Ann Med Res 2021;28(10):1824-9

Annals of Medical Research

DOI: 10.5455/annalsmedres.2021.01.098

Original Article

Comparison of the renal response of bortezomib-based induction and conventional regimen in multiple myeloma patients with renal failure

Ahmet Sarici[1], Emin Kaya[1], Mehmet Ali Erkurt[1], Ilhami Berber[1], Lokman Hekim Tanriverdi[2], Omer Faruk Bahcecioglu[3], Selim Gok[3], Irfan Kuku[1]

[1]Department of Hematology, Faculty of Medicine, Inonu University, Malatya, Turkey
[2]Department of Medical Pharmacy, Faculty of Medicine, Inonu University, Malatya, Turkey
[3]Department of Clinical Pharmacy, Faculty of Pharmacy, Inonu University, Malatya, Turkey

Abstract

Aim: Vincristine-doxorubicin-dexamethasone (VAD) was the commonly used first-line treatment for multiple myeloma (MM) patients with renal failure before bortezomib entered clinical practice. In this trial, we aimed to compare the effect of VAD and bortezomib-cyclophosphamide-dexamethasone (VCD) chemotherapy regimens on improving kidney function in MM patients with renal failure.

Materials and Methods: The records of MM patients in our center between January 2010 and February 2020 were retrospectively analyzed. Patients who received VAD or VCD as a first treatment chemotherapy protocol and whose initially estimated glomerular filtration rate (eGFR) was 50 mL/min/1.73 m^2 and below were included in the study. Patients were divided into two groups according to the chemotherapy regimens they received.

Results: Sixty one MM patients (VAD: 26, VCD: 35) were included in the study. No significant difference was found between the VAD and VCD groups when the baseline, 1st and 2nd month eGFRs were compared (p>0.05). Overall renal response rate (at least minor response) in the VCD group at the end of the 1st month were higher than in the VAD group (p=0.002). Also, renal response rate in the VCD group at the end of the 2nd month were higher than in the VAD group (p=0.033).

Conclusion: In MM patients with renal insufficiency, overall renal response rates have increased with the use of VCD instead of VAD as a standard induction regimen.

Keywords: Bortezomib; chemotherapy; hematology; multiple myeloma; renal failure; vincristine

INTRODUCTION

Multiple myeloma (MM) is a lymphoproliferative disorder in which monoclonal plasma cells proliferate in the bone marrow, resulting in bone destruction, osteopenia and osteolytic lesions. The incidence of MM disease, which accounts for about 15% of hematological malignancies, is 40 people/million/year (1).

Approximately 20-50% of MM patients have renal failure (RF) at the onset of the disease, and dialysis is required in approximately 5% of patients (2-4). The survival of patients whose kidney function improves as a result of anti-MM treatment is longer than those whose kidney functions do not improve. Serious kidney damage secondary to membrane cast nephropathy (MCN) can be seen in patients with serum light chain levels of more than 500 mg/L. MCN was detected in kidney biopsies up to 90% of MM patients with severe acute kidney injury (AKI) (4). The typical histopathological appearance of MCN includes the monoclonal light chain and Tamm-Horsfall protein (uromodulin), often accompanied by proximal tubular damage and tubulointerstitial inflammation (5).

Severe AKI in MM patients is related to an increased risk of mortality. So, it is necessary to be treated as quickly as possible. However, the effect of mild-modified kidney injury on patient outcomes at the time of diagnosis is unclear (6). The degree of kidney injury in diagnosis has been related to the possibility of kidney function recovery. Although there are studies reported that improved survival rates and estimated glomerular filtration rates (eGFRs) in MM patients with AKI as a result of recent developments in chemotherapy (6-8), overall survival (OS) is still less than those with normal kidney function at the time of diagnosis (6).

