CASE REPORT

Strategy to reduce bortezomib-induced paralytic ileus in patients with myeloma and impaired renal function

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Accepted 14 November 2016

SUMMARY

While bortezomib is known to cause adverse effects involving the autonomic nervous system, gastrointestinal side effects are typically mild. We describe herein a series of patients with myeloma and impaired renal function who developed severe paralytic ileus secondary to bortezomib use. Our patients had other risk factors for paralytic ileus including electrolyte abnormalities and opiate use. The striking commonality in our patients is the development of paralytic ileus with intravenous bortezomib in the setting of reduced renal function, followed by ileus resolution with bortezomib dose reduction. We discuss the existing literature on this subject and propose a strategy in order to reduce the risk of paralytic ileus in these patients. Upfront bortezomib dose reduction to 1 mg/m² intravenously in patients with myeloma with a glomerular filtration rate (GFR) of <30 mL/min may prevent paralytic ileus, while not compromising the clinical outcomes. Our conclusions will have to be validated in larger studies.

BACKGROUND

Bortezomib is a selective and reversible proteasome inhibitor used to treat newly diagnosed and refractory cases of multiple myeloma. It is known to cause adverse effects involving peripheral and autonomic nervous systems, though studies of the latter phenomenon have been limited.¹ Herein, we describe two cases of paralytic ileus secondary to bortezomib use in multiple myeloma patients with impaired renal function. We discuss briefly the existing literature on this subject and propose strategies on how to reduce the risk of paralytic ileus in these patients.

CASE PRESENTATION

Case 1

A 75-year-old Hispanic man, with a medical history of atrial fibrillation and chronic kidney dysfunction, presented in June 2014 with progressive generalised weakness, bone pain and 20 lb weight loss over the previous 2 months. He had a history of a right-sided nephrectomy over 40 years prior (indication unknown per patient). Family history included uterine cancer in his mother at age 60. Physical examination was remarkable for moderate pallor and slight confusion, but no other abnormal physical findings. Laboratory results were the following haemoglobin of 12.5 mg/dL (normal range 14–18 mg/dL), creatinine of 3.6 mg/dL (normal range 0.8–1.3 mg/dL) and GFR 18 mL/min (normal GFR >60 mL/min). Corrected serum calcium was

14.8 mg/dL (normal range 8.5–10.4 mg/dL). No other major electrolyte abnormalities were noted throughout his hospital stay. Of note, previous tests showed a creatinine of 1.1 mg/dL with GFR >60 mL/min and normal serum calcium 6 months prior. Bone survey showed scattered lytic lesions in the axial and appendicular skeleton. Haematology/oncology workup revealed a normal serum protein electrophoresis and a κ -free light chain (FLC) of 1490 mg/dL (normal range 0.33–1.94 mg/dL), consistent with κ -FLC multiple myeloma. Cytogenetic and fluorescence in situ hybridisation studies of the bone marrow were normal.

Case 2

A 71-year-old Caucasian woman, with medical history of hypertension and atrial fibrillation, presented in October 2014 with renal failure (creatinine 2.4 mg/dL (normal range 0.6–1 mg/dL); GFR 21 mL/min), anaemia (haemoglobin of 9.8 mg/dL (normal range 12–16 mg/dL)) and osteolytic lesions. She also had mild hypokalaemia and moderate hypomagnesaemia, which were successfully repleted during the hospital stay. Family history included chronic renal failure in her father. Physical examination showed moderate pallor and 2+ pedal oedema, but unremarkable cardiac and respiratory exams. Serum protein electrophoresis showed a tiny M-spike, decreased γ -globulin and increased serum lambda-FLC (lambda-FLC of 569 mg/dL (normal range 0.57–2.63 mg/dL)). She was diagnosed with lambda-FLC multiple myeloma. Cytogenetic and fluorescence in situ hybridisation studies of the bone marrow were normal.

