Case Report

Chemotherapy induced diarrhea: A case report

Abstract

Background: Chemotherapy induced diarrhea (CID) is one of the most serious side‑effects during cancer treatment, which can cause severe dehydration and malnutrition, or even death. Most of the CID patients could recover in a few weeks under sufficient supportive treatment.

Case presentation: We presented a complicated and long‑lasting diarrhea induced by Tegafur Gimeracil Oteracil Potassium Capsule(S‑1), which is widely used in Japan and China as an oral fluorouracil medicine. We analyzed the process and mechanism of complicated CID in order to offer experiences for other doctors.

Conclusion: The genesis of CID is believed a complicated process resulting from combination and interaction of multiple factors including gene mutation and enzyme deficiency, intestinal mucosa inflammation, dysbacteriosis as well as nervous system disability.

Keywords: diarrhea, CID, S‑1, fluorouracil

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Received: February 04, 2018 | **Published:** February 16, 2018

Abbreviations:

CID, chemotherapy induced diarrhea; S‑1: Tegafur Gimeracil Oteracil Potassium Capsule; ENS, enteric nervous system

Introduction

Although chemotherapy in the field of gastrointestinal cancer has greatly expanded, the use of fluorouracil is still a suitable and effective choice.[1–3] The gastrointestinal side‑effects of fluoruracil include nausea, vomiting, diarrhea, and ulceration, all of which present major complications resulting in prolonged hospitalization and alterations, or even cessation, of therapy.[4–7]

Chemotherapy induced diarrhea(CID) is definitely one of the most severe side‑effects of chemotherapy.[8–10] It is usually under‑appreciated and poorly treated compared with other side effects like myelosuppression. We present a case of severe diarrhea induced by Tigafur Gimeracil Oteracil (S‑1), perhaps the safest oral fluorouracil, who was diagnosed and treated in department of gastrointestinal surgery of Peking University Shenzhen Hospital. We aim to analyze the process and mechanism of CID.

Case presentation

Case history

A 56 years old male patient was admitted by Peking University Shenzhen Hospital with a chief complaint of upper abdominal pain and distension after meals for 4 months. The patient was diagnosed as gastric antrum adenocarcinoma by endoscopic biopsy and received an operation of open distal gastrectomy (Billroth I reconstuction)+D2 lymph node dissection. The post operative pathological analysis revealed a gastric moderately and poor‑differentiated adenocarcinoma with lymphnode infiltration (pT2N2M0). About 3 weeks after surgery, the patient received chemotherapy of S‑1 alone strategy. The dosage of medication was 60mg bid (twice per day) Day1‑28 every 6 weeks for 6 cycles (BSA=1.64□). On the 21st day of first cycle, the patient suffered from a continuous left upper abdominal colic pain and severe diarrhea and readmitted by our hospital. His excrement was a non‑bloody, dark yellow, watery content approximately 3‑ times per day. Physical examination revealed tenderness and rebound tenderness at left upper abdomen. The bowel sound was hypereactive, 12 times per minute.
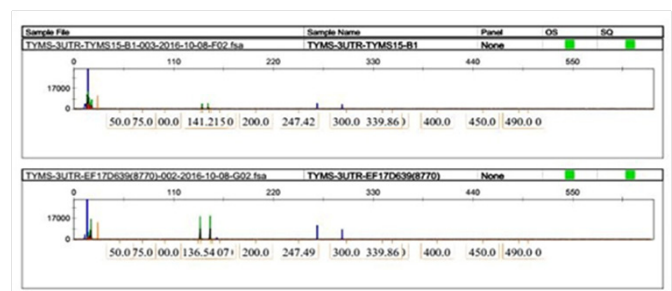

Figure 1 The result of Gene test revealed polymorphysm of gene TYMS.

Examination and treatment

After admition, doctors in our center suspended his chemotherapy and started supportive treatment. However, the patient's condition did not get better, the diarrhea frequency and white blood cell count increased gradually, at the same time, the albumin level and hemoglobin level decreased as a result of the consumption of severe diarrhea. Also, the patient suffered from a severe imbalance of water and electrolyte. Then we started to pay special attention to this case and try to find out the cause of his diarrhea. We gave the patient several times of stool culture and test of clostridium difficile toxin A&B, which revealed a negative result. A 5‑FU metabolism related genome test was also conducted to evaluate the sensitivity and tolerance of the patient for S‑1. The results revealed a genetic polymorphysm of gene TYMS, as well as a negative polymorphysm of gene DPD and MTHFR, which indicate a relatively good tolerance and sensitivity for the application of 5‑FU based chemotherapy (Figure 1). The CT‑scan conducted during the hospitalization periods revealed severe inflammation and edema on intestinal wall (Figure 2). The therapy was applied along with the serum evaluation and other examination. The supportive treatment includes fluid transfusion, management of water and electrolytic balance as well as albumin and blood transfusion when necessary. The pharmacological treatment is the combination of Glutamine, Celecoxib, Loperamide as well as Octreotide. The treating course is described in Figure 3.

Figure 2 The CT-scan revealed severe inflammation of intestine.
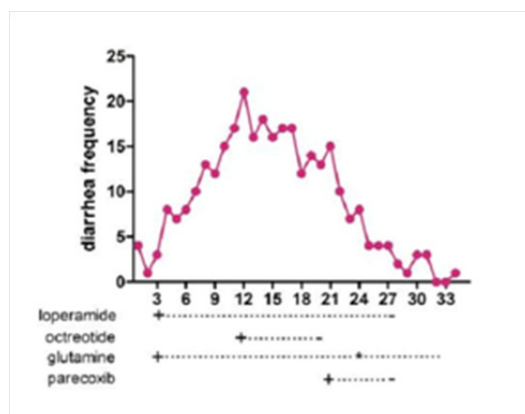

Figure 3 The change of diarrhea frequency and application of medicine.

