Severe adverse events due to dihydropyrimidine dehydrogenase deficiency in a Japanese patient with colon cancer taking capecitabine: a case report

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Abstract

Fluoropyrimidine has been commonly used not only in unresectable cases of metastatic colorectal cancer, but also in adjuvant therapy. Dihydropyrimidine dehydrogenase (DPD) is an enzyme encoded by the *DPYD* gene, which is responsible for the rate-limiting step in pyrimidine catabolism and breaks down more than 80% of standard doses of 5-fluorouracil (5-FU) and capecitabine, an oral prodrug of 5-FU. The lack of enzymatic activity increases the half-life of the drug, resulting in excess drug accumulation and toxicity which may lead to life-threatening side effects. There have been several published case reports about DPD deficiency in patients with colorectal cancer in Western countries. However, case reports of DPD deficiency in Japanese patients with colorectal cancer are rare because measuring DPD activity is not covered by public medical insurance in Japan, and it is not examined in our daily clinical practice currently. Therefore, we think that it is important to accumulate such case reports for further understanding. This report describes the case of a Japanese patient with colon cancer who experienced severe side effects while taking capecitabine, due to DPD deficiency. A 68-year-old man with ascending colon cancer underwent curative laparoscopic right hemicolectomy. Because final pathologic staging was Stage IIIa, standard adjuvant chemotherapy with capecitabine (3600 mg/body/day, days 1–14, every 3 weeks) was started on postoperative day 50. After 2 weeks, he started to experience Grade 3 diarrhea and was admitted to the hospital on postoperative day 66. On day 70, the patient had Grade 4 febrile neutropenia. Antibiotics and granulocyte-colony-stimulating factor were administered until his blood tests recovered to the normal degree. After 1 week of diarrhea, antidiarrheal agents were administered, and the patient gradually recovered. During the occurrence of diarrhea, specimen cultures were negative for infection. He was discharged on day 21 of the hospital stay. DPD deficiency was suspected, and 2 weeks later the DPD activity of the peripheral blood mononucleocytes was examined. The result was 10.3 U/mg protein which was remarkably low (reference range 22.6–183.6 U/mg protein), and DPD deficiency was diagnosed. We always must consider the possibility of DPD deficiency in patients who experience severe side effects while taking capecitabine.

Keywords Fluoropyrimidines · Dihydropyrimidine dehydrogenase deficiency · Colon cancer · Capecitabine · Side effects

Abbreviations

5FU 5-fluorouracil
JSCCR Japanese Society for Cancer of the Colon and Rectum

CTCAE Common Terminology Criteria for Adverse Events
WBC White cell count
CRP C-reactive protein
MEPM Meropenem
G-CSF Granulocyte-colony stimulating factor
CT Computed tomography
LVFX Levofloxacin
ELISA Enzyme-linked immunosorbent assay

The original version of this article was revised: In the original version of this article, unfortunately the word “phosphate” in Figure 1 has been misspelt as “phosohate”. Figure 1 is replaced.

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Introduction

Colon cancer is responsible for more than 50,000 deaths annually in Japan, and the number of patients diagnosed with colon cancer is increasing [1]. Currently, the combination of cytotoxic anticancer agents such as fluoropyrimidine [5-fluorouracil (5-FU), S-1, and capecitabine], oxaliplatin, or irinotecan with molecular targeted drugs has been widely adopted. In particular, fluoropyrimidine has been frequently used not only in cases of unresectable metastatic colorectal cancer, but also in adjuvant therapy [2]. Dihydropyrimidine dehydrogenase (DPD) is an enzyme encoded by the *DPYD* gene, and it is responsible for the rate-limiting step in pyrimidine catabolism and breaks down more than 80% of standard doses of 5-fluorouracil (5-FU) and capecitabine, an oral prodrug of 5-FU.

