Bortezomib overcomes the negative prognostic impact of renal impairment in a newly diagnosed elderly patient with multiple myeloma: A case report

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Abstract. Multiple myeloma (MM) is a common B-cell hematological malignancy in the clinic. Bortezomib is the first-in-class proteasome inhibitor that has been approved for the treatment of patients with MM in the bone marrow. The present study report the case of an 83-year-old man who showed marked weakness, fatigue and a poor appetite. The patient was admitted to the Department of Nephrology due to severe renal impairment (RI). Immunofixation electrophoresis indicated a λ light chain-positive status. There were 19.2% plasmablasts and proplasmacytes in the bone marrow. Positivity for the cell surface markers cluster of differentiation (CD)13, CD33, CD38 and human leukocyte antigen-antigen D-related was detected by flow cytometry. The patient was diagnosed with MM, λ light chain type, stage IIIB, and received bortezomib and dexamethasone regimen chemotherapy. RI was improved following the chemotherapy, and plasmablasts and proplasmacytes were almost eliminated. The Hb level was maintained at ~90 g/l. Overall, the present case report suggests that bortezomib may be safe and effective for elderly patients, even those >80 years of age, with severe RI.

Introduction

As one of the most intractable malignancies, multiple myeloma (MM) has characteristics of infiltration and growth of plasma cells, the most differentiated cells in the B-cell lineage, in the bone marrow. MM typically affects elderly patients, with ~33% patients are older than 75 years at diagnosis (1). MM is divided into two distinct genetic subtypes based on chromosome content. The incidence of standard risk is 60% and median overall survival (OS) is 8-10 years. The incidence of intermediate is 20% and median OS is 4-5 years. The incidence of high risk is 20% and median overall OS is 3 years (2). Ramsenthaler *et al* (3) reported that the most prevalent symptoms were fatigue (98.8%, 95% CI 98.1-99.2%), pain (73%, 39.9-91.7), constipation (65.2%, 22.9-92.2) and tingling in the hands/feet with 53.4% (0.4-99.7). The most common problems were decreased physical functioning (98.9%, 98.2-99.3), decreased cognitive functioning (80.2%, 40-96.1) and financial difficulties (78.4%, 39.1-95.4). Renal impairment (RI) is a common feature of symptomatic MM and may cause major management problems (4). RI affects up to 50% of patients with MM (5). Renal failure (RF) is detected in between 20 and 30% patients at the onset of MM, and in 50% of patients during its progression (6). The prognosis of patients with MM has significantly improved following the introduction of novel concepts of immunomodulation and proteasome inhibition in myeloma therapies (7). Bortezomib is the first-in-class proteasome inhibitor that has been approved for the treatment of patients with MM in the bone marrow. The present study reports the case of a newly diagnosed MM patient, aged 83 years, in whom RI was successfully treated with a bortezomib-based regimen.

Case report

An 83-year-old man was admitted to Lanzhou General Hospital, Lanzhou Command, (Lanzhou, Gansu, China) on February 25, 2015, due to marked weakness, fatigue and a poor appetite. The patient was admitted to the Department of Nephrology due to severe RI (Fig. 1), with 647.0 μmol/l creatinine (normal, (35-97 μmol/l), 26.60 mmol/l urea (normal, 2.40-8.20 mmol/l), 520.0 μmol/l uric acid (normal, 90.0-420.0 μmol/l) and 8.5 mg/l cystatin-C (normal, 0.00-1.16 mg/l). Blood routine showed anemia with 61 g/l Hb, 512 mg/dl immunoglobulin (Ig)G, 21.9 mg/dl IgA and 8.5 mg/dl IgM. There were local cystic changes on the parietal bone, as determined by X-ray (Fig. 2), and an anomalous area of increased radioactivity on the left side of the 9th vertebral rib joints, as determined by Technetium-99 m radionuclide bone imaging (injected, 25 mCi) (Fig. 3). Immunofixation electrophoresis (8) indicated a λ light chain-positive status. In

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Abbreviations: MM, multiple myeloma; RI, renal impairment; FLCs, free light chains; MGUS, monoclonal gammopathy of undetermined significance

