




Accidental Ixazomib Overdose in a Patient With Multiple Myeloma

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Abstract

Multiple myeloma is the second most common hematological malignancy. Ixazomib is the first oral proteasome inhibitor approved in the United States for the management of multiple myeloma who have received at least one prior treatment. The availability of oral chemotherapeutic agents for the management of multiple myeloma has made it easier for patients who do not have to come to the hospital for chemotherapy infusions. However, many barriers are associated with oral chemotherapy, and one of them is a misinterpretation of instruction which can have deleterious effects. In this case report, we present a case of a 69-year-old male with multiple myeloma who accidentally took ixazomib daily for 3 days instead of the weekly regimen and thus coming into the hospital with an overdose. In this report, we focus on the adverse effects associated with ixazomib toxicity and how to manage the adverse reactions. Although there is no antidote available for ixazomib, supportive care is very essential in these patients.

Keywords

ixazomib, chemotherapy, overdose, toxicity, multiple myeloma

Introduction

Multiple myeloma is a neoplastic proliferation of plasma cells and the second most common hematological malignancy.¹ Proteasome inhibitors are one of the mainstay treatments for the management of multiple myeloma.² Ixazomib is the first oral proteasome inhibitor approved in the United States for the management of multiple myeloma who have received at least one prior treatment.² Ixazomib is a reversible proteasome inhibitor that inhibits 20S proteasome. Use of oral ixazomib, lenalidomide, and dexamethasone has shown significantly longer progression-free survival when compared with placebo, lenalidomide, and dexamethasone.³ The availability of oral chemotherapeutic agents for the management of multiple myeloma has made it easier for patients who do not have to come to the hospital for chemotherapy infusions. This has become more relevant during the coronavirus disease-2019 pandemic as we attempt to limit exposure in the infusion areas. One of the many barriers associated with oral chemotherapy includes misinterpretation of instruction that can lead to potential adverse events. In this case report, we describe a patient who had an accidental overdose of ixazomib.

Case Presentation

A 69-year-old male with a history of Stage III immunoglobulin G Lambda multiple myeloma. He had been treated with bortezomib, lenalidomide, and dexamethasone. He had completed 5 cycles of cyclophosphamide, bortezomib, and dexamethasone. Due to the coronavirus disease-2019 pandemic and to prevent exposure to hospital for chemotherapy infusions, he was transitioned to an oral chemotherapy regimen. He was initiated on ixazomib 3 mg, dexamethasone 36 mg, and lenalidomide 25 mg. He was started on a regimen of ixazomib 3 mg to be taken on days 1, 8, and 15; dexamethasone 36 mg on days 1, 8, 15, and 22; and lenalidomide 25 mg on days 1 to 22. The patient, instead of taking ixazomib weekly, took the ixazomib daily for 3 days.

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Table 1. Patient's Laboratory Values Tabulated From the Day of Admission to the Day of Discharge.

