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# Velcade (Bortezomib): Treatment for patients diagnosed of multiple myeloma complicated by renal failure

**Bayoud Wael, Nasr Fadi**

*Universite Saint-Joseph, Campus des Sciences Médicales de l'USJ,*
*Rue de Damas, Achrafieh Beyrouth, Liban*

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***Corresponding Author***

*Wael Bayoud*

*E-mail: wael.bayoud@hotmail.com*
*Address:*
*Universite Saint-Joseph,*
*Campus des Sciences Médicales*
*Rue de Damas,*
*Achrafieh Beyrouth, Liban*

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## ABSTRACT

Renal failure is a common feature of multiple myeloma and a major management problem. Velcade is a proteasome inhibitor and some studies proved that it can be used in multiple myeloma.

**Patients and methods**. We evaluated 18 patients with new diagnosed or relapsed/refractory multiple myeloma and renal failure, defined as a sustained estimated creatinine clearance (CrCl) < 50ml/min, calculated by the Cockcroft-Gault formula, despite volume replacement and reversal of hypercalcemia. All patients received bortezomib-based regimens.

**Results**. The overall response rate (ORR) was 77.8% (14/18) including 5 CR, 2 VGPR, 4 PR, 3 MR (according to EBMT criterias). The median time to response was 55 days and it was correlated with myeloma status and myeloma response. Of the 4 nonresponding patients, 1 has SD and 3 have PD. A better quality of life with a better survival were noted after treatment. All patients witnessed a renal response: 9CRR, 3PRR and 6MRR.The median time to renal response was: 36 days. CrCl > 30 ml/min was independently correlated with a better renal response and a better time to renal response. 4 of 5 patients undergoing dialysis became dialysis independent. 88% of the adverse reactions were grade 1 and 2.

**Conclusion**. Bortezomib is an effective and a safe treatment for Multiple Myeloma complicated of renal failure for patients with new, refractory and relapsed disease. Bortezomib is better used as a first line therapy giving better myeloma response and a better renal response.

## INTRODUCTION

Approximately 30% of patients with diagnosed multiple myeloma (MM) present with baseline renal dysfunction, with 1% to 13% having renal failure requiring dialysis support. The presence of renal failure has been considered a negative prognostic indicator associated with decreased response, shorter survival and early mortality (Augustson et al.2005) in patients treated with conventional chemotherapy.

Many types of renal failure exist in MM, but according to (Ivanyi et al. 1990), tubular light chain cast nephropathy is the most common cause of renal failure in MM: it is observed in about 30% of patients (Herrera et al. 2000). Many drugs and combinations are available for treating MM, and first line therapy depends on whether the patients will undergo hematopoietic cell transplantation or not. Treatment options such as melphalan-based chemotherapy (Knudsen et al. 2000, Torra et al.1995, and Vigneau et al. 2002) and high-dose chemotherapy with autologous stem cell transplantation are not frequently used if renal failure is present because of lack of benefits, excessive toxicities, early mortality, and/or the need for dose reductions and treatment discontinuations.

Bortezomib (PS-341, Velcade) is a selective, and reversible proteasome inhibitor (inhibits the Chymotrypsin-like protease) that has

been shown to induce cell death in many tumor models, including prostate, colon, and pancreatic cancer and multiple myeloma (MM) (Cusack et al., 2001; Hideshima et al., 2001).

## MATERIALS AND METHODS

The study population consists of 18 patients, older than 18 years old, diagnosed of MM with renal failure, and who were treated with Bortezomib (VELCADE) in Hotel Dieu Hostpital (Lebanon) between January 2008 and June 2010. RI was defined as a sustained estimated creatinine clearance (CrCl) < 50ml/min, calculated by the Cockroft–Gault formula, despite volume replacement and reversal of hypercalcemia. Besides anti-myeloma treatment, all patients received supportive care which included rigorous intravenous hydration, alkalization of urine, correction of hypercalcemia and discontinuation of all nephrotoxic agents. Renal dialysis was offered to all patients with an appropriate indication. The data analysis demanded simple statistical calculations.