TREATMENT

Case 1

He was started on intravenous hydration and received calcitonin nasal spray for symptomatic hypercalcaemia. Zoledronate was considered but decided against given significantly impaired kidney function. Bortezomib at 1.3 mg/m² intravenous on days 1, 4, 8 and 11 every 3 weeks and dexamethasone 40 mg intravenous daily were started. Hypercalcaemia improved and kidney function stabilised with this treatment. However, he developed moderate thrombocytopenia secondary to bortezomib. He also developed abdominal pain and distension on day 14 of bortezomib treatment and could not keep any food down. Abdominal X-ray suggested paralytic ileus (figure 1). He was placed in NPO status for several days, and a nasogastric tube

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To cite: Keating M, Dasanu CA. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-217000

Figure 1 Plain abdominal radiographs showing two cases of paralytic ileus secondary to bortezomib, case 1 (above) and case 2 (below).

was placed for decompression. He improved clinically and tolerated a diet prior to discharge. Renal failure persisted throughout his stay. He continued bortezomib as an outpatient at a reduced dose of 1 mg/m² intravenously on days 1, 4, 8 and 11.

Case 2

She was treated initially with haemodialysis. A regimen consisting of twice-weekly intravenous bortezomib at 1.3 mg/m² 2/3 weeks, and weekly dexamethasone was administered as an inpatient. She returned to the hospital 3 weeks later with intractable back pain secondary to a pathologic T9 fracture. Of note, by that time she had completed two cycles of bortezomib (1.3 g/m²) and low dose dexamethasone. Opiates were used to control her pain. The patient developed abdominal distension and constipation, and an abdominal X-ray was consistent with paralytic ileus (figure 1). In addition, the patient developed worsening peripheral neuropathy. Paralytic ileus resolved with nasogastric decompression and NPO status. She received erythropoietin injections for anaemia of renal failure. Creatinine waxed and waned over the course of admission but ultimately improved to 1.6 mg/dL with a GFR of 34 mL/min prior to discharge. Bortezomib dose was reduced to 1 mg/m², and she had no further gastrointestinal symptoms.

OUTCOME AND FOLLOW-UP

Case 1

He remained relapse-free until June 2015. No further symptoms suggesting paralytic ileus were observed in the interim.

Case 2

She did not have any further instances of paralytic ileus. Unfortunately, she developed pneumonia, septicemia and multi-organ failure, which led to her demise 3 months later.

DISCUSSION

In a previous study, between 22% and 37% patients with multiple myeloma have not been able to tolerate bortezomib treatment due to side effects.² Neurotoxicity accounts for an important percentage of clinically significant adverse events. The mechanism of bortezomib-induced peripheral neuropathy has been defined on a molecular level and is closely tied to impaired axonal transport and alterations in tertiary DNA structure.¹ Peripheral nerve damage due to bortezomib has been described in animal models and clinical trials in humans.^{3 4} Autonomic nerve injury, on the other hand, can manifest as gastrointestinal side effects which are typically mild. More serious gastrointestinal side effects such as paralytic ileus, intestinal obstruction and toxic megacolon are rare.³ The exact mechanism of bortezomib-induced paralytic ileus has yet to be defined. An immunofluorescence study of autonomic nerve fibres in the skin has provided objective evidence of bortezomib's impact on the autonomic nervous system.⁴

Per Naranjo nomogram, the causal relationship between bortezomib and paralytic ileus in our patients is at least probable. Autonomic nerve fibre injury likely plays a significant role in the occurrence of this gastrointestinal side effect. Description of a case of a complete heart block secondary to bortezomib by

Dasanu in 2011⁵ lends further credence to the impact of bortezomib on the autonomic nervous system. Several cardiac rhythm abnormalities have been reported in clinical trials as well. Collectively, these findings support a damaging effect of bortezomib on the autonomic nervous system as a whole.

