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Bortezomib - Induced Paralytic Ileus: Uncommon but Crucial

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ABSTRACT
Bortezomib is a targeted anti - cancer medication used primarily to treat Multiple Myeloma and Mantle Cell Lymphoma in adults. It is classified as a Protease Inhibitor, which works by reversibly inhibiting the protein complex responsible for degrading damaged proteins within cells.[1] We report the case of a patient with Multiple Myeloma who developed Paralytic Ileus while on Bortezomib.

KEYWORDS: Multiple Myeloma, Protease Inhibitor, Paralytic Ileus, VRd, KPD

INTRODUCTION

Paralytic Ileus, also known as Adynamic Ileus, is a condition where the normal wave- like muscle contractions or peristalsis that move food, fluids and gas through the intestines are temporarily paralyzed. The neuromuscular dysfunction affects the enteric nervous system, particularly the myenteric and submucosal plexuses, resulting in impaired propulsion of intestinal contents and subsequent accumulation of gas and fluids within the bowel [2]. The common causes are abdominal surgery, electrolyte imbalances like low potassium, trauma or inflammation in the abdomen, infections like gastroenteritis or peritonitis. Certain medications, including Opioids, Anticholinergics, Antipsychotics, Tricyclic Antidepressants, Muscle Relaxants, Alpha - Glucosidase Inhibitors, and Antineoplastic agents, have also been implicated in the development of Paralytic Ileus. [3][4][5][6]

Bortezomib is a unique boron-containing drug that inhibits the proteasome, a protein complex involved in degrading intracellular signalling proteins. It disrupts NF-κB signalling, which normally helps cells survive and proliferate. By blocking proteasome activity, Bortezomib prevents the breakdown of IκB, keeping NF-κB inactive and reducing survival signals in cancer cells. It also promotes apoptosis by increasing Bax protein levels. Bortezomib is primarily indicated for the treatment of haematological malignancies like Multiple Myeloma and Refractory Mantle Cell Lymphoma. These conditions typically involve overexpression of NF-κB. The common side effects are peripheral neuropathy, diarrhoea, fatigue, bone marrow depression, especially thrombocytopenia. Rare side effects are posterior reversible encephalopathy syndrome (PRES), Severe autonomic neuropathy, Thrombotic Thrombocytopenic Purpura(TTP) and Tumor lysis syndrome.

CASE REPORT

A 64-year-old male patient, who was diagnosed with Multiple Myeloma on 2024 was admitted owing to complaints of abdominal pain in the past 2 days. Pain was acute in onset, gradually progressed over 2 days, diffuse in nature, colicky type, not radiating to other sites. It was associated with multiple episodes of vomiting, non-bilious, non-projectile, mixed with food particles. The patient gives a history of undergoing chemotherapy with VRd regimen (Bortezomib – 1.3 mg/m^2, Lenalidomide – 5 mg and Dexamethasone – 40mg, Cycle 4 Dose 2) 2 days back following which he developed abdominal pain and vomiting. Patient also suffers from hypovitaminosis (vitamin D) and Acute Kidney Injury (not on any medications). There is no history of long-standing infections, Diabetes Mellitus or any electrolyte imbalances. His routine blood investigations showed leucocytosis (TC-13690 microlitres) and mild anemia (Hb-11.5 g/dL), his LDH was also elevated to 305 units per litre, Potassium levels were normal (4.47 mmol/L). An X-ray abdomen was done which showed multiple air fluid levels. Contrast-Enhanced Computed Tomography (CECT) was done to rule out acute intestinal obstruction and no obstructing lesions were identified. Continuous RT aspiration was done. Abdominal girth was serially monitored. Sips of water intake was started: followed by clear liquid diet, full liquid diet and thereafter soft diet. In the absence of any other probable causes including abdominal surgery, electrolyte imbalances like low potassium, trauma or inflammation in the abdomen, infections like gastroenteritis or peritonitis, we came to the conclusion that Paralytic Ileus was mostly caused by the Bortezomib injection. So, it was decided to reduce the dose of Bortezomib to 1g from the next cycle of chemotherapy. The patient became hemodynamically stable with symptomatic management and hence discharged.

DISCUSSION

Paralytic Ileus is a rare but important complication in patients receiving Bortezomib for Multiple Myeloma. It will be occurring as functional bowel paralysis, typically with symptoms such as constipation, abdominal distension and reduced or absent bowel sounds, without evidence of mechanical obstruction [7]. If left untreated, paralytic ileus can cause or may lead to bowel ischemia, perforation, infection, or sepsis, which may be life threatening [8].

The precise mechanism by which Bortezomib induces Paralytic Ileus remains unclear, but current evidence points to several contributing factors. Bortezomib is known to cause neurotoxicity, particularly involving the autonomic nervous system, which regulates gastrointestinal motility; damage to these nerves can impair peristalsis and lead to ileus. Additionally, by inhibiting the proteasome, Bortezomib disrupts normal protein degradation and cellular function, which may indirectly affect the neural and muscular components of the gastrointestinal tract, further contributing to motility disturbances.

In 2023, anecdotal case reports have been published which shows the association between Bortezomib and development of GI side effects. The patient took 2 doses of Bortezomib for Multiple Myeloma and later developed severe back pain, constipation and lethargy which was identified as Ileus [9]. In 2024, another case report described a 79-year-old male patient who developed abdominal distension and constipation following administration of Bortezomib at a dose of 1.3 mg/m². These gastrointestinal adverse effects were attributed to Bortezomib therapy due to the causal relationship. Consequently, the patient was transitioned to an alternative treatment regimen consisting of Carfilzomib, Pomalidomide, and Dexamethasone (KPD regimen) for further management of his condition [7]. According to VigiAccess, the global database reflecting adverse effects of various medications, a total of 163 cases of Bortezomib-induced paralytic ileus have been reported worldwide. Paralytic ileus accounts for approximately 2% of

all gastrointestinal disorders associated with Bortezomib. The causality was determined to be "Probable" using the WHO-UMC Causality Assessment Scale. The type of ADR was classified as "Type A" according to the Rawlins-Thompson Classification and was assessed as "Level 4a, Moderate" in terms of severity based on the Modified Harwig's Scale. As per the WHO criteria, the seriousness of the reaction was categorized as "Hospitalization – initial/prolonged", and the outcome of the reaction was deemed "Recovering". Additionally, according to the Schumock and Thornton scale, the ADR was deemed "Non-Preventable".

Clinicians should be aware of the potential risk of Bortezomib - Induced Paralytic Ileus, particularly in patients presenting with unexplained gastrointestinal symptoms during treatment. It could worsen in patients suffering from long standing illnesses or kidney issues etc. Prompt recognition and intervention are essential to prevent serious complications. In cases where such adverse effects occur, discontinuation or dose modifications of Bortezomib should be considered based on the severity of symptoms. If Bortezomib is contraindicated or not tolerated, an alternative regimen such as KPD—Carfilzomib, Pomalidomide, and Dexamethasone— or similar may be initiated. Additionally, patients should be counselled regarding the risk of paralytic ileus associated with Bortezomib therapy and advised to promptly report any related symptoms.

CONCLUSION

Bortezomib is a chemotherapeutic agent which is used for the treatment of Multiple Myeloma and Lymphoma. This case report highlights the association between Bortezomib and development of Paralytic Ileus even on limited doses. Paralytic Ileus is a rare side effect of Bortezomib, but can be fatal if left undiagnosed or untreated. Routine monitoring of gastrointestinal function, prompt evaluation of symptoms such as abdominal distension, constipation, or pain, and timely discontinuation or dose adjustment of Bortezomib can significantly improve outcomes.

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