## RESULTS

The patients' baseline characteristics are shown in table A. Among the 18 patients with MM, 12 (67%) were men, and 6 (33%) were women. The median age of the patients at the start of bortezomib treatment was 68.8 years old (range 52-79 years old). 15 patients (83.3%) belonged to the elderly group (65 and above). The distribution of MM types was as follows: 8 (44%) with IgG, 5 (28%) with IgA, 1 (5.6%) with IgD, 3 (16.7) with lambda light chain only and 1 (5.6%) with kappa light chain. Among those 18 patients, 9 (50%) had a heart disease before the initiation of the bortezomib regimen. 5 patients (28%) had a coronaropathy (Coro), 2 (11% ) had non obstructive cardio- myeopathy (NOCM) and 2 (11%) had pulmonary hypertension (PH) 11 patients (61%) were newly diagnosed of MM, 4 patients (22%) had relapsed MM, and 3 patients (16.7%) had refractory MM. 11 patients received VD regimen (bortezomib + dexamethasone), 3 patients received VMDT (bortezomib +, dexamethasone + thalidomide + melphalan), 2 patient received VDT (bortezomib + dexamethasone + Thalidomide) and 2 patients received PAD (bortezomib + dexamethasone + doxorubicin).

The total number of bortezomib cycles gives was 63, giving 3.5 cycle/patient (range 1-5). Furthermore, 4 patients had not a detectable M protein pic in the serum protein electrophoresis, but a detectable pic in the urine: those patients had Bence Jones proteins. Among the 14 patients with detectable serum M protein, the median was 4335 mg/dL before treatment and 3240 mg/dL after treatment Among the 18 patients, the median urine M protein was 4.9 g/24h/patient before the initiation of the Bortezomib regimen, and 2.9 g/24h/patient after all the cycles of bortezomib were taken. In addition, the B2M median level was 8.4 before treatment and 7.1 after treatment The overall response rate (ORR) was 77.8% (14/18) including 5 CR, 2 VGPR, 4 PR, 3 MR (according to EBMT criterias). The median time to response was 55 days. Of the 4 nonresponding patients, 1 has SD and 3 have PD. ISS stage III and DSS Stage III decreased after treatment, with an increase in stage I, which highlights the amelioration after treatment.

**Table A. characteristics of patients**

| Patient | Gender | Age | Myeloma type | Status of MM | Actual regimen | Heart condition |
|---|---|---|---|---|---|---|
| 1 | M | 60 | IgG | New | VD | NOCM |
| 2 | M | 68 | IgG | New | VD | X |
| 3 | F | 69 | IgA | Refractory | PAD | X |
| 4 | M | 71 | IgG | Relapsed | VD | PH |
| 5 | M | 72 | IgA | Relapsed | VD | X |
| 6 | M | 62 | IgG | New | VD | X |
| 7 | M | 78 | IgD | Refractory | VMDT | Coro |
| 8 | M | 77 | IgG | Refractory | PAD | PH |
| 9 | F | 67 | IgA | New | VD | NOCM |
| 10 | M | 65 | Lambda λ | New | VD | X |
| 11 | F | 69 | IgG | Relapsed | VMDT | PH |
| 12 | M | 52 | IgA | New | VD | X |
| 13 | F | 68 | Kappa ϰ | New | VD | Coro |
| 14 | M | 68 | IgG | New | VD | X |
| 15 | F | 75 | IgG | New | VD | Coro |
| 16 | M | 72 | IgA | New | VDT | Coro |
| 17 | M | 79 | Kappa ϰ | Relapsed | VMDT | Coro |
| 18 | F | 66 | Kappa ϰ | New | VDT | X |

**Table B. renal response after Bortezomib Treatment**

| Patient | Number of cycles | CrCl ml/min | | Dialysis | | Renal response | Time to renal response (days) |
|---|---|---|---|---|---|---|---|
| | | Before | After | Before | After | | |
| 1 | 2 | 49.4 | 62 | No | No | CRR | 12 |
| 2 | 2 | 44 | 66 | No | No | CRR | 17 |
| 3 | 5 | 5.4 | 17 | Yes | Yes | MRR | 70 |
| 4 | 4 | 31 | 52 | No | No | CRR | 29 |
| 5 | 5 | 13 | 31 | No | No | PRR | 30 |
| 6 | 5 | 27 | 44 | No | No | MRR | 35 |
| 7 | 4 | 21 | 53 | No | No | CRR | 23 |
| 8 | 5 | 7 | 28 | Yes | No | MRR | 60 |
| 9 | 3 | 29 | 40.1 | No | No | MRR | 35 |
| 10 | 3 | 38 | 66 | No | No | CRR | 26 |
| 11 | 5 | 8.2 | 33 | Yes | No | PRR | 60 |
| 12 | 5 | 4 | 23 | Yes | No | MRR | 55 |
| 13 | 1 | 47.7 | 63.4 | No | No | CRR | 15 |
| 14 | 4 | 10 | 34 | No | No | PRR | 49 |
| 15 | 4 | 14 | 58 | No | No | CRR | 30 |
| 16 | 2 | 35.8 | 62 | No | No | CRR | 28 |
| 17 | 3 | 9 | 28.8 | Yes | No | MRR | 60 |
| 18 | 1 | 40.9 | 60.1 | No | No | CRR | 18 |

