Gastroparesis as a significant gastrointestinal adverse event during intensive chemotherapy for solid cancer

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Abstract

Proper management of chemotherapy-related gastrointestinal toxicities is essential to maximize therapeutic outcome for malignancies. Gastroparesis is characterized by delayed gastric emptying without gastrointestinal obstruction. Although it has not been well recognized as a complication of chemotherapy for solid malignancies, we here report a case of gastroparesis apparently due to neurotoxicity of high-intensity taxane- and platinum-based chemotherapy for a solid tumor. The patient experienced late-onset gastric dysmotility as evidenced by an abnormally dilated stomach even after cessation of feeding for several days. The gastroparesis was successfully controlled with a 5-HT₄ receptor agonist, resulting in recovery of gastric motility and allowing completion of curative anticancer treatment. Despite its rarity in patients with solid cancers, gastroparesis should be recognized as a potential cause of persistent upper abdominal symptoms during neurotoxic chemotherapy in such individuals, given that a delay in its management may be detrimental to survival outcome.

Introduction

Gastrointestinal toxicity is a common complication of chemotherapy and can result in an undesirable delay in or dose reduction of such treatment, potentially affecting curability of the target malignancy. A prominent example of such a gastrointestinal adverse event (GIAE) is chemotherapy-induced nausea and vomiting (CINV), the management of which has been well established [1]. Other conditions have not been fully characterized as GIAEs, however. We here report a case of gastroparesis as an important GIAE during platinum- and taxane-based intensive chemotherapy for solid cancer.

Case Report

A 73-year-old man was diagnosed with human papilloma virus (HPV)–negative stage IVA oropharyngeal cancer (cT4N2bM0) as a cause of swallowing difficulty. He had undergone distal subtotal gastrectomy with Billroth I reconstruction for duodenal ulcer at 33 years of age. As a curative treatment of the oropharyngeal cancer, induction chemotherapy with docetaxel, cisplatin, and fluorouracil (TPF) was initiated with nutritional support by nasogastric tube feeding. The TPF regimen consisted of docetaxel at 75 mg/m² followed by cisplatin at 75 mg/m² on day 1, and fluorouracil at 750 mg/m² on each of days 1 to 5, of a 3-week cycle.

At 18 days after initiation of chemotherapy, the patient presented with upper abdominal distention, resulting in a complete interruption of enteral nutrition. He was alert and afebrile. He did not have a medical history or symptoms suggestive of psychiatric disorders or neurodegenerative disorders such as parkinsonism, and medications known to impair gastrointestinal motility had not been administered for at least 2 weeks. Blood analysis did not show any abnormalities reflecting acute kidney injury, liver injury, electrolyte disturbance, or endocrinopathy, including hyperglycemia. Abdominal computed tomography (CT) scans revealed an abnormally dilated stomach without intestinal dilation (Fig. 1a and 1b). Esophagogastroduodenoscopy (EGD) after discontinuation of enteral feeding for 3 days showed marked

impairment of gastric emptying characterized by a large amount of gastric content, although mechanical obstruction and mucosal damage were not apparent (Fig. 1c). CINV could be excluded because it rarely occurs later than 1 week after the start of chemotherapy [1]. We therefore diagnosed the patient with chemotherapy-induced gastroparesis according to clinical practice guidelines [2], and we prescribed oral mosapride (15 mg/day). His symptoms improved immediately within 24 hours, and repeated abdominal CT scans showed normal gastric emptying (Fig. 1d).

Concurrent chemotherapy with high-dose cisplatin (100 mg/m² on day 1, of a 3-week cycle) and definitive radiotherapy with 70 Gy in 35 fractions was then initiated, with mosapride treatment being maintained. This curative chemoradiotherapy was completed successfully without recurrent gastrointestinal symptoms, and the patient remained alive with no disease progression at 8 months after the treatment onset.

Discussion

We here describe a case of gastroparesis during a course of intensive cytotoxic chemotherapy for curative treatment of solid cancer. The rapid diagnosis of this condition allowed prompt treatment with mosapride and a complete recovery of gastric motility, which in turn allowed the safe completion of subsequent definitive chemoradiotherapy with high-dose cisplatin. Gastroparesis has not been well recognized as a chemotherapy-induced adverse event in patients with solid cancers.

