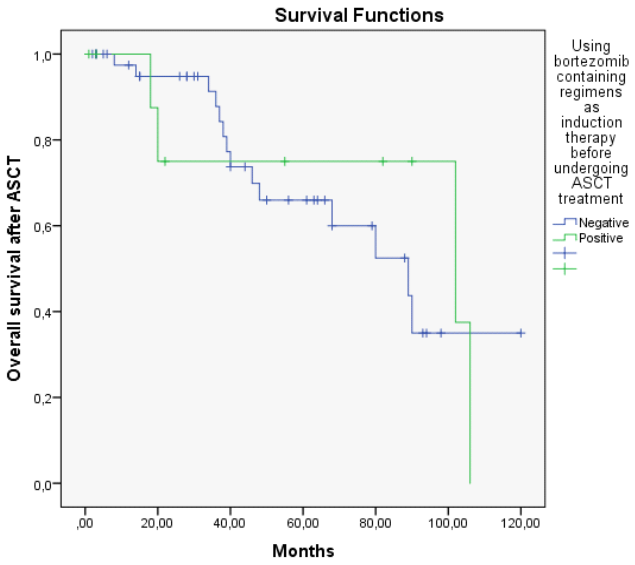

Figure 3: The effect of using bortezomib containing regimen as induction therapy before ASCT treatment for 57 patients undergoing ASCT

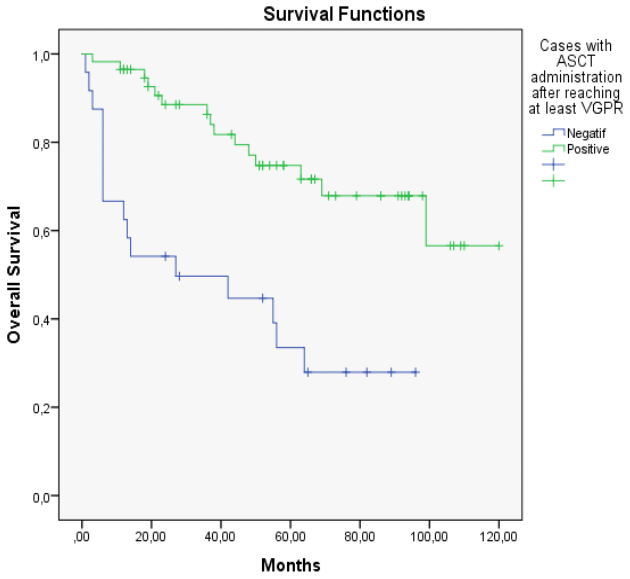

Figure 4: The OS analysis of the cases with ASCT after reaching at least VGPR (CR plus VGPR)

Table 1: The comparisions to demographic features of MM patients according to treatment

N = 96	Bortezomib-Containing Regimen (n 66) %	VAD (n 30) %	P
Gender			
Female	28 (42.4%)	12 (60%)	0.259
Male	38(57.6%)	18 (40%)	
Presence of B symptome	31 (47%)	8 (26.7%)	0.075
B_2–microglobulin (≥ 5.5 mg/L)	32 (48.5%)	6 (40%)	0.582
Serum albümin (≥ 3.5 g/dL)	45 (68.2%)	22 (73.3%)	0.398
LDH ≥220 g/dL	44 (66.7%)	22 (73.3%)	0.343
Hemoglobin (<10 gr/dL)	29 (43.9%)	18 (60%)	0.108
Serum calcium (≥ 12 mg/dL)	11 (16.7%)	6 (00%)	0.580
Early stage (ISS 1-2)/ Advance stage (ISS 3%)	35 (53%)	18 (60%)	0.340
	31 (47%)	12 (40%)	
ISS(İnternational Staging System)			
I	14 (21.2%)	4 (13.3%)	
II	21 (31.8%)	14 (46.7%)	
III	31 (47%)	12 (40%)	
Presence of extrameduller mass	18 (27.3%)	8 (26.7%)	0.579
Presence of osteolytıc lesions	48 (72.7%)	18 (60%)	0.156
Presence of compresion fracture	23 (34.8%)	10 (33.3%)	0.538
Presence of splenomegaly	7 (10.6%)	4 (13.3%)	0.469
Presence of hepatomegaly	5 (7.6%)	2 (6.7%)	0.620
Relapse patients in the first 2 years	5 (7.6%)	4 (13.3%)	0.293
Serum creatinine (>2 mg/dL)	24 (36.4%)	12 (40%)	0.452
Partial Response in second month of treatment	48 (72.7%)	24 (80%)	0.310
Partial Response Before ASCT	55 (86.4 %)	22 (73.3%)	0.105
Complete Response Before ASCT	5 (7.6%)	2 (6.7%)	0.620
No Comorbidity	52 (78.8%)	20 (66.7%)	0.890
Undergoing ASCT	47 (71.2%)	20 (66.7%)	0.413