Concerning Karnofsky Performance Stage, 17 patients (94.4%) had KPS <70 before treatment and 10 (59%) after treatment. In addition, the mean KPS was 35 (range:10-80) before treatment and 52 (range 10-90) after treatment.

Concerning ECOG score, the mean was 3 before treatment and 1.8 after treatment. It is essential to remember that the higher the KPS, the better quality of life, and the lower the ECOG, the better quality of life.

Before treatment, the median Hb was 9.7 (range:7.9-11.5), the median number of platelets was 209000 (range 100000-408000), median LDH was 2312 (range: 599-6870), the median albumin level was 3 (range: 1.3-5.1) and the median calcemia was 11.3 (range 8.3-13.5), the % of plasma cell was 29% and The median number of bone lesions was 2. After treatment, the median Hb was 9.1(range 6.1-10.6), the median number of platelets was 106000 (range 19000-290000), the medina LDH was 605.4 (range 150-1300), the median albumin level was 3.5 (range:1.9-5) and the median calcemia was 10.8 (range:8.4-13.1), the % of plasma cell was 19.4%. the medina number of bone lesions was 1.55.

### Reversal of renal impairment

3 types of renal response are identified: Complete response [CR] renal: baseline GFR < 50 mL/min improving to > 60. Partial response [PR]renal: baseline GFR < 15 improving to > 30 to< 60. Minimal response [MR]renal: baseline GFR <15ml/min improving to >15 but <30 or base line GFR >15 to < 30 improving to >30 to < 60. According to table B, the median pretreatment creatinine clearance level was 24.1 ml/min (range 4-49.4). The median post treatment CrCl was 45.6 ml/ min (range 17-66). Remarquebaly, a renal response was noted in all patients. In fact, 9/18 patients (50%) had their CrCl >50 ml/min (CRR), meaning that they are not considered in renal failure after treatment. In addition, 3 patients (17%) had PRR and 6 patients (33%) had MRR. 4 of 5 patients undergoing dialysis became dialysis independent. Time to renal response was calculated from the date of initiation of treatment until the date when criteria for renal response were first met. The median time to renal response was: 36 days.

### Adverse reactions

According to table C, 85 side effects were noted among those 18 patients, giving around 4.7 side effects/patient. 22 (26%) were hematologic events, 16 (19%) were digestive events, 7 (8%) were infectious events, 13 (15% were nervous sytem events and 27 (32%) were other conditions. Among those adverse reactions, 44 (52%) were grade 1, 31 (36%) were grade 2, 6 (7%) were grade 3 and 4 (5%) were grade 4. The repartition of side effects figures in diagram. As expected for bortezomib based therapy, the most common adverse event was reversible thrombocytopenia (Diagram 1). Diaphragms 2 show the repartition of each category of AE according to the different grades.

## DISCUSSION

MM was effective in newly diagnosed MM, relapsed MM and even refractory MM, as shown through the decrease in B2M, LDH, serum M protein, urine M protein, % of plasma cell in Bone marrow biopsy levels, as well as in decrease in bone lytic lesions number. (Harousseau et al. 2006) and (Richardson et al. 2005) showed that Bortezomib has achieved high response rates and disease-free survival for patients with both refractory/ relapsed MM and newly diagnosed MM Bortezomib was more effective in patients newly diagnosed of MM (compared to refractory/relapsed disease: 4/5 of CR patients were newly diagnosed.