Received: 03.02.2021 **Accepted:** 10.03.2021 **Available online:** 15.10.2021
Corresponding Author: Ahmet Sarici, Department of Hematology, Faculty of Medicine, Inonu University, Malatya, Turkey
E-mail: ahmetsarici@inonu.edu.tr

For MM patients eligible for autologous hematopoietic stem cell transplantation, three to four cycles of induction chemotherapy is recommended prior to transplantation (9). However, it has been reported that the use of alkylating agents during induction therapy causes a lower response in MM patients with AKI than bortezomib-based regimens (8). Bortezomib is a proteasome inhibitor that inhibits DNA proliferation and induces apoptosis. The reason why it is used safely in patients with kidney injury is that the pharmacokinetic properties of bortezomib are not affected by RF (10).

Vincristine-adriamycin-dexamethasone (VAD) was the commonly used first-line treatment for MM patients with RF before bortezomib entered clinical practice. In this trial, we aimed to compare the effect of VAD and bortezomib-cyclophosphamide-dexamethasone (VCD) chemotherapy regimens on improving kidney function in MM patients with RF.

MATERIALS and METHODS

This study was approved by the local ethical committee of Inönü University, Medical Faculty on 18 February, 2020 under the number 2020/261. The records of newly diagnosed MM patients in our center between January 2010 and February 2020 were retrospectively analyzed. Patients who received VAD or VCD as a chemotherapy protocol and whose initially eGFR was 50 mL/min/1.73 m^2 and below were included in the study. The eGFR values of the patients were calculated using the "Modification of Diet in Renal Disease" formula. Patients with chronic RF were not included in the study. All patients were divided into two groups according to the first line chemotherapy regimens they received. Patients' baseline, 1st and 2nd month eGFR values were compared between the VAD and VCD groups. In addition, statistical analysis of the change of basal, 1st and 2nd month eGFR values within the groups was performed.

As a different assessment, renal responses were evaluated according to the criteria recommended by the International Myeloma Group. Accordingly, in patients with an initial eGFR below 50 mL min, eGFR after treatment was above 60 mL/min was considered as a "complete response". In patients with an initial eGFR of less than 15 mL/min, improvement of eGFR to 30–59 mL/min was considered "partial response". The improvement of eGFR to 15-29 mL/minute in patients with an initial 15 mL/min of eGFR, or improvement of eGFR to 30–59 mL/minute in patients with an initial eGFR of 15-29 mL/minute was considered "minor response" (11).

The VAD chemotherapy protocol was repeated every 28 days. Vincristine 0.4 mg/day and doxorubicin 9 mg/m^2/day were administered on the 1st, 2nd, 3rd and 4th days, dexamethasone 40 mg was administered between the 1st and 4th days, between the 9th and 12th days, and between the 17th and 2th days. The VCD chemotherapy protocol was repeated every 21 days. Bortezomib 1.3 mg/m^2/day was administered on the 1st, 4th, 8th, 11th days, cyclophosphamide IV 500 mg/m^2/day was administered on the 1st and 8th days, and dexamethasone 40 mg/day was administered on the 1st, 2nd, 4th, 5th, 8th, 9th, 11th, and 12th days.

The normality of the distribution of the eGFR, age, total protein, albumin, and sedimentation data was evaluated through the Shapiro-Wilk test. According to the results obtained from the normality test, Friedman's test was used to compare the eGFR values of each group measured at different times. Mann-Whitney U test was used to compare continuous variables (age, total protein, albumin, sedimentation, eGFR) and chi-square test was used to compare categorical variables (such as gender, renal response rate vs.) between the VAD and VCD groups. The values of "p" which are less than 0.05 were considered statistically significant. Jamovi 1.1.9.0 for Mac OS was used for the data analysis.

RESULTS

Sixty one MM patients were included in the study. Forty of these patients were male (65.57%) and 21 were female (34.43%). As a chemotherapy regimen, 26 patients received VAD and 35 received VCD. Characteristic features of the patients are given in Table 1. There was no significant difference in the characteristics of patients except for age and myeloma subtype between VAD and VCD groups ($p>0.05$). Patients in the VCD group were older than patients in the VAD group ($p=0.007$). The percentage of patients with light chain myeloma in the VAD group was higher than in the VCD group ($p=0.048$).