Gastroparesis is characterized by delayed gastric emptying in the absence of a mechanical obstruction [3]. It is generally associated with diabetes mellitus, prior gastric surgery, the use of antimotility medications, viral infection, and neurological, endocrine, or collagen vascular disorders, all of which were not considered as causes of gastroparesis in the present case. The proband had undergone distal subtotal gastrectomy, but the many years that had elapsed since the surgery excluded the probability of it being a principal cause of his gastroparesis. Most cases of postsurgical gastroparesis thus occur within 1 year after surgery, with its occurrence after several years being rare [4].

Chemotherapy-induced gastroparesis has been recognized as a rare complication of high-dose chemotherapy such as myeloablative regimens prior to bone marrow transplantation in patients with blood cancers [5, 6]. However, as far as we are aware, there is only one case report of this condition associated with chemotherapy for solid tumors [7]. This report from 1987 also suggested that gastroparesis might result from cumulative toxicity of platinum-based chemotherapy. The total dose of cisplatin administered before the occurrence of gastroparesis in this previous case was > 500 mg as a result of the prescription of a highly aggressive regimen for germ cell tumor, with such a dose no longer being administered in current standard practice. The present case is therefore unique with regard to the development of gastroparesis after administration of a single dose of cytotoxic chemotherapy currently used for the treatment of certain types of solid cancer. Oncologists should thus be alert to the possibility of this unfamiliar event as a complication of intensive chemotherapy even in the current era.

Peripheral neuropathy is a major adverse event of several types of chemotherapy including that with taxanes and vinca alkaloids as well as platinum agents. This condition presents usually as sensory neuropathy, although sometimes as autonomic neuropathy [8]. Gastroparesis is caused by a disruption of coordination of multiple systems required for gastric motility including gastric smooth muscles, autonomic nerves, and specialized pacemaker cells, the intestinal cells of Cajal [3]. The intensive taxane- and platinum-based chemotherapy administered for the present patient is implicated as a main contributor to the induction of his gastroparesis because of its potential to cause autonomic neuropathy, although whether cisplatin or docetaxel was more responsible for the development of gastroparesis remains unknown. Drug-induced neuropathy was previously found to be more severe for the combination of cisplatin and docetaxel than for either drug alone at similar doses [9].

Management of gastroparesis often requires pharmacological therapy including macrolide antibiotics and 5-HT₄ receptor agonists in addition to dopamine or dopamine receptor antagonists [2]. Refractory cases may require further intervention such as the administration of tricyclic antidepressants, serotonin reuptake inhibitors, and gastric electrical stimulation. Such treatment is distinct from that of CINV, for which 5-HT₃ receptor antagonists and benzodiazepines as well as dopaminergic antagonists are generally prescribed [1]. Oncologists should therefore note the possibility of gastroparesis as a differential diagnosis for chemotherapy-induced GIAE, especially when the patient has received multiple neurotoxic agents.

In conclusion, we here report a case of gastroparesis that was likely caused by intensive neurotoxic chemotherapy for solid cancer and which was successfully treated by proper management with a 5-HT₄ receptor agonist. Although gastroparesis during chemotherapy for solid cancer is rare, it is important that it be recognized early because a delay in its management can be detrimental to treatment outcome for the concomitant malignancy. The possibility of gastroparesis should thus be considered when patients present with persistent upper abdominal symptoms after the onset of neurotoxic chemotherapy for solid cancer.

Declarations

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Authors' contribution

Tomohiro Nakayama and Koji Haratani acquired and interpreted the clinical information of the current case. Takashi Kurosaki, Kaoru Tanaka and Kazuhiko Nakagawa revised it critically for important intellectual content. All authors read and approved the final manuscript.

Availability of data materials

Not applicable.

Code Availability

Not applicable.