| Table C. Adverse reaction | | | | |
|---|---|---|---|---|
| **Adverse reaction** | **Patients' numbers with grade 1** | **Patient's numbers with grade 2** | **Patients' number with grade 3** | **Patients' number with grade 4** |
| **Hematologic events** | | | | |
| Thrombocytopenia | 3-6- 9-15 | 5- 10- 13-17 | 4-11 | 12 |
| Leukopenia | 4-7-15 | 1- 18 | | |
| Anemia | 4-10-15 | 8-11 | | 5 |
| **Gastrointestinal events** | | | | |
| Diarrhea | 12 | 5-9-16 | 1 | |
| Nausea | 1-4-8 | 11 | | |
| Vomiting | 4-12 | 11 | | |
| Constipation | 1-3 | 8-18 | | |
| Infection | | | | |
| Pneumonia | 6-15 | 7 | 1 | |
| Herpes zoster | 2-7-17 | | | |
| **Nervous system events** | | | | |
| Peripheral sensory Neuropathy | 2-6-14-17 | 3-10 | 16 | 18 |
| Dizziness | 1-9 | 4-16-18 | | |
| **Other conditions** | | | | |
| Headache | 2-8 | 4 | | |
| HT | 3-8-17 | 4-5 | | |
| Dyspnea | 14 | 16 | | |
| Fatigue | 1-3-8-16-18 | 10-13 | | |
| Ileus | 9 | | 3 | |
| Pyrexia | 7-10 | 11-15 | | 4 |
| Allergic reaction | 7 | 16-18 | | |

And the median time to response is correlated with Myeloma status. (Roussou et al. 2010) showed that Bortezomib-based regimens may be the preferred treatment for newly diagnosed myeloma patients with RI. Furthermore, the median time to response is correlated with Myeloma response (EBMT criterias): 45 days for CR patients, 47.5 for VGPR patients, 56 for PR patients and 76 for MR patients. Bortezomib was able to reduce B2M in most of the patients of this study, which shows that survival rate must be increased in those patients. In addition, Bortezomib ameliorated the quality of life for patients. It was clear through the increased KPS and ECOG scores after treatment. 7/9 of CRR belongs to patients having 30<CrCl<50, while all the MRR and PRR response belonged only to the severe renal failure patients (CrCl<30ml/min). furthermore, the median time to renal response was 21 days for patients with baseline CrCl> 30 ml/min and 46 days for patients with baseline CrCl<30 ml/min. CrCl > 30 ml/min was independently correlated with a better renal response and a better time to renal response. The study suggests that bortezomib treatment has a potentially positive impact on renal function. In fact, all patient witnessed an amelioration of their renal function. (Chanan-Khan et al. 2005), (Ludwig HL et al. 2005) and (Mohrbacher et al. 2005) concluded that Bortezomib is able of a complete or near complete reversal of severe renal dysfunction. In addition, the better renal response is correlated with a shorter time to response. the median time to response was 22 days for CRR patients, 46 days for PRR patients and 52.5 days for MRR patients All patients witnessed a renal response, even with a PD or SD response. We can conclude that Bortezomib ameliorated renal function not only by reducing myeloma's severity but also through a direct effect on kidneys. Bortezomib has a potent inhibitory action on nuclear factor-kappaB (NF-KB) activity, which is strongly activated in renal tubular cells of patients with proteinuria and its inhibition significantly reduced inflammation and fibrosis in an experimental model of glomerulonephritis

(Herrera et al.2007). A recent publication also showed that bortezomib induces survival signals in renal tubular cells (Sarkozi et al. 2008) and reduce cystatin-C (a sensitive marker of RI) levels in patients with relapsed myeloma (Terpos et al.2009). In addition, the repartition of renal response wasn't correlated to the repartition of myeloma response, proving that Bortezomib has a direct effect on renal function. 4/5 patients who were undergoing hemodialysis, became dialysis-independent after bortezomib treatment. These observations is consistent with recent reports from other investigators who noted improvement in renal function. In fact (Chanan-Khan et al. 2005) concluded that bortezomib regimen can be used in MM patients requiring dialysis, with manageable toxicities. Bortezomib used in combination with high-dose dexamethasone has been reported to result in higher response rates in patients with MM and renal failure (Kastritis et al.2007). Malani et al reported rapid reversal of renal failure in four patients with MM and renal dysfunction (Malani et al.2006). Ludwig et al treated eight cases of MM and renal failure with bortezomib (Ludwig et al.2007). Seven of these patients were newly diagnosed and had not received any chemotherapy before. Five patients showed reversal of renal failure. Jaganath et al described their experience with 10 patients of MM with impaired renal function and observed that serum creatinine levels improved after treatment with bortezomib and high-dose dexamethasone (jagannath et al.2005). The majority of AE were grade 1 and 2. No discontinuation of treatment was required in any of the patients.

Roussou et al, 2008 concluded in their data that bortezomib based regimens can be administered to myeloma patients with renal impairment and their toxicity and efficacy are similar to those observed in patients without renal impairment

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