Table 2: Response rates obtained after treatment with Bortezomibe containing regimens and VAD protocols in induction cycle

	VAD N: 30	**Treatment with Containing Bortezomib Regimens N:66**	**P**
Partial Response in second month of treatment	24 (33.3%)	48 (66.7%)	0.310
Partial Response Before ASCT	24 (30.4%)	55 (69.6%)	0.448
Complete Response Before ASCT	2 (28.6%)	5 (71.4%)	0.620
Very Good Partial Respose Before ASCT	12 (26.7%)	33 (73.3%)	0.246
Relapse disease in the first 2 years	5 (55.6%)	4 (44.4%)	0.293

Table 3: Response rates were compared after treatment with Bortezomibe containing regimens and VAD protocols in induction cycle for patients undergoing ASCT

	VAD n: 20 (%)	Treatment with Containing Bortezomib Regimens n:54 (%)	P
Partial Response in second month of treatment	16 (80 %)	40 (74.1%)	0.422
Partial Response Before ASCT	16 (80 %)	47 (87 %)	0.337
Complete Response Before ASCT	2 (10 %)	4 (7.4 %)	0.519
Very Good Partial Respose Before ASCT	8 (40 %)	27 (50 %)	0.308
post-ASCT relapse disease in the first 2 years	0 (0%)	5 (9.3%)	0.196

RESULTS

The standart treatment approach for MM cases who are younger than 65 years old, is high-dose therapy with ASCT after induction chemotherapy (10). İn our study, we compared with the treatment by VAD protocol and the bortezomib containing regimens as induction chemotherapy for ASCT eligible multiple myeloma patients. When we observed the status of the achieving of response to the treatment (PR, CR, VGPR, PD, relapses disease) in pre-ASCT or post-ASCT period, and the survival time (OS, PFS) on the follow-up period, we could not find a difference. İt was shown in our work in accordance with the literature that the total survival of the patients who had ASCT longer than the patients who did not[11].

In 1990's, VAD protocol were usually applied for pre-ASCT induction chemotherapy. But later in 2005, the first step therapy for multiple myeloma has been shifted to novel agent including proteosome inhibitors such as bortezomib and carfilzomib, immunomodulatory drug such as lenalidomide, monoclonal antibody targeted agent such as daratumomab[12,13].

The response ratio of VAD protocol in our data was approxiametely similar in previously published data[14,15]. In the past study was showed to that the response rate of VAD protocol for induction treatment is approxiametely 10% for the rate of CR[16]. In our study determined too that the rate of CR for VAD induction treatment was 16.7 percent. İn the different study, it was showed that the rate of CR or VGPR was 13% by using VAD protocol in pre-ASCT period, respectively. Again, in this study, the rate of relapse after single ASCT in the first 2 years was found to be 17% [14]. İn the other study evaluated that the rate of CR, VGPR and PR by VAD protocol for pre-ASCT induction chemotherapy was 5 percent, 12 percent and 61 percent, respectively [17]. İn the newly diagnosed MM cases that prepared by 200 mg melphalan as conditioning regimens for ASCT and VAD inductiopn chemotherapy was found 6 percent as relaps rate for post-ASCT period in first 2 years[17]. In our study, the relapse rate of MM patients in post ASCT 2 years was 13.3 percent with VAD induction chemotherapy and 7.6 percent by bortezomib conditioning regimens and there was not statistically significant difference. In a previously study, pre-ASCT induction regimens by bortezomib containing regimens with VAD protocol were compared to each other, as a result, CR and VGPR ratios were higher in the bortezomib group in the pre-ASCT period, but similar to our findings, the survival in post-ASCT period did not differ according to the induction regimen [18].