Key words: multiple myeloma, renal impairment, bortezomib

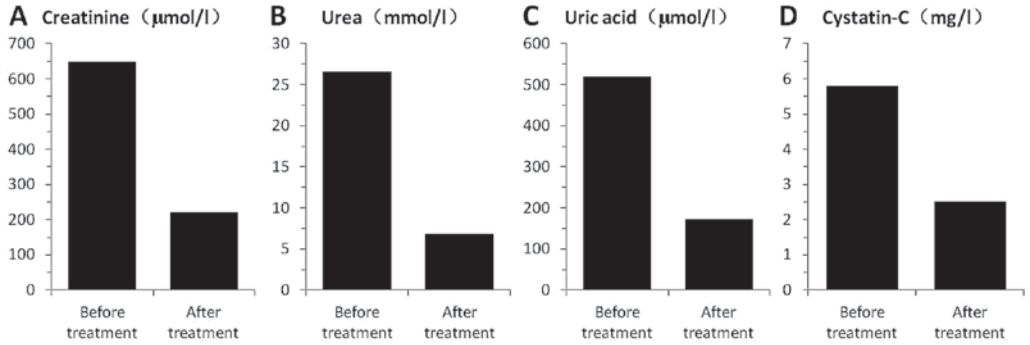

Figure 1. Kidney function was greatly improved following bortezomib treatment, as demonstrated by changes in (A) creatinine, (B) urea, (C) uric acid and (D) cystatin-C.

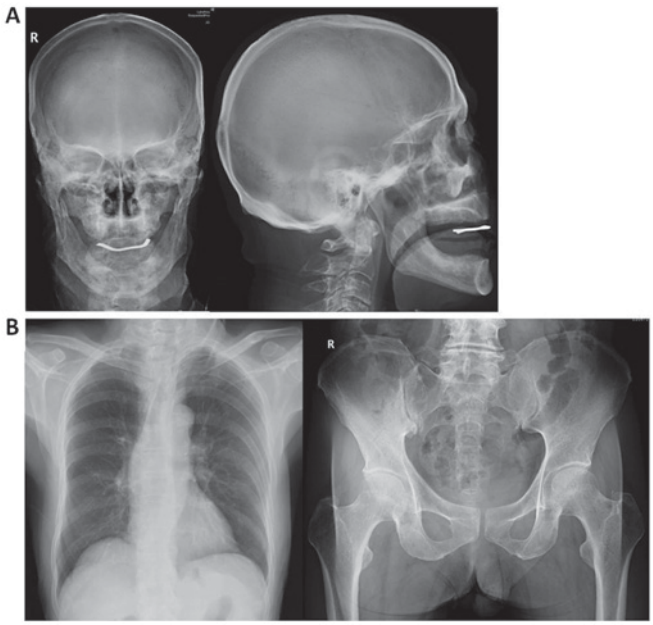

Figure 2. Radiographic representation. (A) Local cystic change on the parietal bone. (B) Normal chest and pelvic X-ray.

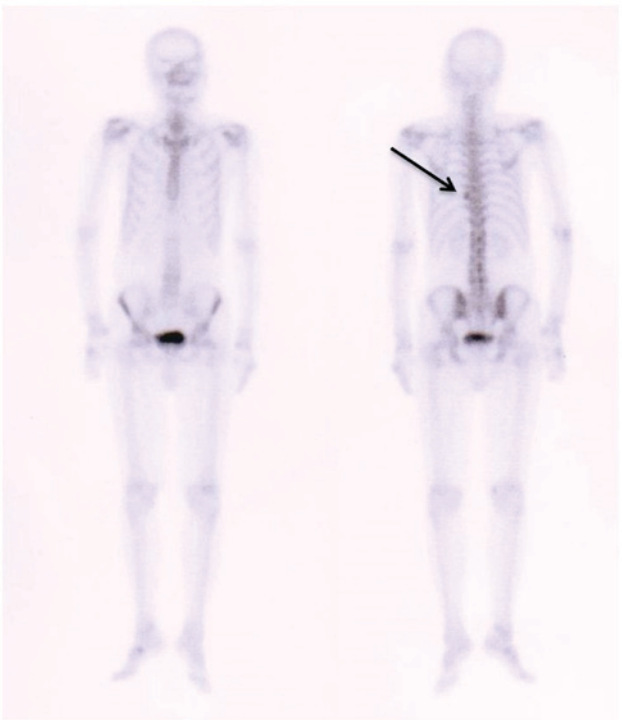

Figure 3. Anomalous area of increased radioactivity on the left side of the 9th vertebral rib joints (arrow), as determined by Technetium-99 m radionuclide bone imaging.