There are a variety of risk factors linked to paralytic ileus, some of which were present in our patients (table 1).⁶ We propose that bortezomib be added to this list, particularly in the setting of renal impairment. We believe that the hypercalcaemia in case 1 and the opiate use/hypokalaemia/hypomagnesaemia in case 2 had a cumulative effect on the patients' paralytic ileus. Coexisting risk factors for paralytic ileus are virtually given in many hospitalised patients. The striking commonality between our two cases is the development of paralytic ileus with intravenous bortezomib in the setting of reduced renal function, followed by ileus resolution with bortezomib dose reduction.

Anticipation of bortezomib side effects, with appropriate adjustments to the dose and frequency of bortezomib administration, is key in prevention and management of side effects. Administration of adequate fluids/motility agents/laxatives minimises severe gastrointestinal side effects. Certainly, the antiemetic properties of dexamethasone, often combined with bortezomib in patients with multiple myeloma, are of benefit as well. Oftentimes, the bortezomib dose or frequency is reduced, or the drug is even terminated due to severe side effects. A retrospective analysis of 22 patients with relapsed or refractory myeloma showed a particularly high incidence of gastrointestinal side effects. Circa 31.6% of twice-weekly bortezomib patients and only 5.9% of once-weekly bortezomib patients developed paralytic ileus.² The study concluded that once-weekly bortezomib administration may reduce gastrointestinal side effects without compromising clinical efficacy.⁷

A recent paper by Lee *et al*⁸ called into question the chemotherapy paradigm in which cytotoxic effects of chemotherapy are expected to emerge within the first cycle of treatment. The authors hypothesise that some acute toxicities of molecular targeted therapies may not emerge until subsequent treatment cycles. To support their hypothesis, they took a meta-analytic approach to toxicity data from 14 bortezomib dose-finding trials which included over 13 000 toxicity events. Of note, some of

the trials used bortezomib in combination with chemotherapy. Their conclusions on the appropriate dose of bortezomib provide a framework for dose selection in patients such as our own case series. They found the cumulative incidence of dose-limiting toxicity at five cycles to be 0.52 for a bortezomib dose of 1.3 mg/m² vs 0.37 for a bortezomib dose of 1 mg/m². Meanwhile, Kaplan-Meier estimates of progression-free survival were not significantly different between the two dose groups. The cumulative incidence of dose reduction or treatment termination due to toxicity over the same time period was 0.38 for a bortezomib dose of 1.3 mg/m² vs 0.24 for a bortezomib dose of 1 mg/m².⁸ This report will have to be taken seriously given the magnitude of toxicity data and the downstream effect of dose-finding trials on clinical practice.

Of newly diagnosed patients with multiple myeloma, 20–40% of cases are complicated by renal insufficiency.⁹ The prominence of renal impairment in patients with multiple myeloma had to be accounted for in the search for effective multiple myeloma treatments. Bortezomib is primarily cleared by the liver rather than the kidneys and has been associated with improvement in kidney function and even complete reversal of renal dysfunction. An ideal multiple myeloma agent would maximise treatment of multiple myeloma and return of kidney function while minimising side effects. The dosing regimen of bortezomib is based on how quickly proteasome activity recovers after inhibition.¹⁰ There appears to be a clinical benefit in reducing the bortezomib dose in patients with impaired renal function. We are aware that other sources recommend once-weekly doses in the setting of renal dysfunction, but this is not the FDA-approved regimen.

The route of bortezomib administration, that is, intravenous versus subcutaneous, may impact the development of paralytic ileus in this patient population. Bortezomib has been associated with a lower incidence of peripheral neuropathy when administered via the subcutaneous route. Furthermore, the theory of a route-dependent side effect profile is not unique to bortezomib as can be seen in studies of other chemotherapeutic agents such as azacitidine. We found no studies exploring the incidence of ileus with subcutaneous bortezomib administration, but this is an intriguing point of further study.