Baseline, 1st and 2nd month eGFR values of both groups are given in Table 2. There was no significant difference in baseline eGFR values of VAD and VCD groups ($p> 0.05$). In both groups, a significant difference was detected when the eGFR values at the 1st and 2nd months were compared with the baseline values ($p<0.05$). However, the baseline, 1st and 2nd month eGFR values of VAD and VCD groups were similar ($p>0.05$).

Considering the renal response criteria suggested by the International Myeloma Group as a different evaluation, in the VAD group, 10 (38.46%) patients had complete response at the end of the first month, while 10 (38.46%) patients had no response. In the VCD group, 11 (42.31%) patients had complete response at the end of the first month, while 2 (7.69%) patients had no response. Renal response in our patients to chemotherapy regimens are given in Table 3. At the end of the second month, in the VAD group, 9 (39.13%) of the patients had complete response and 6 (26.09%) patients had no response. In the VCD group, 10 (45.45%) patients had complete response and 1 (4.55%) patient had no response. Renal response rate (at least minor response) in the VCD group at the end of the first month were higher than in the VAD group (94.28% vs 61.54%, $p=0.002$). Also, renal response rate in the VCD group at the end of the second month were higher than in the VAD group (96.78% vs 73.91%, $p=0.033$).

Table 1. Population characteristics of the treatment groups

Parameters	VAD Group	VCD Group	p values
Gender	**p=0.604**		p=0.604
Male, n	18	22	
Female, n	8	13	
Age, mean±SD	61.5±9	68.2±9.2	p=0.007
Stage of Renal Function*, baseline (eGFR, mL/min/1.73 m²)			p=0.336
Stage 1 (≥90)	0	0	
Stage 2 (60-89)	0	0	
Stage 3 (30-59)	6	14	
Stage 4 (15-29)	12	14	
Stage 5 (<15)	8	7	
Myeloma subtype			
IgA	6	7	p=0.772
IgG	10	22	p=0.059
IgM	0	1	p=1
Light chain	10	5	p=0.048
Anemia, baseline (Hb<10 g/dL)			p=0.604
Yes	18	22	
No	8	13	
Plasma calcium level, baseline (mg/dL)			p=0.614
≥11.5, n	9	10	
<11.5, n	17	25	
Plasma LDH level, baseline (IU/L)			p=0.813
≥300, n	6	9	
<300, n	20	26	
Total protein, baseline (g/dL)	8.2±2.3	8.9±2.3	p=0.192
Plasma albumin, baseline (g/dL)	2.6±0.7	2.7±0.7	p=0.554
Plasma sedimentation, baseline (mm/h, 1st hour)	50±30	61±31	p=0.338

eGFR: estimated glomerular filtration rate, IgA: Immunoglobulin A, IgG: Immunoglobulin G, IgM: Immunoglobulin M, LDH: Lactate dehydrogenase

Table 2. eGFR values during the treatment in the study groups

	VAD Group	VCD Group
Baseline (eGFR, mL/min/1.73 m²)	20 (5-47)	28 (5-49)
After 1st month (eGFR, mL/min/1.73 m²)	42 (5-123)[a]	50 (7-95)[a]
After 2nd month (eGFR, mL/min/1.73 m²)	48 (7-124)[a,b]	54 (7-139)[a,b]

Data are expressed as median (min–max)
[a] p<0.05: Significant compared to baseline value in the same column,
[b] p<0.05: Significant compared to 1st month value in the same column
eGFR: estimated glomerular filtration rate, VAD: Vincristine-adriamycin-dexamethasone, VCD: bortezomib-cyclophosphamide-dexamethasone

Table 3. Renal response to the chemotherapy regimens.

Parameters	VAD Group, n (%)		VCD Group, n (%)	
	After 1st month	After 2nd month	After 1st month	After 2nd month
Complete response	10 (38.46%)	9 (39.13%)	16 (45.71%)	17 (54.84%)
Partial response	0 (0%)	1 (4.35%)	4 (11.43%)	3 (9.68%)
Minor response	6 (23.08%)	7 (30.43%)	13 (37.14%)	10 (32.26%)
No response	10 (38.46%)	6 (26.09%)	2 (5.72%)	1 (3.22%)
Total number of patients	26	23	35	31

VAD: Vincristine-adriamycin-dexamethasone, VCD: bortezomib-cyclophosphamide-dexamethasone

In a subgroup analysis of 15 patients (10 VAD, 5 VCD) with light chain myeloma, VCD treatment was found to be superior to VAD therapy in terms of at least minimal response to treatment at the end of 1st month (100% vs 20%, p=0.007). At the end of the second month, although response rates with VCD were higher than VAD, this was not significant (100% vs 50%, p=0.208).

