A POSSIBLE RARE COMPLICATION OF BORTEZOMIB TREATMENT: ACUTE PANCREATITIS

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Abstract: *Bortezomib is a chemotherapy drug which changed radically the treatment response and the prognosis of the patients with multiple myeloma. Besides the well-known side effects (among which fatigue, gastrointestinal, hematologic, and cardiac events, peripheral polyneuropathy), there are also rare adverse effects such as acute pancreatitis. We present the case of a patient of 72 years old, who, during the treatment with bortezomib accompanied by corticosteroids, after an episode of paroxysmal atrial fibrillation, has developed, at the next cycle, abdominal pain, nausea, vomiting, bloating and elevated serum and urine amylases, without X-ray computed tomography noticeable changes, except for a thin blade of fluid in Douglas space. The evolution was favourable after giving up bortezomib and with conservative treatment for its digestive disorder. This case is discussed in comparison with others, similar in literature.*

Cuvinte cheie: *Bortezomib, fibrilaţie atrială paroxistică, mielom multiplu, pancreatită acută*

Rezumat*: Bortezomibul este un chimioterapic care a schimbat radical răspunsul la tratament şi prognosticul pacienţilor cu mielom multiplu. Pe lângă efectele adverse bine cunoscute (dintre care menţionăm astenia, manifestările gastrointestinale, hematologice, cardiace, polineuropatia periferică), există şi efecte adverse rare, cum este pancreatita acută. Prezentăm cazul unei paciente de 72 de ani care, în cursul tratamentului cu Bortezomib însoţit de corticoterapie, după un episod de fibrilaţie atrială paroxistică, a prezentat, la următoarea cură, dureri abdominale, greţuri, vărsături, meteorism şi creşterea valorilor amilazemiei şi amilazuriei, fără modificări sesizabile computertomografic, exceptând o fină lamă de lichid în spaţiul Douglas. Evoluţia a fost favorabilă după renunţarea la Bortezomib şi cu tratament conservator pentru afecţiunea digestivă. Este discutat acest caz în comparaţie cu altele, similare, din literatură.*

CASE REPORT

A 72-year-old female patient was admitted to the Hematology service of Sibiu Emergency County Clinical Hospital, shortly after establishing the diagnosis of stage IIIA IgG multiple myeloma. The diagnosis was made based on the presence of hyperproteinemia (12.06 g/dL) with a monoclonal growth of immunglobulins G (6968 mg/dL) with the decrease of the other types of immunglobulins (IgM 15 mg/dL, IgA 12 mg/dL, IgE 3.18 mg/dL), bone marrow infiltration by myeloma cells in a ratio of 70-80% (mostly one- or multinucleolate plasma cells with atypias) and bone lesions (shown on X-ray computed tomography): osteoporosis stained with multiple locations in the skull and pelvis, multiple osteolytic lesions (pool, T2 and T4 vertebras, cuneiform compaction of T7 vertebra) + osteolytic tumour mass in the right iliac wing, left sacral wing and round the backbone T2, invading the adjacent soft tissues and spinal canal, up to the spinal cord.

Among the biological tests, we mention: slightly increase of serum alkaline phosphatase (156 mg/dL) and creatinine (1.14 mg/dL); blood glucose level was normal, as transaminases, gamma-glutamyl transpeptidase, serum calcium, blood count and urine exam. As related diseases we note: colonic diverticulosis, left ovarian cyst, hiatal hernia and gastroesophageal reflux disease.

The patient continued the first course of polychemotherapy started in another department: bortezomib 2 mg/day i.v. on days 8, 11, 15, 18, with added methylprednisolone 100 mg/day i.v. on days 15, 16 and 18, 19, under protection with odansetron, metoclopramide, omeprazole and then ranitidine, and potassium supplement orally.

We gave her an i.v infusion of 4 mg zoledronic acid in 100 ml of NaCl0.9% for 30 minutes and treated acute bronchitis with amoxicillin + clavulanic acid 1.2g at 12 hours.

During hospitalization, there occurred an episode of paroxysmal atrial fibrillation, which has been converted to synusal rhythm with amiodarone (initial i.v. infusion, then, orally).