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Compliance with Ethical Standards

Conflict of interest

K Haratani has received honoraria from AstraZeneca K.K.; lecture fees from AS ONE Corporation, AstraZeneca K.K., Bristol-Myers Squibb Co. Ltd., Chugai Pharmaceutical Co. Ltd., MSD K.K., and Ono Pharmaceutical Co. Ltd.; Research funding from AstraZeneca K.K., and MSD K.K.. K Tanaka. has received honoraria from Eisai Co. Ltd., AstraZeneca K.K., Merck Biopharma Co. Ltd., Bristol-Myers Squibb Co. Ltd., Ono Pharmaceutical Co. Ltd., MSD K.K., and Kyowa Kirin Co. Ltd.. K Nakagawa. received honoraria from AbbVie Inc., Amgen Inc., Astellas Pharma Inc., AstraZeneca K.K., Bayer Yakuhin Ltd., Bristol Myers Squibb Co. Ltd., Care Net Inc., Chugai Pharmaceutical Co. Ltd., Eli Lilly Japan K.K., Daiichi Sankyo Co. Ltd., Hisamitsu Pharmaceutical Co. Inc., Kyorin Pharmaceutical Co. Ltd., Kyowa Kirin Co. Ltd., Nichi-Iko Pharmaceutical Co. Ltd., Medical Mobile Communications Co. Ltd, Merck Biopharma Co. Ltd., Merck Serono Co. Ltd., MSD K.K., Nippon Boehringer Ingelheim Co. Ltd., Nippon Kayaku Co. Ltd., Novartis Pharma K.K., Pfizer Japan Inc., Ono Pharmaceutical Co. Ltd., Roche Diagnostics K.K., Taiho Pharmaceutical Co. Ltd., Takeda Pharmaceutical Co. Ltd. Thermo Fisher Scientific K.K., 3H Clinical Trial Inc.; consulting fee from Eli Lilly Japan K.K., Kyorin Pharmaceutical Co. Ltd., Ono Pharmaceutical Co. Ltd., Pfizer Japan Inc., Takeda Pharmaceutical Co. Ltd.; and research funding from AbbVie Inc., Astellas Pharma Inc., AstraZeneca K.K., A2 Healthcare Corp., Bayer Yakuhin Ltd., Bristol Myers Squibb Co. Ltd., Chugai Pharmaceutical Co. Ltd., CMIC Shift Zero K.K., Covance Japan Inc., Daiichi Sankyo Co. Ltd., Eisai Co. Ltd., Eli Lilly Japan K.K., EPS Corporation., EPS International Co. Ltd., GlaxoSmithKline K.K., ICON Japan K.K., IQVIA Services JAPAN K.K., Japan Clinical Research Operations, Kissei Pharmaceutical Co. Ltd., Kyowa Kirin Co. Ltd., MSD K.K., Medical Research Support, Merck Serono Co. Ltd., Merck Biopharma Co. Ltd., Mochida Pharmaceutical Co. Ltd., Nippon Boehringer Ingelheim Co. Ltd., Novartis Pharma K.K., Ono Pharmaceutical Co. Ltd., Otsuka Pharmaceutical Co. Ltd., PAREXEL International Corp., Pfizer Japan Inc., Pfizer R&D Japan G.K., PPD-SNBL K.K, PRA HEALTHSCIENCES, Sanofi K.K., SymBio Pharmaceuticals Limited., Syneos Health, Sysmex Corporation, Taiho Pharmaceutical Co. Ltd., Takeda Pharmaceutical Co. Ltd.; and has patents pending with Daiichi-Sankyo Co. Ltd., (WO2015048804A2, WO2018123999A1, and WO2018159582A1) and Ono Pharmaceutical Co. Ltd and Sysmex Co. Ltd., (Japanese Patent 2018-59834). The other authors declare that they have no competing interests.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

The patient provided written consent for publication of the present case report.

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Figures

Figure 1

Gastroparesis indicated by computed tomography (CT) and esophagogastroduodenoscopy (EGD). (a, b) Contrast-enhanced CT scans of the patient performed 3 days after discontinuation of enteral feeding through a nasogastric tube (arrows) showed an abnormally dilated stomach (a) without intestinal dilation (b). (c) EGD revealed a large amount of gastric content despite the discontinuation of tube feeding for more than 3 days, without evidence of gastric outlet obstruction or mucosal impairment. (d) CT confirmed complete resolution of delayed gastric emptying 13 days after the onset of treatment with mosapride, even after resumption of enteral feeding by the nasogastric tube (arrows).