DISCUSSION

In the myeloma study conducted by Medical Research Council (MRC), the mortality rate within 100 days of entry is 30 percent in patients with a creatinine value >200 µmol/L at the time of diagnosis. This rate is approximately 10 percent in patients with creatinine value <200 µmol/L at the time of diagnosis (12). In a trial that combined data from the MM studies between 1980 and 2002, it was stated that RF was responsible for 28% of early deaths (13).

As a result of multivariate analysis conducted in a study that examined 775 MM patients, RF was found to be an independent risk factor for mortality. The prognosis of patients who needed dialysis was poor and the mean survival was 3.5 months (14). The frequency of this complication has decreased with current novel pharmacological agents. Between 2001 and 2011, 133 patients with newly diagnosed MM and RF were treated with novel agent based regimens (bortezomib-based, thalidomide-based and lenalidomide-based regimen). A remarkable improvement in renal function was achieved in 77% of patients on the bortezomib-based regimen, 55% of patients on the thalidomide-based regimen, and 43% of patients on the lenalidomide-based regimen. According to the trial, 50% (5/10) of patients who need dialysis became independent from dialysis (15).

In a trial defined as RF when the creatinine level was above 177 µmol/L, RF was observed in 94 patients. Compared to patients whose kidney function did not improve as a result of treatment, higher survival was observed in the group whose kidney function improved. It was stated that the renal recovery was better in patients with a serum calcium level >2.88 mmol/L and lower amount of proteinuria (<1g/day) (3).

With the widespread addition of dexamethasone to standard chemotherapy regimens, better kidney functions have been reported in MM patients with RF. In a trial, which included 41 newly diagnosed MM patients, dexamethasone-based regimens reversed renal failure by 73% in all patients within a median 1.9 months. In patients receiving dexamethasone and novel agents (thalidomide and/or bortezomib) in the chemotherapy regimen, the renal response rate was 80% in a median of 0.8 months (16). In our trial, renal response rate (at least minor response) of all patients at the end of second month was 87.04% (47/54).

In a two-center trial, most patients had severe RF at presentation with a median GFR of 9 mL/min/1.73 m2 and 61.5% of patients required dialysis support. On day 21, a 60% reduction in free light chains was related to improved renal function for 80% of patients. As a result of this trial, 62.5% of patients who need dialysis (15/24) became independent from dialysis. OS was significantly related to renal response. The median OS was 42.7 months for those with improved renal function, and 7.8 months for those who did not (17). Since the effects of differences in renal functions on survival are undeniable, the treatment regimen to be chosen is significant on survival.

In a trial evaluating the effectiveness of novel drugs used in MM, median OS was 33 months in patients with RF, while it was 52 months in patients with normal renal function, and this difference was statistically significant (p<0.001). Median OS was 2.25 years in patients treated with conventional regimen, and 5 years in patients treated with novel agents (8).

In the trial conducted by Costa and his colleagues, which included 14 MM patients with RF at the time of diagnosis, the efficacy of the VCD combination regimen on kidney function was investigated. As a result of this trial, a complete response was obtained in 5 (35.7%) patients, partial response in 4 (28.5%) patients and minor response in 1 (7.1%) patient (18). In our study, 94.28% of patients who received VCD responded to the treatment (at least minor response) at the end of the first month and 96.78% at the end of the 2nd month.

Ludwig et al. evaluated the impact of bortezomib-based regimen on renal recovery in eight progressive myeloma patients presenting with acute RF (GFR<20 mL/min). After bortezomib-based therapy, RF reversed in approximately 63% of patients with acute myeloma-related RF (at least partial response) (19). In our study, the VCD regimen caused at least partial response in 64.52% (20/31) of patients after two months of treatment.