The patient was discharged and returned 10 days later to continue chemotherapy. On this coming she presented dry cough and was afebrile; a throat swab was collected, which was negative. She received 2mg/zi bortezomib on days 1 and 4 + 8mg/day dexamethasone on days 1, 2 and 4, 5 and after that she presented nausea, vomiting, abdominal pain, flatulence, and biological samples pleaded for acute pancreatitis: amylasemia 433 U/L, amylasuria 1050 U/L, which required the discontinuation of chemotherapy.

The X-ray computed tomography examination performed pointed only a fine blade of fluid in Douglas space

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and a right basal pleural effusion in small quantity. A phase balance showed IgG 1900 mg/dL.

The digestive disease evolution was favourable under parenteral hydration, ranitidine, metoclopramide, antibiotherapy.

Acute bronchitis, present upon admission, treated with amoxicillin + clavulanic acid, evolved into bronchopneumonia with parapneumonic effusion, diseases requiring broad-spectrum empiric antibiotherapy (meropenem, colistin) and antifungal therapy (voriconazole, and then fluconazole), with favourable evolution.

We note that blood cultures and stool collected during the febrile episode on the 7th day after admission were negative, as well as the urine sample taken on the 14th day, but isolate Enterobacter was found in throat exudate. The evolution of the respiratory diseases was favourable. Due to the temporary suspension of oral food ingestion and subsequent poor nutrition (because she had anorexia) a severe hypoproteinemia (3.5 g/dL comparing with 9.4 g/dL – the value upon admission) occurred gradually, accompanied by hypoproteinemic oedema until anasarca, which have required human albumin, fresh frozen plasma and diuretics administration. The evolution was slowly favourable: ascites and oedema disappeared.

Then, she received a course of polychemotherapy that was different compared to the previous: melphalan 14 mg/day, orally, 4 days + methylprednisolone 125 mg/day, i.v., 4 days + thalidomide 100 mg/day, orally, which continued at home, under protection with dalteparinum 5000 IU/day s.c. Because this chemotherapy cycle has been well tolerated, we can conclude that corticosteroids were not the cause of acute pancreatitis, but probably bortezomib or its association with corticosteroids. She was discharged after a month of hospitalization, clinically improved, with an amylasemia of 140 U/L and a proteinemia of 5.9 g/dL.

Bortezomib is a proteasome inhibitor useful in the treatment of multiple myeloma, including refractory or rapidly progressive forms.(1) Alone, bortezomib produced a response rate of 51% in newly diagnosed patients.(2)

Its efficacy is superior to previous polychemotherapic regimes with melphalan, cyclophosphamide, vincristine and prednisone or melphalan + prednisone.(3) Moreover, its administration has been shown to be superior to high-dose dexamethasone in the patients who relapsed or in those treated with 1-3 lines of chemotherapy.(1)

However, about half of patients are resistant to bortezomib, and during its administration, they may develop acquired resistance through mutation and overexpression of proteasome β5 subunit.(7) Its combination with dexamethasone in the newly diagnosed patients leaded to a response rate of 82-90%. This was the reason I associated corticosteroids to bortezomib.(4) In addition, it can be administered to patients with renal failure appeared in the development of myeloma nephropathy or having another etiology.

Bortezomib inhibits the action of caspases involved in the apoptosis of myeloma cells, inhibits NFkB factor that is involved in the development of resistance to conventional chemotherapy and inhibits the expression of certain molecules involved in repairing DNA damaged by chemotherapy in myeloma cells. It has the property to sensitize target cells to alkylant agents or anthracyclines.(5)

The combination of bortezomib with immunomodulatory products such as lenalidomide or thalidomide, administered in small doses, increases the activity of the first, (5.6) but these immunomodulatory drugs are not included on the list of the National Cancer Programme in Romania and are expensive.

