JOURNAL OF ONCOLOGY PHARMACY PRACTICE

Case Report

J Oncol Pharm Practice
2019, Vol. 25(2) 507–511

DOI: 10.1177/1078155217746228
journals.sagepub.com/home/opp
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Treatment of vincristine-induced ileus with metoclopramide: A case report

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Abstract

Introduction: Acute lymphoblastic leukemia is an invasive malignancy which ought to be treated with several cytotoxic medications. Vincristine-based regimen is among the most commonly used regimens for the treatment of adult acute lymphoblastic leukemia. Peripheral neuropathy caused by vincristine provides a limitation in dose administration and can influence the treatment outcome and patient's quality of life.

Case presentation: Ileus and constipation occurred as a result of autonomic neuropathy in a 58-year-old man who underwent vincristine-based regimen for acute lymphoblastic leukemia treatment. Despite the administration of several laxative agents for constipation, the complication did not improve. So metoclopramide as a prokinetic agent was administered intravenously, and patient bowel movement and defecation started after 24 h.

Conclusions: There is no approved protocol for vincristine-induced autonomic neuropathy treatment; thus, prokinetic agents such as metoclopramide can be considered as an option for ileus treatment after ruling out the possibility of bowel obstruction. Prophylactic stool softeners should be administrated in all patients undergoing chemotherapy with vincristine to prevent gastrointestinal motility disorders.

Keywords

Vincristine, neuropathy, metoclopramide, ileus, acute lymphoblastic leukemia

Date received: 14 October 2017; revised: 11 November 2017; accepted: 12 November 2017

Introduction

Acute lymphoblastic leukemia (ALL) is the malignancy of lymphocyte precursor cells which occurs in children and adults. ALL is the most common malignancy in children, but its incidence in adults is approximately one in 100,000. ALL should be treated with intensive and various chemotherapeutic agents because of its heterogeneous characteristics which are dependent on the disease and patient as well. Several induction regimens are used for the treatment of ALL in adults.[1] The combination of vincristine and corticosteroids is utilized frequently for the management of ALL in different phases of therapy.[2] Vincristine is a vinca alkaloid which commonly causes peripheral neuropathy which affects the motor, sensory, and autonomic nerves.[3] Although the exact mechanism of vincristine neuropathy is yet to be fully understood, some studies showed that vinca alkaloids degenerate axons and impair axonal transportation by disruption of microtubule function.[4,5] Among vinca alkaloids, vincristine is the most common agent associated with autonomic neuropathy.[4] Autonomic neuropathy can be presented as constipation, urinary retention, impotence, and orthostatic hypotension.[6] Gastrointestinal autonomic

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dysfunctions, such as bloating, constipation, ileus, and abdominal pain, are the most common with vincristine.[1] Patients who received vincristine commonly experienced autonomic neuropathy, 50% of them suffered from constipation and colicky abdominal pain while paralytic ileus rarely occurred.[7] Chemotherapy-induced constipation was observed in 80–90% of patients receiving vincristine. Because vincristine induced-constipation can progress to paralytic ileus, prophylactic stool softeners are recommended for all patients receiving this agent.[8] Despite the wide administration of vincristine in hematologic malignancy, limited data have been extracted from the few existing case reports regarding the manifestations and management of vincristine-induced ileus.[9]

The investigated effective intervention for vincristine neurotoxicity is treatment discontinuation or dose and frequency reduction.[1] This work reports a patient with vincristine-induced ileus who was successfully treated with metoclopramide.

Case presentation

A 58-year-old man was referred to the Hematology-Oncology Research Center and Stem Cell Transplantation of Shariati Hospital affiliated with Tehran University of Medical Sciences, Tehran, Iran, with the diagnosis of B-cell ALL. The patient did not have any past medical history of gastrointestinal disease (e.g. gastric ulcer, Crohn's disease, ulcerative colitis, gastric reflux, constipation, etc.), diabetes, and underlying peripheral neuropathy. He was given ciprofloxacin (500 mg twice daily), fluconazole (100 mg twice daily), acyclovir (200 mg twice daily), and trimethoprim-sulfamethoxazole (160–800 mg three times per week) as infection prophylaxis before admission.

