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Secondary Prophylaxis of Docetaxel Induced Diarrhea with Loperamide: Case Report

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Diarrhea is a common adverse event of docetaxel with 20%-40% of incidence and severe diarrhea occurs in 5%-6%. Several treatment guidelines for chemotherapy induced diarrhea (CID) exist, however the prophylaxis for that is not well known. We describe a new prophylactic approach for the CID with loperamide. A 72-yr-old male patient with stage IV non-small-cell lung cancer developed diarrhea repeatedly after docetaxel-cisplatin chemotherapy. His diarrhea persisted despite treatment including loperamide and fasting. However, the diarrhea was successfully prevented when loperamide was given before and after the chemotherapy. To our knowledge, this is the first report of prophylactic approach for the CID with loperamide.

Key Words: Docetaxel; Diarrhea; Loperamide

INTRODUCTION

Many chemotherapeutic agents including irinotecan, 5-fluorouracil, capecitabine, docetaxel, paclitaxel, doxorubicin, interferon, and gefitinib are commonly associated with diarrhea (1). The mechanism of chemotherapy induced diarrhea (CID) is not entirely understood but is believed to be primarily secretory, and may have an exudative component (2). Main aims of standard guidelines for CID are to reduce the volume of diarrhea, to treat dehydration aggressively, and to use antibiotics if needed (2, 3). And in pharmacological managements, loperamide plays a main role (1-4). But prophylaxis for CID is not well established.

Docetaxel is a semi-synthetic taxane, with considerable activity against several types of solid tumors including breast, ovarian, gastric, prostate and non-small-cell lung cancers. Docetaxel binds to and stabilizes tubulin, thereby inhibiting microtubule disassembly which results in cell cycle arrest at the G2/M phase and cell death (5). Frequent side effects of docetaxel include fluid retention, neurosensory events, alopecia, cutaneous events, stomatitis, nausea, vomiting, diarrhea, and neutropenia. Diarrhea develops in 20%-40% of patients with docetaxel-containing chemotherapy and severe diarrhea in 5%-6% (6).

In this report, we describe a new prophylactic approach for the docetaxel induced diarrhea with loperamide in a patient with non-small-cell lung cancer.

CASE DESCRIPTION

A 72-yr old male patient was diagnosed with stage IV non-small-cell lung cancer (NSCLC) in March 2012. He was treated with weekly docetaxel-cisplatin (DP) chemotherapy: docetaxel 35 mg/m^2 and cisplatin 30 mg/m^2 on day 1 and 8 every 3 weeks. During the 1st cycle, grade 3 nausea and vomiting developed from day 3 of chemotherapy. Thus fasting, parenteral nutritional support, and hydration with intravenous administration of metoclopramide and lorazepam were given. During the 2nd cycle, neither nausea nor vomiting but grade 3 diarrhea (8-10 stools per day) developed from day 4 and he was admitted to hospital on day 6. Diarrhea was profuse and watery without blood or pus. Grade 3 dehydration was combined while there was no abdominal pain, tenderness or fever. Stool studies including culture revealed neither pathogen nor white/red blood cells. Laboratory examinations including white blood cell count, erythrocyte sedimentation rate, and C-reactive protein were within normal limits. Fasting, parenteral nutritional support and hydration with oral loperamide, starting with 4mg followed by 2 mg every 2 hr, were done. Despite of the management, diarrhea continued until day 9 of chemotherapy. On day 10 of his 2nd cycle, diarrhea was resolved and he started diet on day 12, but diarrhea redeveloped. The same management with loperamide was done and the diarrhea was resolved on day 15. Chemotherapy at day 8 of the 2nd cycle was delayed to day 16 and given with 20% reduced dose. After 3 days, grade 3 diarrhea de-

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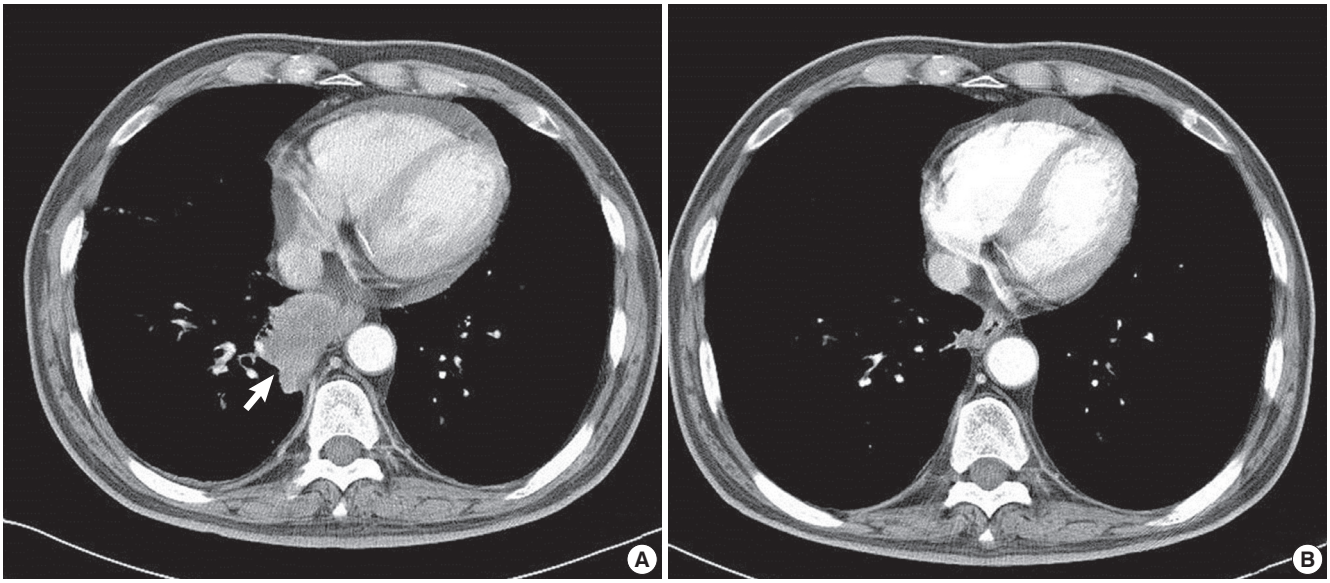