The patient was discharged after 34 days' hospitalization. The symptoms were totally recovered. About 2 weeks after his dischargement, the patient recieved a gastrointestinal Endoscope test, which revealed anastomositis without other abnormality (Figure 4). During the whole treating course, the useful advices we could get from guidlines and past publications are really limited. The sufficient treatment is based on the detailed serum evaluation and early application of supportive treatment and pharmacological treatment.
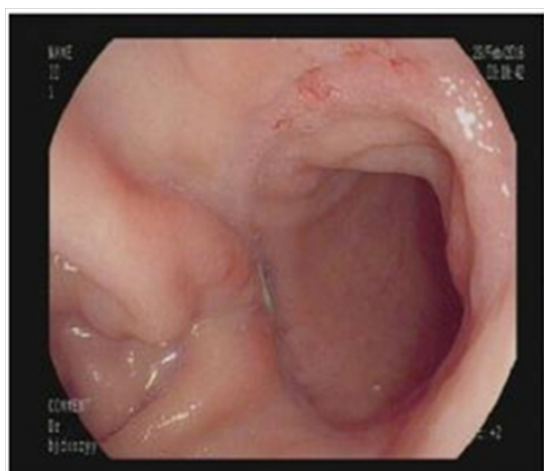

Figure 4 The result of post-operative endoscopic test revealed anastomositis.

Discussion

CID is a dangerous and often under-appreciated complication. According to the past study, CID results in treatment alternation in about 60% of the patients, complete termination of chemotherapy in 15% of the patients. The most severe CID could last for 10 years after chemotherapy. The severe dehydration related to CID would increase the early death rates in 5% of the patients under chemotherapy.[1–4]

Doctors had been trying to find out the mechanism of the disease. The susceptibility of patient for the physiological change was closely related to the metabolism of anti-cancer medications. So we had paid special attention to the genes related to the enzymes for 5-FU degradation in our case. The main physiological change of the disease include malnutrition and dehydration, intestinal mucosa inflammation and bowel wall thickenning or ulceration, intestinal dysbacteriosis, which all appeared in our case above.

Chemotherapy agent metabolism deficiency

The molecular basis of chemotherapy agent toxicity (fluorouracil toxicity in this article) has been widely known as the dihydropyrimidine dehydrogenase deficiency. Which exists 3-5% in the general population?[11–13] The reduction of DYPD leads to the prolonged existance of 5-FU or its metabolic intermediate products in serum and tissue fluid, resulting in the toxicity raction of intestinal mucosa and other related organs. Besides, more than 50 more gene polymorphisms have potential relationship with the fluorouracil metabolism.[14,15] There are still a large number of analyses needed to figure out every possible signal pathway of CID genesis.

Gastrointestinal mucositis

Although most of the patients didnot recieve endoscopy in the acute stage to make diagnosis for CID, it is still believed by researchers that the CID is a by-product of gastrointestinal mucositis.[16–19] The pathological change of GI mucositis include crypt ablation, villus blunt as well as epithelial atrophy in the GI tract, resulting in dysbacteriosis and abnormally activated secretion. In addition, the mucosal inflammation also plays an important role in the process of diarrhea.[20,21] The inflammation was mediated by activation of nuclear factor-kappa B, interleukin-1, cyclooxygenase-2 and prostaglandin E2, et al accroding to the former researches. There are also some researches trying to figure out the significance of AIDs (such as NSAIDs) application in the treatment of CID.[22–25] The results of this analysis may influence the current therapeutic strategies towards CID.

Dysbacteriosis

The intestinal dysbacteriosis is believed to be one of the most common causes of diarrhea. Recent studies showed that chemotherapeutic administration has effects on intestinal microbial composition and fecal microbiota.[26,27]. The dsybacteriosis could aggravate the inflammation and mediate the modulation of inflammation response, resulting in the excreption and dehydration.[28–30] In some of the guidelines for CID, the antibiotics and probiotics are recommended in the therapy.

Enteric nervous system damage

The enteric nervous system (ENS) is one of the main divisions of the nervous system. ENS consists of a mesh-like serious of neurons, which govern the function of GI system. It is usually known as the second brain due to its own independent reflex activity from the CNS.[31,32] The neurons of ENS located in the submucosal plexus

of gastrointestinal tract to mediate the movement of mascularis and mucosal reaction to stimulation. Which work together with the endocrine and paracrine and autocrine system to mediate the movement of fluid between the body fluid and gastrointestinal tract? When the metabolism of anti‾cancer medicine becomes abnormal, especially for the platinum, the exits of medicine in the mucosa induce damage to the ENS, and result in myenteric neuronal loss and increase of amplitude of neurally induced contractions. This mechanism has been ignored for a very long time until recent years.

As we have discussed above, the genesis of chemotherapy induced diarrhea is believed a complicated process resulting from combination and interaction of multiple factors including gene mutation and enzyme deficiency, intestinal mucosa inflammation, dysbacteriosis as well as nervous system disability. However, there are still puzzles and questions in all of the possible mechanisms.[33–37] Medications towards these mechanisms still cannot work very well in quite a number of cases. Further studies and researches are needed for us to know about this disease and make the pharmacological treatment strategy more sufficient.

Acknowledgements

Conflicts of interest

The authors declare that they have no competing interests.

Patient consent form

The data of this patient has been collected from the clinical data system of the Peking University Shenzhen Hospital with the permission of both the hospital and the patient, at the same time, the data and figures presented in this article is totally anoymous. Publication of such data does not compromise anonymity or confidentiality or breach local data protection laws.

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