Brief report

Activity and safety of bortezomib in multiple myeloma patients with advanced renal failure: a multicenter retrospective study

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Patients with multiple myeloma (MM) frequently present with concomitant renal dysfunction, and those requiring dialysis have particularly poor outcomes. Bortezomib is a reversible proteasome inhibitor with significant activity in MM. This retrospective case analysis evaluated the feasibility and activity of bortezomib-based therapy in MM patients (n = 24) requiring dialysis support for advanced renal failure. All but 1 patient were undergoing dialysis at the time of therapy. Patients received bortezomib alone or bortezomib-based combination therapy. Among 20 patients with available response data, overall response rate (complete response [CR] + partial response [PR]) was 75%, with 30% CR + near CR. One patient was spared dialysis, and 3 other patients became independent of dialysis following bortezomib-based treatment.

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Introduction

According to recent reports, approximately 30% of patients with diagnosed multiple myeloma (MM) present with baseline renal dysfunction,1,4 with 1% to 13% having renal failure requiring dialysis support.2,6 A number of studies have shown that the severity of renal impairment significantly affects the prognosis of patients with MM.1,4,6 Renal dysfunction has been associated with shorter survival or early death,1,4 posing challenges in delivering effective and safe treatment options.

Bortezomib is a first-in-class proteasome inhibitor indicated for the treatment of MM patients after 1 prior therapy. A recent subanalysis of patients with impaired renal function from two phase 2 studies showed that renal dysfunction did not appear to have a negative impact on response rates, toxicity, or treatment discontinuation in patients with relapsed and/or refractory MM receiving bortezomib therapy.7 To further examine the safety and activity of bortezomib-based therapy in MM patients with more severe renal impairment, we designed this retrospective analysis to include patients who required dialysis support at the time of bortezomib administration.

Patients and methods

Consecutive patient cases were identified from 4 institutions in the United States experienced in myeloma treatment. The patient eligibility criteria included a diagnosis of MM, age at least 18 years, treatment with bortezomib alone or in combination with other agents, and renal failure requiring dialysis at the time of bortezomib treatment. Data on demographics, treatment schedule, response (by European Group for Blood and Marrow Transplantation [EBMT] criteria8), and adverse events were collected and analyzed using descriptive statistics. Patient consent was not required, because the collected data were existing information. The study protocol and data collection forms were approved by the institutional review board committees at all participating centers.

Results and discussion

We have analyzed data collected from the records of 24 patients treated between May 30, 2003, and November 10, 2005. Patient demographics and baseline disease characteristics are provided in Table 1. All patients were scheduled to commence dialysis at the time of bortezomib administration. However, only 23 (96%) of 24 patients received dialysis, because 1 patient who rapidly responded to bortezomib therapy no longer required dialysis support (Document S1, available on the Blood website; see the Supplemental Document link at the top of the online article). Eighty-three percent of patients received bortezomib at a dose of 1.3 mg/m2 given in combination with other agents such as dexamethasone, thalidomide, and doxorubicin (Table 1). Patients received a median of 5 cycles (mean, 7 cycles) of bortezomib treatment.

Most adverse events were graded mild to moderate and were manageable (Table 2; n = 18). As expected for bortezomib-based therapy, the most common adverse event was reversible thrombocytopenia (39%), with no bleeding events. Mean platelet levels remained at least $150 \times 10^9/L$ at the time of initiation of each cycle (ie, day 1) of bortezomib treatment (n = 15). Among the 18 patients for whom data were available, 8 patients...
including 1 patient who was spared dialysis after a rapid response to treatment, 2 patients who no longer required dialysis support after achieving a CR, and a fourth patient who became independent of dialysis following a minimal response to therapy. In the case of the fourth patient, normalization of renal function may not have been primarily attributable to bortezomib-based therapy.

At the present time, no standard guidelines have been established to treat MM patients with renal failure requiring dialysis. The presence of concomitant renal dysfunction has been considered a negative prognostic indicator associated with decreased response, shorter survival, and early mortality in patients treated with conventional chemotherapy. Patients with irreversible renal dysfunction or requiring dialysis have a particularly poor prognosis, with a median survival of less than 4 months.2-3 Treatment options such as melphalan-based chemotherapy and high-dose chemotherapy with autologous stem cell transplantation have limitations in this patient population because of suboptimal survival benefits, excessive toxicities, early mortality, and/or the need for dose reductions and treatment discontinuations. The recent introduction of targeted agents such as thalidomide (or the thalidomide analog, lenalidomide) has improved outcomes for MM patients. However, there is limited information regarding their safety and activity in the subgroup of high-risk MM patients with dialysis-dependent renal failure. Thalidomide has been associated with a high incidence of severe and potentially fatal hyperkalemia, particularly in patients undergoing hemodialysis.13,14 Lenalidomide has been shown to undergo substantial elimination via the kidneys and may therefore be associated with greater toxicities in patients with impaired renal function. In fact, patients with significant renal insufficiency were routinely excluded from clinical trials; postmarketing studies of lenalidomide in MM patients with renal dysfunction are currently underway.