total, 19.2% plasmablasts and proplasmacytes were detected in the bone marrow (Fig. 4A), and the cell surface markers cluster of differentiation (CD)13, CD33, CD38 and human leukocyte antigen-antigen D related were positively detected by flow cytometry, as described previously (9). Chromosome analysis showed that the patient was 46, XY. Immunoglobulin heavy chain gene fracture restructuring was positive (14%), as detected by fluorescence *in situ* hybridization of the patient's bone marrow cells (10). These specific tests were performed as MM may be accompanied by gene and chromosome mutations. For example, the patients who presented with chromosomal abnormalities del17p, t(14;16) or t(14;20) were genetically defined as high-risk features (7). 1q21 amplification also has very important prognostic value in multiple myeloma. Amp1q21 is one of the most common chromosomal abnormalities in patients with new-onset MM and may appear in the course of disease progression. The presence of amp1q21 is an important prognostic factor and should be included in the diagnostic study at disease onset and progression (11). The patient was transferred to Department of Hematology on February 28, 2015. The patient's Karnofsky performance status (12) score was 70. A diagnosis of MM, λ light chain type, stage IIIB (Durie-Salmon system) (13), was formed, and bortezomib and dexamethasone regimen chemotherapy was administered from March 2, 2015 (bortezomib, 1.3 mg/m2, intravenous injection, days 1, 4, 8 and 11; dexamethasone, 40 mg, intravenous drip, days 1-4, 8-11). On March 1 and March 3, 300 ml red blood cells were transfused into the patient. RI was greatly improved following the bortezomib-based chemotherapy (Fig. 1), and plasmablasts and proplasmacytes were virtually eliminated, with only 0.8% mature plasmacytes left in the bone marrow (Fig. 4B). The Hb level was maintained at ~90 g/l. The patient declined further bortezomib treatment due to numbness and pain in the hands and fingertips. On April 23, 2015, the patient was administered a melphalan and prednisone regimen (melphalan, 4 mg/m2, oral administration, days

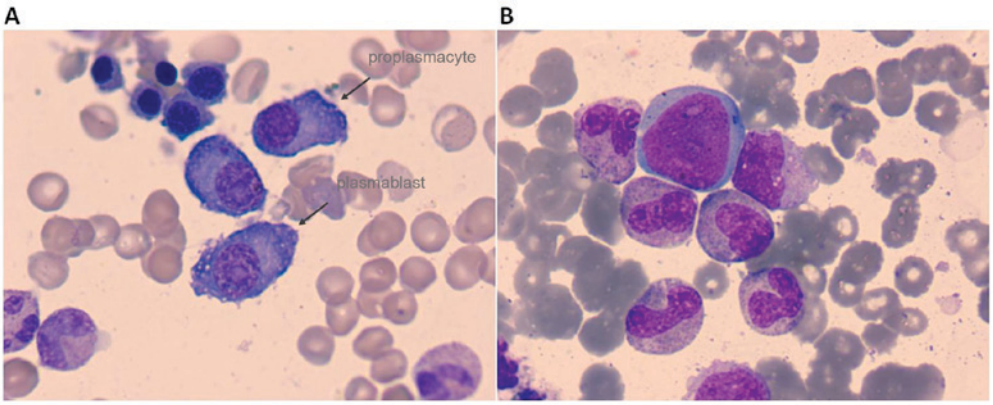

Figure 4. Plasmablasts and proplasmacytes were eradicated in the bone marrow following bortezomib treatment. (A) Prior to treatment; and (B) following treatment (magnification, x1,000).

1-4; prednisone, oral administration, 40 mg/m2, days 1-7). The patient was discharged from hospital on 28 April 2015, with 100 mg thalidomide prescribed every night for the long-term. The patient is currently under follow-up every 4-6 weeks. Written informed consent was obtained from the patient for the publication of the present study.

Discussion

MM is a clonal B-cell malignancy that causes bone destruction and affects the immune system. Approximately 70% of myeloma patients are >60 years old and 90% are >50 years old. RI is a frequently occurring complication of symptomatic myeloma. Moderate or severe RI occurs in 20-40% of newly diagnosed patients, 10% of who may require dialysis (14-18). Antimyeloma therapy should be immediately administered for the improvement of RI.

It has been suggested in retrospective studies (19,20) that the results for MM patients with RI treated with novel front-line agents may have improved such that RI may no longer have a negative prognostic impact (21,22), particularly when using modern three-drug combination regimens (23).

Bortezomib is the first-in-class proteasome inhibitor that has been approved for the treatment of patients with MM; it has a half-life independent of renal clearance (24) and data from initial phase II and III trials, as well as data from patients undergoing dialysis, indicating that bortezomib is safe to use in patients with renal dysfunction (25,26), even in those undergoing dialysis (27), without the requirement for dose adjustments. In addition, certain studies have indicated that, with regard to RI, the favorable activity of bortezomib may also be as a result of a protective effect on renal cells, and due to inflammatory and fibrotic cascade inhibition within the microenvironment of the kidney (28,29). However, with regard to RI, rapid and marked antimyeloma action, and being non-renal metabolite, are the most significant advantages of using bortezomib (30-32). The present data showed that kidney function can rapidly be improved in MM patients, and even in older patients, such as the 83-year-old treated in the present study. The treatment appears to be safe and effective, and prospective trials (33,34) showing high drug response rates of myeloma and the kidneys in patients with moderate RI, in particular to bortezomib, have further supported this stance. Another common observation is that renal response correlates with tumor response and is more common in newly diagnosed patients, compared with late-state patients (35,36). The data from the present study are consistent with this observation.