To date, bortezomib side effects have not been directly linked to renal function. Bortezomib-induced peripheral neuropathy has not been correlated to patients' renal function or other baseline characteristics.⁷ However, a dose dependency of bortezomib-related side effects has been identified. Peripheral neuropathy is likely a dose-dependent side effect, which can be attenuated with dose reductions from 1.3 to 1 mg/m² or with increased time intervals between bortezomib treatments.⁹ Our two patients experienced thrombocytopenia and worsening peripheral neuropathy, respectively. These side effects improved after the dose of bortezomib was decreased. This strengthens the credibility of the association between bortezomib and paralytic ileus as per Naranjo probability.

Bortezomib administration has been studied in patients with multiple myeloma and kidney disease. In a prospective study of 18 newly diagnosed patients with multiple myeloma and renal impairment (creatinine of 2 mg/dL or greater), one patient experienced recurrent ileus.¹¹ Therefore, we advocate considering reduction of bortezomib dose to 1 mg/m² in patients with myeloma and renal impairment (GFR <30 mL/min) to prevent excessive toxicity including paralytic ileus and achieve better clinical outcomes. This adjustment should be made especially in the face of other known risk factors for paralytic ileus such as renal impairment, opiate use, electrolyte imbalances, recent

Table 1 Medical risk factors for paralytic ileus

Category	Entities
Infectious	Septic shock, herpes zoster, pneumonia, intra-abdominal tuberculosis, peritoneal or retroperitoneal infection
Inflammatory	Systemic sclerosis, systemic lupus, inflammatory bowel disease
Gastrointestinal	Acute pancreatitis, perforated peptic ulcer, peritonitis
Cardiovascular/cerebrovascular	Myocardial infarction, congestive heart failure, stroke
Metabolic	Electrolyte abnormalities (hypokalaemia, hyponatremia, hypo/hypermagnesaemia, hypercalcaemia), severe hypothyroidism, diabetic ketoacidosis, liver failure, renal failure, alcohol abuse
Pharmacologic	Antidepressants, opiates, anticholinergics, phenothiazines, benzodiazepines, laxatives, calcium channel blockers, anti-Parkinsonian agents, amphetamines, cytotoxic agents, catecholamines, clonidine, sodium valproate
Epidemiologic	Advanced age, increased body mass index

Adapted with permission from Bernardi *et al*.⁶ Surgical risk factors are not included in this table.

surgery and uncontrolled diabetes. Our argument is that patients with multiple myeloma and renal impairment are particularly vulnerable to paralytic ileus when treated with bortezomib, and the incidence of paralytic ileus further increases when other risk factors are present in addition to renal impairment and bortezomib administration. We feel that patients with myeloma such as those described in our series, who carry additional risk factors for paralytic ileus including renal impairment, should be started on a reduced bortezomib dose of 1 mg/m². Despite the primary liver clearance of bortezomib, there could be a small fraction of renal clearance which likely contributes to the association between renal impairment and bortezomib side effects such as ileus. It is interesting to note that our patients had light chain disease, and further research is needed to determine whether the correlations observed in our case series are specific to the patients with light chain disease or apply to patients with myeloma at large.

We believe that the newer proteasome inhibitors on the market such as carfilzomib and ixazomib are likely to become first-line treatment options given their superior progression-free survival data and toxicity profiles. In addition, studies of bortezomib can facilitate this transition and provide insights into the toxicity of

proteasome inhibitors as a class of antineoplastic agents. Furthermore, bortezomib studies will allow us to fine-tune dose optimisation protocols of the newer agents, while keeping pace with the booming number of new anticancer agents.

Contributors MK and CAD have contributed equally to the data gathering, analysis, additional research and proofreading involved in the composition of this manuscript.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- ▶ Patients with myeloma who carry risk factors for paralytic ileus and have renal impairment should be started on a reduced bortezomib dose of 1 mg/m² intravenously.
- ▶ Cytotoxic effects of molecular targeted therapies do not always emerge on the first treatment cycle, and these effects may manifest on subsequent treatment cycles.
- ▶ Studies of bortezomib can facilitate the transition to superior proteasome inhibitors by providing insights into the toxicity of proteasome inhibitors as a class of antineoplastic agents.

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