Case Report

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Bortezomib-induced acute pancreatitis: Case report and review of the literature

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Abstract

Acute pancreatitis is a rare complication of chemotherapy agents. We describe the case of a patient with multiple myeloma who developed acute pancreatitis after treatment with bortezomib, a proteasome inhibitor commonly used in the treatment of this disease. We reviewed the available medical literature on this topic, and found other seven similar cases, all after intravenous bortezomib. Our case is the first one occurring with the subcutaneous route of administration.

Keywords

Bortezomib, proteasome inhibitors, acute pancreatitis

Introduction

Acute pancreatitis is a potentially life-threatening inflammation of the pancreas, most commonly induced by alcohol consumption and biliary stones. Medications can also induce acute pancreatitis, but they are a rare cause of it, because the incidence is estimated to be approximately 1.4%.[1,2] Bortezomib is a proteasome inhibitor approved by the Food and Drug Administration (FDA) for the treatment of patients with multiple myeloma (MM) in May 2003.[3] Bortezomib is a dipeptide boronate that inhibits the chymotrypsin-like activity of the 26 S proteasome. This consists of two 19 S regulatory complexes and a 20 S proteolytic core. The proteolysis is mediated by three subunits of the 20 S core: the b1 subunit has a caspase-like activity, the b2 subunit has a trypsin-like activity, and the b5 subunit has a chymotrypsin-like activity.[4] Proteins are first tagged with ubiquitin, and then degraded in the proteasome enzyme complex. The 19 S regulatory complexes bind the ubiquinated proteins and direct them to the 20 S core. Thus, the inhibition of the proteasome ultimately leads to cell apoptosis and death because of the accumulation of misfolded proteins within the endoplasmic reticulum.

The most common adverse reactions of bortezomib are decreased blood counts (mainly thrombocytopenia), gastrointestinal disturbances (nausea, vomiting, anorexia, diarrhea, and constipation), peripheral neuropathy, rash, fever, fatigue, dyspnea, and myalgias.[5] Rare adverse effects include cardiac arrhythmias and acute pancreatitis. Here we report a case of bortezomib-induced acute pancreatitis, and we review the literature on this topic. We found seven cases of bortezomib-induced acute pancreatitis published in the medical literature as of July 2014.[6–12]

Case report

A 67-year-old Caucasian male was diagnosed with lambda light chain MM in June 2014. The bone marrow biopsy revealed 36% plasma cells, and skeletal survey showed multiple lytic lesions. He received treatment with bortezomib 1.3 mg/m^2 subcutaneously (SC) once a week, lenalidomide 15 mg on days 1–21 every 28 days, and dexamethasone 40 mg orally once a week. Four weeks after the initiation of therapy, the patient was hospitalized because of severe epigastric pain due to acute pancreatitis. Serum amylase and lipase were

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557 IU/L and >4000 IU/L, respectively. He received supportive measures, including intravenous (IV) fluids, nasogastric tube placement, and opioid narcotics in the medical intensive care unit, and symptoms resolved after 11 days. Bortezomib was held during the hospitalization, and it was resumed two weeks later. The patient again developed intense abdominal pain, associated with elevation of pancreatic enzymes. Given the recurrence, bortezomib was discontinued, and symptoms resolved within one week, after outpatient management with oral fluids and opioid analgesics.

The patient underwent a consultation with the gastroenterology service, which included personal history (directed specifically at alcohol consumption, toxins, and concomitant drugs), family history of pancreatitis, physical examination, laboratory tests (including calcium, triglyceride levels, and serology for infectious agents), and imaging studies with abdominal computed tomography (CT). The results of the work-up did not find any evident cause for the acute pancreatitis, other than the exposure to the chemotherapy agent.

Discussion

Drug-induced pancreatitis is the third most frequent cause of acute pancreatitis, after biliary stones and alcohol consumption.[13] Its diagnosis depends on the exclusion of other possible factors. Although in our patient the causality of the symptoms could be disputed, the exclusion of other causes of acute pancreatitis, along with the reversibility of the symptoms after interruption of the therapy, and the continuation of all concomitant medications, are highly suggestive of a cause–effect relationship. Direct involvement of the pancreas by MM is extremely rare,[14] and we did not find any evidence of it in our patient. The pancreatitis actually occurred while his MM was in partial remission.

To the best of our knowledge, there are seven published cases of bortezomib-induced acute pancreatitis in the literature, and ours is the first report with SC administration, as all other occurred after IV administration. We summarized the main clinical features of those cases in Table 1. The first case was reported by Elouni et al.[6] Another case of acute pancreatitis in a 17-year-old girl with acute lymphoblastic leukemia treated with bortezomib[15] was not included, as she also received L-asparaginase, a chemotherapeutic agent well known to induce acute pancreatitis. Interestingly, abdominal pain with bortezomib has been reported in 11% of patients (http://www.velcade.com/files/PDFs/Velcade_prescribing_information.pdf, accessed on 8/20/14), and additional cases may have been missed, if pancreatic enzymes or abdominal imaging were not performed.

The physiopathology of this complication is unknown. Proposed mechanisms include a direct toxic effect on the pancreatic cells or an allergic/immunologic response to the drug.[13,16] In the published cases, findings at the abdominal CT were normal,[6] or they revealed an edematous pancreas with irregular contours and blurred peripancreatic fat space.[8,9,12] In one case, the CT scan showed a pseudoaneurysmal dilatation of the inferior pancreaticoduodenal artery.[7] This was presumably related to the self-digestion of a vessel wall by the pancreatic enzymes.

The management of drug-induced acute pancreatitis requires discontinuation of the responsible agent and supportive measures, such as IV fluid hydration, nil per os, and analgesics. Published cases had different severity, but all have evolved favorably. It is reassuring that symptoms always resolved within a few days, and no deaths have been observed.

Gastrointestinal side effects of bortezomib therapy usually consist of nausea, vomiting, anorexia, diarrhea, and constipation. However, physicians should also consider the possibility of bortezomib-induced acute pancreatitis, if patients complain of abdominal pain.

Table 1. Summary of eight multiple myeloma cases with bortezomib-induced acute pancreatitis.

Case	Age	Sex	Dose and schedule of bortezomib	Onset of symptoms after drug exposure	Time to resolution of symptoms	Ref
1	67	M	1.3 mg/m^2 SC once a week	1 month	11 days	Our pt
2	58	M	1.3 mg/m^2 IV days 1,4,8,11	6 days	1 week	6
3	78	M	IV, details n/a	1 month	18 days	7
4	67	M	IV, details n/a	4 days	3 days	8
5	47	M	IV, details n/a	11 days	2 days	9
6	72	F	1.3 mg/m^2 IV days 1,4,8,11	1 month	n/a	10
7	58	F	1.3 mg/m^2 IV days 1,4,8,11	1.5 months	Few days	11
8	64	F	1.3 mg/m^2 IV days 1,4,8,11	6 days	10 days	12

Early recognition of this uncommon reaction will allow ordering proper laboratory tests (i.e., serum lipase) to confirm the diagnosis, prompt discontinuation of the drug, and the institution of adequate supportive therapeutic measures.

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Conflict of interest

None declared.

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