A systemic chemotherapy regimen (vincristine plus dexamethasone) and intrathecal regimen (methotrexate, cytarabine, and hydrocortisone) were subsequently started. Table 1 presents the patient's initial drug list. He received three doses of vincristine without a prophylactic stool softener and was then transferred to the hematology ward. One day after the third dose of vincristine (day 15), the patient complained of abdominal pain, feeling of fullness, nausea, and inability to pass the stool for seven days. The patient had not experienced similar conditions before. Upon physical examination, he had a tender and distended abdomen with weak bowel sounds as well as stable vital signs. Oral Bisacodyl (5 mg twice a day) was ordered immediately as a stimulant laxative agent. The next day, lactulose (20 ml three times a day) was added to the patient's medication regimen as an osmotic laxative agent and Bisacodyl tablet was changed to a suppository (10 mg BD) due to the lack of response. The patient was subsequently started on normal saline and polyethylene glycol enema along with laxative agents. The therapeutic strategy was ineffective and the patient did not defecate even with the intermittent addition of other laxative agents (magnesium hydroxide, Senna tablet).

Table 1. The patient's initial medications list.

Medications	Dose	Route of administration
Vincristine	2 mg weekly	IV
Dexamethasone	8 mg BD	IV
(MTX, cytarabine, and hydrocortisone)	Every four days	IT
Fluconazole	100 mg BD	Orally
Acyclovir	200 mg BD	Orally
Ciprofloxacin	500 mg BD	Orally
Allopurinol	100 mg TDS	Orally
Pantoprazole	40 mg daily	Orally

BD: twice daily; IT: Intrathecal; IV: Intravenous; MTX: Methotrexate.

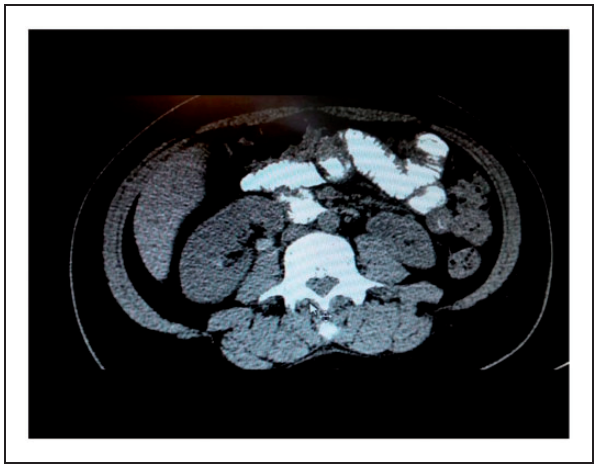

Figure 1. An abdominal CT, dilated loops of bowel.

An abdominal computed tomography (CT) scan was taken due to the gastrointestinal expert consult and revealed dilated loops of bowel (Figure 1). According to the suspected diagnosis of ileus, lack of response to treatment after seven days, and the absence of intestinal obstruction, metoclopramide (10 mg IV QID) was administered as a prokinetic agent. Twenty-four hours after the initiation of metoclopramide, the patient's bowel movements began and he could pass stool again (after eight days). The symptoms of paralytic ileus including abdominal pain and feeling of fullness were completely resolved after 48 h of treatment with metoclopramide. Treatment with vincristine

Table 2. Total neuropathy score.

	Score				
Parameter	0	1	2	3	4
Sensory symptoms	None	Symptoms limited to fingers or toes	Symptoms extend to ankle or wrist	Symptoms extend to knee or elbow	Symptoms above knees or elbows, or functionally disabling
Motor symptoms	None	Slight difficulty	Moderate difficulty	Require help or assistance	Paralysis
Number of autonomic symptoms	None	One	Two	Three	Four or five
Pin sensibility	Normal	Reduced in fingers and/or toes	Reduced up to wrist and/or ankle	Reduced up to elbow and/or knee	Reduced above elbow and/or knee
Vibration sensibility	Normal	Reduced in fingers and/or toes	Reduced up to wrist and/or ankle	Reduced up to elbow and/or knee	Reduced above elbow and/or knee
Strength	Normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis
Tendon reflex	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent, others reduced	All reflexes absent
Vibration sensibility (QST vibration)	Normal to 125% of ULN	126–150% of ULN	151–200% of ULN	201–300% of ULN	>300% of ULN
Sural amplitude	Normal or reduced to <5% of LLN	76–95% of LLN	51–75% of LLN	26–50% of LLN	0–25% of LLN
Peroneal amplitude	Normal or reduced to <5% of LLN	76–95% of LLN	51–75% of LLN	26–50% of LLN	0–25% of LLN

LLN: lower limit of normal; QST: quantitative sensory testing; ULN: upper limit of normal.