Although the response rates and total survival times in our study were not different in treatment by VAD protocol and bortezomib containing regimens, it was clear that there were different results when we look at the literature. İn a study was showed that bortezomibe containing treatment in only initial diagnosed patients had a significantly increase in the CR and VGPR rates but post-ASCT survival and at least PR rates before ASCT were similar by the treatment with bortezomibe containing regimens or VAD protocol for induction[18]. In HOVON-65 / GMMG-HD4 Randomized Phase III Trial, overall survival rates were similar when VAD and PAD (bortezomib-adriamycin and dexamethasone) treatments were compared in the group with normal creatinine value, however, PAD was superior in the group with impaired renal function[19]. İn recent years, bortezomib-containing induction regimens and bortezomib-free induction regimens were compared in the published meta-analysis, it was suggested that CR/VGPR ratio in post-ASCT and OS / PFS was concluded to be superior by the bortezomib containing chemotherapy [20]. According to the IFM 2005-01 Phase III Trial, it was described that CR, at least VGPR and overall response rates were significantly higher with bortezomib plus dexamethasone versus VAD. İn addition, in the same study was showed that CR, at least VGPR rates were significantly higher with bortezomib plus dexamethasone after first transplantation [21]. In our results were showed that pre-ASCT at least PR rates were 83.3% and 100% for bortezomibe containig regimens and VAD protocol, respectively. Our data was determined that at least the PR ratios for the VAD protocol before the ASCT, were higher than the previous publications reporting that the response rates were up to 84%[22, 23].We think that patients should take into consideration basal clinical and laboratory findings, treatment modalities (such as,

bolus or continuous infusion and doxorubicin, and dexamethasone dosage) in order to explain the different results published in previous years about the response rates of the VAD protocols.

Induction therapy prior to ASCT is important to improve the stabilization of organ functions and the patient's performance status. Pre-transplant induction therapy must be at the convenience and low toxicity for stem cell collection process. İt was shown that using VAD protocol or bortezomib containing induction regimens were not different in stem cell mobilization[24,25]. İt is known the VAD chemotherapy is not dangerous normal bone marrow progenitors and provides quick responses[16,26]. In additionally, it should also be noted that VAD protocol has difficulty in administration according to agents containing bortezomib, because hospitalization is required and can be administered by continuous infusion, which can be exhausting for the patient and the physician.

One of the limitations of our study was the lack of genetic risk classification of our patients. In addition, in the group receiving VAD for induction chemotherapy, it is also important to consider which agents are used in second line treatment.

The result of this retrospective comparison showed that respone rates and assessment of survival data were similar in treatment by VAD protocol and bortezomibe containing regimens. We know that ASCT treatment also can be benefit patients with primary refractory disease, because the survey may be due to the total response after ASCT, regardless of the response to induction therapy.

CONLUSION

In our study, it was demonstrated that the OS was similar for bortezomib-containing chemotherapy and VAD as pre-ASCT induction chemotherapy. Both treatments are effective and their toxicity is predetermined and manageable treatment options.Although the applicability of VAD chemotherapy requires hospitalization, we can say that it is still an option in induction due to similar OS rates. However, we think it is appropriate to support our results with more comprehensive studies on this subject.

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All authors have contributed appropriately to be listed and have agreed to the publication of the study results.

CONFLICT OF INTEREST

Authors have no conflicts of interest to declare.

Statement of Ethics

The study protocol was approved by an appropriate ethics committee.

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