Fig. 1. Contrast enhanced computed tomography scan of the chest. (**A**) Lung cancer in the medial aspect of right lower lobe (arrow), prior to chemotherapy. (**B**) Much decrease in size of the lung cancer after 2 cycles of docetaxel-cisplatin chemotherapy.

veloped again and he visited emergency room. The same management with loperamide was done for 3 days and diarrhea was resolved.

We concluded that docetaxel induced his diarrhea because of several reasons: no signs of infection, no use of antibiotics, repeated diarrhea after chemotherapy and little probability of diarrhea with other medications including dexamethasone, palonosetron and cisplatin. Chest computed tomography after 2 cycles of DP showed near complete response according to RECIST v 1.1 (Fig. 1). Thus we decided to continue DP chemotherapy despite of the severe repeated docetaxel induced diarrhea.

On day 1 of the 3rd DP chemotherapy with 20% reduced dose, prophylactic loperamide (2 mg every 8 hr) and fasting was started before administration of chemotherapy. Diarrhea did not develop with 4 days of fasting and 7 days of loperamide. Day 8 DP of 3rd cycle was delayed due to grade 2 asthenia and started on day 15. On day 15, prophylactic loperamide was started before chemotherapy and fasting was started after administration of chemotherapy. The duration of fasting and administration of loperamide were shortened to 2 and 5 days, respectively. The 3rd cycle was completed without diarrhea. Subsequent cycles of DP chemotherapy with 20% reduced dose could be given without diarrhea by virtue of loperamide. Now he finished 6 cycles of DP and which resulted near CR.

DISCUSSION

Diarrhea is one of the most common side effects of chemotherapy and docetaxel is commonly associated with diarrhea. CID can significantly affect the quality of life and may result fatal outcome either directly or indirectly from suboptimal therapy. The pathogenesis of CID is unclear and the studies about CID have focused on irinotecan. It is believed that toxicity to rapidly dividing crypt cells of the gut leads destruction and/or augmentation of intestinal enzymes. This disturbs the balance between absorption and secretion, and alters the osmotic gap in the gut, thereby resulting increased secretion of fluids and electrolytes into the stool (4, 7). Recently, it has been suggested that alterations to intestinal tight junctions play a pivotal role in the pathogenesis of CID (8).

Loperamide is an antidiarrheal agent with many actions of mechanisms: antisecretory, antiperistaltic effect inhibiting the calcium-binding protein calmodulin and direct effect on the gastrointestinal wall by interacting locally with neuronal mechanisms. Thereby, loperamide prolongs transit time, increases viscosity and bulk density, and reduces fecal volume and loss of fluids and electrolytes (9, 10).

In treatment of CID, several guidelines exist and loperamide plays a main role (1-4). But the prophylaxis of CID is not well established. Some guidelines recommend octreotide, a somatostatin analogue, for the prevention and the treatment of refractory CID (1, 2, 11). But octreotide is not easy to use due to the cost and the method of administration (injection).

In this patient, fasting and aggressive hydration with electrolyte supplements were started and loperamide was given for the management of CID. However severe diarrhea persisted more than 10 days. Despite the severe diarrhea, the tumor response was excellent, thus DP chemotherapy was continued with the prophylactic approach. Oral loperamide with regimen of 2 mg every 8 hr successfully prevented docetaxel induced diarrhea. Loperamide is easy to administer and cost effective. The

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role of loperamide in the prophylaxis of CID requires further studies including appropriate dosing and duration.

Rarely docetaxel induced colitis is reported and which is usually associated with acute abdominal pain, tenderness, febrile neutropenia, hemorrhagic diarrhea or oral stomatitis (12, 13). The mechanism of the colitis is proposed: initial mucosal damage; bacterial invasion; secretion of bacterial endotoxins; hemorrhage; ulceration; and ischemia, possible necrosis (14). In this case, he presented no suspicious symptoms or findings for colitis. But clinicians should consider colitis in a patient with docetaxel induced diarrhea because the outcome of colitis can be fatal and the use of loperamide in that case can worsen the outcome.

In conclusion, although further studies about the appropriate dosing and the schedule are required, we suggest oral loperamide as a prophylactic use in the CID: 2 mg every 8 hr from day 1 (starting before chemotherapy) to 5. Additionally, clinicians should concern the possibility of the docetaxel induced colitis when CID is suspicious.

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