In a trial, newly diagnosed MM patients were randomized to receive induction therapy with VAD or bortezomib based regimen (PAD: bortezomib, doxorubicin, dexamethasone). In this study, MM patients with serum creatinine greater than 2 mg/dL were evaluated as having RF. There were 45 patients with RF in the VAD group and 36 patients with RF in the PAD group. At presentation, patients with RF showed that the PAD arm was remarkable superior for progression-free survival (p=0.004) and OS (p<0.001) (20).

In a study, the post-treatment renal response rates of 81 patients (36 PAD, 45 VAD) with an initial creatinine ≥2 mg/dL were analyzed (21). No significant difference was found in the renal response of both groups after treatment (PAD: 81% vs. VAD: 63%, p=0.31). Unlike our study, this study did not directly compare two regimens (VAD vs VCD). Unlike this study, we found the renal response rates at the 1st and 2nd months better in the VCD group (p=0.002, p=0.033 respectively) than in the VAD group.

In a trial conducted between 2005 and 2014, 130 newly diagnosed MM patients with RF were treated with a VAD regimen, bortezomib-based regimen or thalidomide including regimen. 56.1% of the patients who received a bortezomib-based regimen, 38.9% of the patients who received a thalidomide-based regimen, and 28.6% of the patients who received VAD had renal complete response

(p=0.033) (22). In our study, although we did not find a significant difference in complete response rates between the VAD and VCD groups, there was a significant difference in overall renal response rates.

In the retrospective case analysis conducted by Breitkreutz et al. twenty-seven patients who diagnosed with newly MM and underwent stem cell mobilization after first-line induction therapy were evaluated. A bortezomib-based regimen was administered to a total of 13 patients, and the consequence of this group was compared to 14 patients who received a VAD-based regimen. The median duration of dialysis dependence after the initiation of treatment was 6.1 months in the bortezomib-based regimen and 17.1 months in the VAD-based regimen. However, this difference (17.1 months vs 6.1 months) in median duration of dialysis dependency was not statistically significant (p=0.38). Following induction chemotherapy, 35.7% of the conventional arm and 38.5% of the bortezomib-based arm taken off from dialysis (23). While this study included only dialysis-dependent patients, our study included patients with a baseline eGFR less than 50. Unlike this study, we found the overall renal response rates at the 1st and 2nd months better in the VCD group than VAD group.

Although there are conflicting data on this issue in the literature, we have shown the superiority of VCD, a bortezomib-based regimen, over VAD in terms of renal response, even in the short-term follow-up (1-2 months) of our patients.

LIMITATIONS

Limitations of our study are relatively few number of patients, retrospective design and missing data of some patients.

CONCLUSION

In studies comparing bortezomib-based regimens and conventional regimens (VAD etc.), conflicting results were obtained in terms of renal response. In our study in which VAD and VCD groups were compared, overall renal response rate at the end of the 1st and 2nd month is higher in VCD group than VAD group. In MM patients with renal insufficiency, overall renal response rates have increased with the use of a bortezomib-based regimen (VCD) instead of VAD as the standard induction regimen..

Competing Interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical Approval: This study was approved by the local ethical committee of Inonu University, Medical Faculty on 18 February, 2020 under the number 2020/261.