| Laboratory test (reference range) | Day 1 | Day 3 | Day 5 | Day 8 | Day 10 | Day 15 | Day 20 | Day 24 |
|---|-------|-------|-------|-------|--------|--------|--------|--------|
| White blood cells ($4-10 \times 10^3/\mu\text{L}$) | 2.9 | 3.3 | 6.2 | 4.8 | 9.9 | 4.7 | 3.7 | 4.2 |
| Red blood cells ($4.6-6.1 \times 10^6/\mu\text{L}$) | 2.36 | 1.98 | 2.31 | 2.31 | 2.31 | 2.39 | 2.33 | 2.52 |
| Hemoglobin (13.5-18 g/dL) | 8.0 | 6.6 | 7.7 | 7.6 | 7.7 | 7.9 | 7.8 | 8.3 |
| Hematocrit (41% to 53%) | 23.7 | 20.0 | 22.6 | 22.4 | 22.3 | 23.4 | 22.5 | 24.3 |
| Platelets ($150-400 \times 10^3/\mu\text{L}$) | 70 | 34 | 40 | 88 | 127 | 273 | 275 | 249 |
| Sodium (136-145 mmol/L) | 132 | 142 | 138 | 132 | 132 | 134 | 133 | 130 |
| Potassium (3.4-5.1 mmol/L) | 3.8 | 3.6 | 3.5 | 3.3 | 3.6 | 4.1 | 4.2 | 4.1 |
| Chloride (98-107 mmol/L) | 104 | 116 | 117 | 109 | 105 | 104 | 101 | 99 |
| Bicarbonate (22-29 mmol/L) | 17 | 17 | 15 | 17 | 17 | 21 | 24 | 22 |
| Blood urea nitrogen (8-23 mg/dL) | 110 | 74 | 33 | 8 | 7 | 7 | 10 | 8 |
| Creatinine (0.70-1.20 mg/dL) | 2.62 | 1.38 | 1.00 | 0.66 | 0.81 | 0.75 | 0.88 | 0.75 |
| Glucose (70-140 mg/dL) | 179 | 122 | 91 | 85 | 91 | 97 | 129 | 116 |

He was admitted with nausea, fatigue, and profuse watery diarrhea. He also had developed a diffuse macular rash in his lower extremities extending to the part of his lower abdomen, which was non-pruritic. Initial blood pressure on arrival was 79/51 mm Hg. He was afebrile, and his pulse was 84 beats per minute. Laboratory studies throughout the hospital course are listed in Table 1. He was initiated on a fluid bolus with 2 L and was started on maintenance fluids. His blood pressure improved initially; however, due to worsening of blood pressure, he required transfer to the medical intensive care unit. He was initiated on norepinephrine infusions to maintain mean arterial blood pressure above 65 mm Hg. He was empirically initiated on vancomycin, cefazolin, and metronidazole. A diarrhea panel obtained for several common gastrointestinal pathogens (Table 2) was negative. A computed tomography image of the abdomen was obtained, which showed scattered regions of mild mural thickening and the presence of mild inflammation in the small bowel loops suggesting possible enteritis. One out of the 2 blood cultures collected at the time of admission returned positive for methicillin-resistant *Staphylococcus aureus* (MRSA) from the port site. His antibiotics were ultimately changed to daptomycin. He underwent transthoracic and transesophageal echocardiography, which did not show any evidence of vegetation and he completed a course of 2 weeks of intravenous daptomycin for MRSA along with the removal of the port.

Hemodynamic and laboratory parameters improved over the first week of admission; however, the patient continued to have ongoing diarrhea. He initiated on loperamide and diphenoxylate without improvement. General surgery was consulted and determined no surgical intervention was deemed necessary. He was then started on octreotide with improvement in diarrhea. He was ultimately discharged in stable condition to a subacute rehabilitation center. His chemotherapy was not initiated on discharge. His chemotherapy was then initiated 2 months post-discharge and was changed to carfilzomib and dexamethasone and he currently is in stable condition.

Table 2. An Exhaustive Stool Polymerase Chain Reaction Tests for Many Intestinal Pathogens Were Negative.

| Test performed | Polymerase chain reaction result |
|--|----------------------------------|
| <i>Campylobacter</i> spp | Not detected |
| <i>Clostridium difficile</i> toxin A/B genes | Not detected |
| <i>Plesiomonas shigelloides</i> | Not detected |
| <i>Salmonella</i> spp | Not detected |
| <i>Vibrio</i> spp | Not detected |
| <i>Vibrio cholerae</i> | Not detected |
| <i>Yersinia enterocolitica</i> | Not detected |
| Enterococcal <i>Escherichia coli</i> | Not detected |
| Enteropathogenic <i>Escherichia coli</i> | Not detected |
| Enterotoxigenic <i>Escherichia coli</i> | Not detected |
| Shiga-like toxin <i>Escherichia coli</i> | Not detected |
| <i>Cryptosporidium</i> | Not detected |
| <i>Cyclospora cayetanensis</i> | Not detected |
| <i>Entamoeba histolytica</i> | Not detected |
| <i>Giardia lamblia</i> | Not detected |
| Adenovirus F 40/41 | Not detected |
| Astrovirus | Not detected |
| Norovirus G1/G2 | Not detected |
| Rotavirus A | Not detected |
| Sapovirus | Not detected |

Discussion

The coronavirus disease-2019 pandemic has had an impact on the health care systems throughout the world and has affected cancer-related care. The availability of oral chemotherapy agents has led many oncologists to transition patients to oral regimens.