Overall, toxicities were manageable and similar to those seen in patients with relapsed and/or refractory MM enrolled in the pivotal phase 2 SUMMIT15 and CREST16 trials, the phase 3 APEX17 trial, and other studies evaluating bortezomib-based therapies in previously treated MM.18-20 Given the retrospective nature of the analysis, the safety data for our study may have been underreported; nevertheless, the results from available data appear encouraging. Moreover, the patients in this study were able to receive a median of 5 cycles (or mean of 7 cycles) of bortezomib-based therapy, comparable to previous reports in patients with normal renal function.15,16

### Table 1. Demographics, pretreatment characteristics, and treatment schedule in 24 patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>50</td>
</tr>
<tr>
<td>Median age, y (range)</td>
<td>59 (41-82)</td>
</tr>
<tr>
<td>IgG/IgA/IgD/light chain only, %</td>
<td>29/25/4/42</td>
</tr>
</tbody>
</table>

### No. of prior therapies

| Median (range) | 2 (0-6) |
| None, no. (%)  | 1 (4)   |
| 1, no. (%)     | 4 (17)  |
| 2 or 3, no. (%)| 12 (50) |
| 4 or more, no. (%) | 3 (13) |

### Serum creatinine level

| Median, mg/dL (range) | 6.8 (3.1-12.8) |
| More than 2 mg/dL, no. (%) | 22 (92) |
| More than 6 mg/dL, no. (%)  | 15 (63) |
| Unknown, no. (%)         | 2 (8)    |
| Median hemoglobin level,* g/dL (range) | 10.2 (7.4-15.3) |
| Median platelet count,* × 10^9/L (range) | 186 (25-369) |

### Etiology of renal failure, no. (%)

- Progressive MM: 14 (58)
- Amyloidosis: 2 (8)
- Renal cortical atrophy: 1 (4)
- Unknown: 7 (29)

### Bortezomib treatment, no. (%)

- Alone: 2 (8)
- Plus dexamethasone: 6 (25)
- Plus dexamethasone and thalidomide: 4 (17)
- Plus liposomal doxorubicin and thalidomide†: 7 (29)
- Other combinations‡: 4 (17)
- Not specified: 1 (4)

### Bortezomib starting dose, no. (%)

- Less than 1.0 mg/m²: 1 (4)
- 1.0 mg/m²: 3 (13)
- 1.3 mg/m²: 20 (83)

### Median no. of cycles of bortezomib (range)

- 5 (2-20)

### Timing of treatment relative to dialysis, no. (%)

- Before dialysis: 1 (4)
- During dialysis: 1 (4)
- After dialysis§: 20 (83)
- Not reported: 1 (4)
- No dialysis: 1 (4)

### Table 2. Summary of adverse events (all grades) and treatment discontinuation in 18 patients

<table>
<thead>
<tr>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
</tr>
<tr>
<td>Neuropathic pain: 1 (6)</td>
</tr>
<tr>
<td>Peripheral neuropathy: 2 (11)</td>
</tr>
<tr>
<td>Neutropenia: 1 (6)</td>
</tr>
<tr>
<td>Headache: 1 (6)</td>
</tr>
<tr>
<td>Hypertension: 1 (6)</td>
</tr>
<tr>
<td>Infections: 2 (11)</td>
</tr>
<tr>
<td>Thrombocytopenia: 7 (39)</td>
</tr>
<tr>
<td>Platelet count 50 × 10^9/L to less than 150 × 10^9/L: 5 (28)</td>
</tr>
<tr>
<td>Platelet count 25 × 10^9/L to less than 50 × 10^9/L: 2 (11)</td>
</tr>
</tbody>
</table>

### Serious adverse events

- Death due to progressive disease: 1 (6)

### Adverse events leading to discontinuation

- Progressive disease: 6 (33)
- Neuropathic pain: 1 (6)
- Peripheral neuropathy: 1 (6)
The overall response rate and durability of response to bortezomib-based treatments in our dialysis-dependent patients appear comparable to those of MM patients with primarily normal renal function reported in other studies in the relapsed setting. In our study, 83% of patients received treatment after completion of dialysis, suggesting that delivery of bortezomib subsequent to dialysis does not appear to affect the activity of the drug. The present study also suggests that bortezomib treatment has a potentially positive impact on renal function, with normalization of renal dysfunction in a few patients. These observations are consistent with recent reports from other investigators who noted improvement in renal function as well as complete or near-complete reversal of severe renal dysfunction following bortezomib-based combination therapy.

Our study suggests that bortezomib is a well-tolerated, effective option in the subgroup of MM patients with severe renal dysfunction. Preliminary data from the prospective National Cancer Institute pharmacologic trial showed that bortezomib clearance is independent of renal function, and the standard 1.3 mg/m² dose appeared well tolerated in patients with mild to moderate renal dysfunction. Accrual continues for patients having more severe renal dysfunction or requiring dialysis, and further analysis of the results from this study will help characterize the safety profile of bortezomib in this group of patients.

Authorship

Contribution: A.A.C.-K. wrote the paper, participated in the scientific design, and conducted research and patient accrual; J.L.K., J.M., P.G.R., K.C.M., S.L., N.C.M., R.S., J.T., and S.S. conducted patient accrual; and all authors checked the final version of the manuscript.

Conflict-of-interest disclosure: P.G.R., K.C.M., S.L., N.C.M., R.S., and J.T. have no financial relationships to disclose. A.C.K., J.M., and S.S. are members of the advisory board for Millennium Pharmaceuticals, Inc. J.L.K. is a consultant for Millennium Pharmaceuticals, Inc. A.C.K. is a member of the speakers bureau for Millennium Pharmaceuticals, Inc. J.M. is a member of the speakers bureau for Celgene Corporation.

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References

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