Most adverse effects of bortezomib are mild or moderate.(7) Between the most frequently occurring, there are fatigue, digestive manifestations, haematological toxicity and peripheral polyneuropathy.(8)

Cardiac arrhythmias occurred during its administration are rare, but are cited in the literature. This explains, perhaps, the episode of atrial fibrillation occurred in our patient. There was cited in the literature the emergence of a total atrioventricular block after bortezomib and dexamethasone, too.(9)

The first case of acute pancreatitis occurred during the treatment with 2 doses of bortezomib and dexamethasone (+ levothyroxine for hipotiridism) was published in 2010.(10) It is estimated that the incidence of this adverse effect would be of 0.1-2%.(11) That patient presented epigastric pain and serum lipase increased without amylasemia increasing, pancreatic X-ray computed topographic examination looking normal, without peripancreatic fluid collections. Readministration of bortezomib after 10 days produced a second episode of acute pancreatitis, also with epigastric pain and increased lipase level without increased amylasemia, which evolved favourably after stopping bortezomib.(10)

Another case subsequently published of acute pancreatitis appeared in a patient with IgGk multiple myeloma who, after 3 courses of melphalan and prednisone, received a first treatment cycle with bortezomib and dexamethasone. It was manifested by upper abdominal pain, fever, vomiting and haematemesis. He presented a significant increase of serum lipase (544 U/L) with discrete increase of amylasemia (181 U/L).

The X-ray computed topographic examination showed an inflammatory process in the pancreatic head, which led to the development of a lower pancreatic-duodenal artery pseudoaneurysm, which, in dynamics was thrombosed and formed a pseudocyst. Pancreatic enzymes returned to normal values on day 18, when the patient was discharged. After 3 months, pancreatic head was completely cured (imagistically).(12)

All the three cases presented occurred after the treatment with bortezomib + corticosteroids, had different severity, but have evolved favourably. It is important for the clinicians who use bortezomib to consider this possible side effect, too, and carefully monitor the patients for its early detection and to treat it appropriately.

REFERENCES

1. Driscoll JJ, Burris J, Annunziata CM, Targeting the Proteasome with Bortezomib in Multiple Myeloma: Update on Therapeutic Benefit as an Upfront Single Agent, Induction Regimen for Stem-Cell Transplantation and as Maintenance Therapy. Am J Ther. 2012;19(2):133-44.
2. Dispenzieri A, Jacobus S, Vesole DH, Callandar N, Fonseca R, Greipp PR. Primary therapy with single agent bortezomib as induction, maintenance, and re-induction in patients with high risk myeloma: results of the ECOG E2A02 trial. Leukemia. 2010;24(8):1406-11.
3. San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008;359:906-17.
4. Reeder CB, Reece DE, Kukreti V, Chen C, Trudel S, Hentz J, et al. Cyclophosphamide, bortezomib and dexamethasone (CyBorD) induction for newly diagnosed multiple myeloma: High response rates in a phase II clinical trial. Leukemia. 2009;23(7):1337-41.

5. Laubach JP, Mitsiades CS, Roccaro AM, Ghobrial M, Anderson KC, and Richardson PG. Clinical challenges associated with bortezomib therapy in multiple myeloma and Waldenströms Macroglobulinemia. Leuk Lymphoma. 2009;50(5):694-702.
6. Mitsiades N, Mitsiades CS, Poulaki V, Chauhan D, Richardson PG, Hideshima T, et al. Apoptotic signaling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: therapeutic implications. Blood. 2002;99:4525-30.
7. Mateos MV, San Miguel JF. Bortezomib in multiple myeloma. Best Pract Res Clin Haematol. 2007;20(4):701-15.
8. Chen D, Frezza M, Schmitt S, Kanwar, Dou QP. Bortezomib as the first proteasome inhibitor anticancer drug: current status and future perspectives. Curr Cancer Drug Targets. 2011;11(3):239-53.
9. Lee WS, Kim DH, Shin SH, Woo SI, Kwan J, Park KO, et al. Complete Atrioventricular Block Secondary to Bortezomib Use in Multiple Myeloma Yonsei Med J. 2011;52(1):196-8.
10. Elouni B, Salem CB, Zamy M, Sakhri J, Bouraoui K, Biour M. Bortezomib-Induced Acute Pancreatitis. JOP. J Pancreas (Online). 2010;11(3):275-6.
11. Balani AR, Grendell JH. Drug-induced pancreatitis: incidence, management and prevention. Drug Saf. 2008;31:823-37.
12. Destri DL, Innao V, Petrillo G, Cataldo AD. A rare pancreatic pseudoaneurysm in patient with acute pancreatitis and multiple myeloma. Ann Ital Chir. 2011;82:301-4.