The most common adverse effects associated with the use of ixazomib have been noted as thrombocytopenia, neutropenia, diarrhea, fatigue, and peripheral neuropathy.⁴ A case of unintentional overdose from the drug ixazomib has not been previously described in the literature. We would like to highlight the important aspects associated with toxicities from this medication.

Our patient developed thrombocytopenia and leukopenia after the administration of the medication. These are common hematological adverse events associated with ixazomib use. The likely cause of thrombocytopenia in patients treated with ixazomib is inhibition of proteasome, which has been found to inhibit proplatelet formation in mouse and human megakaryocytes.⁵ The recommended management of thrombocytopenia associated with ixazomib use is withholding the drug when the platelet count is $<30\,000/\mu\text{L}$.⁶ Our patient did not require platelet transfusion, and the thrombocytopenia resolved without intervention throughout the hospital course. Our patient also developed leukopenia without neutropenia, which improved without intervention during the hospital course.

Gastrointestinal toxicities have been noted with ixazomib at a higher rate as compared with placebo.³ Our patient developed enteritis from ixazomib overdose as evidenced by computed tomography findings of the abdomen. The mechanism by which ixazomib causes gastrointestinal toxicity remains unclear. However, several mechanisms have been proposed for other proteasome inhibitors, such as an increase in tumor necrosis factor- α receptor 1 expression and the elevated pro-inflammatory cytokines and their effects on the intestinal epithelium.⁷ Our patient's diarrhea was noninfectious in nature and did not improve with the administration of loperamide and diphenoxylate. We thus decided to initiate the patient on octreotide subcutaneous injections for refractory chemotherapy-induced diarrhea. Octreotide is a somatostatin analog that inhibits intestinal hormones including serotonin, vasoactive intestinal peptide, secretin, motilin, and other pancreatic enzymes and regulates intestinal water and electrolyte balance causing net absorption.⁸

There are no known renal or hepatic toxicities associated with ixazomib use.⁶ Our patient developed acute kidney injury at the time of arrival at the hospital. The most likely cause of the acute kidney injury is pre-renal etiology as he had profuse diarrhea leading to intravascular volume depletion, ultimately leading to acute kidney injury, which resolved during the hospital course with intravenous fluid resuscitation. The patient's infection with MRSA could be associated with an immunocompromised state, in addition to infection of the port site.

Although the development of the rash could be associated with an infectious or autoimmune phenomenon, it is possible that overdose of ixazomib had a role in the same. The reported incidence of maculopapular rash is 36% in patients receiving ixazomib, lenalidomide, and dexamethasone.³ The rash associated with ixazomib has been described as a maculopapular rash predominantly on the trunk or the extremities.⁶

Conclusion

With this case report, we would like to highlight the toxicities that could occur in a patient with an unintentional

overdose of ixazomib. With the increase in the availability of oral chemotherapeutic agents, all physicians need to be aware regarding potential toxicities and adverse events that could occur in the event of an overdose. Although no specific antidote is available to the agent ixazomib, supportive care is very essential in these patients, as outlined by the case report.

Author Contributions

Parth J. Sampat: Conceptualizing and writing original draft
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Ethics Approval

Our Institution does not require ethical approval for reporting individual cases.

Informed Consent

Informed consent for patient anonymized information to be published in this article was not obtained from the patient because our institution does not require informed consent for individual case reports with information anonymized.

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