REFERENCES

1. Blade J. Multiple Myeloma. In: Carreras E, Dufour C, Mohty M (eds) The EBMT Handbook. Hematopoietic Stem Cell Transplantation and Cellular Therapies. Cham: Springer, 2019.p.603-7
2. Eleutherakis-Papaiakovou V, Bamias A, Gika D, et al. Renal failure in multiple myeloma: incidence, correlations, and prognostic significance. Leukemıa Lymphoma 2007;48:337-41.
3. Bladé J, Fernández-Llama P, Bosch F, et al. Renal failure in multiple myeloma: presenting features and predictors of outcome in 94 patients from a single institution. Arch Intern Med 1998;158:1889-93.
4. Yadav P, Cook M, Cockwell P. Current trends of renal impairment in multiple myeloma. Kidney Dis (Basel) 2015;1:241-57.
5. Batuman V. The pathogenesis of acute kidney impairment in patients with multiple myeloma. Adv Chronic Kidney Dis 2012;19:282-6.
6. Gonsalves WI, Leung N, Rajkumar SV, et al. Improvement in renal function and its impact on survival in patients with newly diagnosed multiple myeloma. Blood Cancer J 2015; 5:e296.
7. Dimopoulos MA, Delimpasi S, Katodritou E, et al. Significant improvement in the survival of patients with multiple myeloma presenting with severe renal impairment after the introduction of novel agents. Ann Oncol 2014;25:195-200.
8. Uttervall K, Duru AD, Lund J, et al. The use of novel drugs can effectively improve response, delay relapse and enhance overall survival in multiple myeloma patients with renal impairment. PLoS One 2014;9:e101819.
9. Ludwig H, Miguel JS, Dimopoulos MA, et al. International Myeloma Working Group recommendations for global myeloma care. Leukemia 2014;28:981-92.
10. Dimopoulos MA, Kastritis E, Rosinol L, et al. Pathogenesis and treatment of renal failure in multiple myeloma. Leukemia 2008;22:1485-93.
11. Dimopoulos MA, Sonneveld P, Leung N, et al. International Myeloma Working Group Recommendations for the Diagnosis and Management of Myeloma-Related Renal Impairment. J Clin Oncol 2016;34:1544-57.
12. MacLennan ICM, Coope EH, Chapman CE, et al. Renal failure in myelomatosis. Eur J Haematol 1989;43:60-5
13. Augustson BM, Begum G, Dunn JA, et al. Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United Kingdom Medical Research Council trials between 1980 and 2002-Medical Research Council Adult Leukaemia Working Party. J Clin Oncol 2005;23:9219-26.
14. Knudsen LM, Hjorth M and Hippe E. Renal failure in multiple myeloma: reversibility and impact on the prognosis Nordic Myeloma Study Group. Eur J Haematol 2000;65:175-81.
15. Dimopoulos MA, Roussou M, Gkotzamanidou M, et al. The role of novel agents on the reversibility of renal impairment in newly diagnosed symptomatic patients with multiple myeloma. Leukemia 2013;27:423-9
16. Kastritis E, Anagnostopoulos A, Roussou M, et al. Reversibility of renal failure in newly diagnosed multiple myeloma patients treated with high dose dexamethasone-containing regimens and the impact of novel agents. Haematologica 2007;92:546-9.

17. Hutchison CA, Cockwell P, Stringer S, et al. Early reduction of serum-free light chains associates with renal recovery in myeloma kidney. J Am Soc Nephrol 2011;22:1129-36.
18. Costa LJ, Abbas J, Ortiz-Cruz KL, et al. Outcomes of patients with multiple myeloma and renal impairment treated with bortezomib, cyclophosphamide, and dexamethasone without plasma exchange. Eur J Haematol 2012;89:432-4.
19. Ludwig H, Drach J, Graf H, et al. Reversal of acute renal failure by bortezomib-based chemotherapy in patients with multiple myeloma. Haematologica 2007;92:1411-4.
20. Sonneveld P, Scheid C, van der Holt B, et al. Bortezomib induction and maintenance treatment improves survival in patients with newly diagnosed multiple myeloma: extended follow-up of the HOVON-65/ GMMG-HD4 Trial. Blood 2013;122:404.
21. Scheid C, Sonneveld P, Schmidt-Wolf IG, et al. Bortezomib before and after autologous stem cell transplantation overcomes the negative prognostic impact of renal impairment in newly diagnosed multiple myeloma: a subgroup analysis from the HOVON-65/ GMMG-HD4 trial. Haematologica 2014;99:148-54.
22. Bao L, Lu J, Huang X. Reversibility of renal insufficiency in patients with newly diagnosed multiple myeloma and the role of different induction regimens. Blood 2014;124:5749.
23. Breitkreutz I, Heiss C, Perne A, et al. Bortezomib improves outcome after SCT in multiple myeloma patients with end-stage renal failure. Bone Marrow Transplant 2014;49:1371-5.