(2 mg per dose) was continued along with the prophylactic laxatives under close observation of gastrointestinal alterations.

Discussion

Vincristine-induced autonomic neuropathy can be associated with gastrointestinal motility disorders which can be manifested as abdominal pain, constipation, or ileus.[4,8] Gastrointestinal toxicity induced by vincristine appears to be cumulative and dose dependent.[9] Treatment discontinuation and dose reduction are the consequences of neuropathic symptoms which can affect a patient's survival.[6]

Vincristine-induced ileus has previously been reported in few adult ALL patients.[9–12] Leker et al. reported one case of Parkinson's disease who experienced paralytic ileus following chemotherapy with vincristine. They claimed that elderly patients with Parkinson's disease are at high risk for vincristine-induced ileus.[12] Given the limited clinical data, the risk factors for the occurrence of vincristine-induced ileus remain unclear. However, it has been demonstrated that vincristine doses more than 2 mg per dose, older age, concomitant azole antifungal therapy, and other medications that affect vincristine metabolism and elimination, coadministration of other neurotoxic chemotherapy agents, underlying peripheral neuropathy, diabetes, alcohol abuse, higher drug concentration, Caucasian race, duration of treatment, Charcot–Marie–Tooth Disease, Guillain–Barré Syndrome, and the patient's genetic makeup are all associated with vincristine-induced neuropathy.[5,6,9,13] Although neuropathic signs and symptoms can be presented usually after a cumulative dose of 30–50 mg, it may also develop after administration of the first dose.[7,14,15]

The patient was also assessed by the Total Neuropathy Score scale system (TNS; developed by John Hopkins University). TNS is preferable and consists of symptoms and objective scoring which evaluates patient's chemotherapy-induced neuropathy generally.[6] As shown in Table 2, a TNS Score of zero (0) indicates no neuropathy, score of 1–9 mild neuropathy, score of 10–19 moderate neuropathy, and a score of 20 severe neuropathy.[16] Due to lack of peripheral and central neuropathy and the existence of one autonomic symptom, a mild neuropathy was diagnosed for the patient.

Our patient presented clinical features of vincristine-induced paralytic ileus such as abdominal pain, feeling of fullness, nausea, and lack of defecation. The symptoms of gastrointestinal toxicity were complicated one day after the third dose of vincristine (15 days after the first dose). The patient did not receive any other medications which could affect the motor activity of the small intestine. The patient also did not suffer from any underlying disease or condition such as gastrointestinal disease, diabetic gastroparesis, and peripheral neuropathy which inhibited the motility of the small intestine. The suspected diagnosis of paralytic ileus was confirmed by imaging finding which presented dilated loops of bowel.

Data regarding the pharmacological treatment of vincristine-induced paralytic ileus are limited to a few case reports. To date, metoclopramide, sinalide, and prostaglandin F2 have been tried for the management of vincristine-induced ileus along with supportive treatments.[10,11,17] Garewal and Dalton[17] reported three cases of vincristine-induced ileus who were successfully treated with metoclopramide. Metoclopramide as a prokinetic medication promotes gut motility by inhibition of presynaptic and postsynaptic D2 receptors, stimulation of 5-HT3 receptors, and release of acetylcholine. Metoclopramide is widely used for the symptomatic treatment of vomiting, gastroesophageal reflux disease, and gastroparesis in patients undergoing chemotherapy.[18] The patient was given intravenous infusions of metoclopramide 10 mg four times per day after intestinal obstruction rule out, because metoclopramide is contraindicated in gastrointestinal obstruction. The improvement was notable within 24 h of therapy initiation. It has been reported that vincristine-induced neurotoxicity is remarkably reversible but some patients might experience prolonged neurotoxicity.[6]

Conclusions

It should be kept in mind that prophylactic stool softeners should be administrated in all patients undergoing chemotherapy with vincristine to prevent gastrointestinal motility disorders. Although the paralytic ileus was rapidly treated with metoclopramide in our patient and previous case reports, there is no treatment protocol for the management of vincristine-induced ileus. Thus, in our knowledge, prokinetic agents like metoclopramide can be considered as an option to choose for ileus treatment after ruling out the possibility of bowel obstruction.

Acknowledgments

The authors would like to thank all the nurses and the patient who cooperated in conducting this study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

All procedures performed in this study involving human participant were in accordance with the ethical standards of the Ethical Committee of Tehran University of Medical Sciences and with the 1964 Helsinki declaration.

Informed consent

Informed consent was obtained from participant who included in the study.

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