There are several causes of RI in MM patients. The circulating monoclonal light chains are filtered through the glomeruli and reach the proximal tubule where they are catabolized. The free light chains (FLCs) are endocytosed by the cells of the proximal tubule through a receptor-mediated process, which results in their degradation within lysosomes (37-40). Focal loss of microvilli and inhibition of Na-K-ATPase pumps may lead to reabsorption defects (41). Cast nephropathy is another potential cause of RI. In a recent study, 24-h urine protein containing <25% albumin exhibited a sensitivity of 0.98, a specificity of 0.94, a positive predictive value of 0.75 and a negative predictive value of 0.99 for the diagnosis of cast nephropathy (42).

For oliguria cases or when renal function is deteriorating rapidly or during recovery, urine quantification of light chains is unreliable. Serum FLCs have been used for the assessment of patients with light chain amyloidosis and for patients with oligo-secretory disease (43); however, in patients with RI and a significant load of FLCs, the evaluation is not straightforward. In patients with RI, κ and λ light chains increase and the normal κ/λ ratio is different than in patients with normal renal function (44,45). The current response criteria for patients with measurable disease do not use the serum FLCs but the urine 24-h light chain output (46). Furthermore, the correlation of urine light chain excretion and serum FLC levels is not linear, and large variations occur (46). Thus, in patients with significant RI, the evaluation of response to chemotherapy may be challenging.

Serum cystatin-C is a sensitive marker of renal dysfunction that has been applied by nephrologists for a number of years. Terpos *et al* (47) measured serum cystatin-C levels in newly diagnosed and pretreated patients with MM and revealed that levels were increased in patients with myeloma, even in individuals with normal serum creatinine levels. Markers of renal damage, including neutrophil gelatinase-associated lipocalin and kidney injury molecule-1 in the serum and/or

urine, are increased in patients with monoclonal gammopathies, indicating that renal damage is present at an early in the disease course (48). The present results showed that cystatin-C decreased more than 1-fold following bortezomib treatment. This is consistent with the results described by Terpos *et al* (47). The suggestion that a decrease in estimated glomerular filtration rate of >35% within 1 year, without any other identifiable cause, could be used as an indication for therapy is being considered. Reversal of renal dysfunction and significant improvement of renal function have been observed in several studies of patients with MM-related RI, and even certain patients on dialysis became dialysis-independent following treatment with bortezomib (27). However, it is also notable that certain patients who do not achieve an objective myeloma response may also show a significant improvement in renal function (33). Overall, significant improvement of renal function was observed in 77-82% of patients treated with bortezomib-based therapy (20). Furthermore, this improvement appears to be independent of the dose of steroids, although higher doses of dexamethasone may be associated with a shorter time to renal recovery (20).

Although novel therapeutic agents, including the proteasome inhibitor ixazomib and the immunomodulatory drug pomalidomide have been introduced, the prognosis of MM patients remains worse than that of the majority of other hematological malignancies (49,50). In order to achieve any improvements in treatment outcome for MM patients, it is necessary that the molecular pathogenesis of the disease is understood to a greater extent. A phase of asymptomatic expansion of clonal plasma cells, also known as monoclonal gammopathy of undetermined significance (MGUS), is progressed through by all MM cases (51,52). The linear evolution of MM from MGUS to terminal phases, such as that of extramedullary tumors and plasma cell leukemia via the accumulation of novel mutations, is a long-held belief (51,52). However, previous studies using next-generation sequencing revealed the complex genomic architecture of MM. At each progression step, novel mutations are acquired together with subclonal evolution from reservoir clones with branching patterns. Individual subclones may carry novel mutations and distinct phenotypes, including that of drug sensitivity (53). Furthermore, at the MGUS stage, minor clones are already present, which could expand further along in the clinical course, causing relapse and/or leukemic conversion (54). The final aim of treatment is to eliminate all clones, including subclonal populations with distinct biological characteristics. This may be achievable by further the improvement of treatment strategies that reflect the genomic landscape of the disease.

In summary, the present case indicates that bortezomib is safe for MM patients >80 years old. The present study also proved that bortezomib can improve the RI of myeloma patients with a creatinine level of >600 μmol/l, and even of those patients >80 years old. However, further cases are required to confirm these findings.

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