True deficiency of DPD affects approximately 5% of the overall population. In these patients, the lack of enzymatic activity increases the half-life of the drug, resulting in excess drug accumulation and toxicity [3]. In addition, 3–5% of the population has a partial DPD deficiency due to sequence variations in the *DPYD* gene, which potentially limits their ability to fully metabolize capecitabine, resulting in toxicity [4–7]. Severe side effects in patients from Western countries with colon cancer while taking capecitabine due to DPD deficiency have been reported in several papers.

However, since measuring DPD activity is not covered by public medical insurance in Japan, and it is not examined in our daily clinical practice at this time, no full case reports of DPD deficiency in Japanese patients with colorectal cancer could be found in the English literature in PubMed. This report describes the case of a patient with colon cancer who experienced severe side effects while taking capecitabine, due to DPD deficiency. We think that it is important to accumulate such case reports here also in Japan for further understanding and to warn doctors who are involved in colon cancer treatment and chemotherapy who are not familiar to DPD deficiency.

Case report

A 68-year-old man with ascending colon cancer underwent curative laparoscopic right hemicolectomy. There were no complications in his postoperative course, and he was discharged on postoperative day 8. Final pathologic staging was Stage IIIa (poorly differentiated adenocarcinoma, pT4a, N1, M0) by the 8th Japanese Classification of Colorectal Carcinoma [8]. Based on the Japanese Society for Cancer of the Colon

and Rectum (JSCCR) guidelines, standard adjuvant chemotherapy with capecitabine (3600 mg/body/day, days 1–14, every 3 weeks) was started on postoperative day 50. After 2 weeks of taking capecitabine, the patient developed severe diarrhea occurring more than 7 times per day [Grade 3 adverse event defined by the Common Terminology Criteria for Adverse Events (CTCAE) 4.0]. At that time, blood test results were within normal limits. Although the patient was administered intravenous fluid at the outpatient clinic for 3 continuous days, he still had severe diarrhea, and he was admitted to the hospital on postoperative day 66. His body temperature was 37.7 °C, and laboratory studies revealed a white blood cell count (WBC) of 5400/mm³ and a C-reactive protein (CRP) count of 2.82 mg/dL. He was first treated with amino acid infusion and solid food with lactobacillus products was withheld. By the evening, his body temperature had increased to 38.6 °C.

On hospital day 4, the patient's body temperature was above 39 °C. The next day his white blood cell count decreased to 1100/mm³. He was diagnosed with Grade 4 febrile neutropenia and was treated with antibiotics [Mero-penem (MEPM) g/day] and granulocyte-colony-stimulating factor (G-CSF) (Nartograstim 50 µg/day). Blood cultures and stool cultures were collected repeatedly (that was 4 sets of blood culture taken every 4 days and 2 times of stool culture) during his hospitalization, never having any positive results. Stool cultures were also negative for clostridium difficile. G-CSF was administered until his WBC level reached the normal range, which took 4 additional days. Oral intake of solid food was started on hospital day 7, and the patient's subjective symptoms gradually improved. Nevertheless, his body temperature remained abnormally high, and on hospital day 9, a computed tomography (CT) scan was performed to determine the cause of the high fever. Massive severe enterocolitis was detected with no additional findings.

Two days later (hospital day 11), MEPM was changed to oral Levofloxacin (LFVX). After additional 5 days (hospital day 16), the patient continued to have diarrhea. Therefore, we prescribed codeine phosphate for symptom relief. The diarrhea was under control by hospital day 19, and intravenous fluids were terminated. He was discharged on hospital day 21 (Fig. 1). Because the severe side effect was apparently caused from taking capecitabine, DPD deficiency was suspected. Two weeks later, the DPD activity of the peripheral blood mononucleocytes was examined by enzyme-linked immunosorbent assay (ELISA) [9], in terms of protein concentration at Chugai Pharmaceutical Co., Ltd. with patient's informed consent. The result was 10.3 U/mg protein, which was remarkably low (reference range of 22.6–183.6 U/mg protein) and DPD deficiency was diagnosed. The patient is now under observation with no further chemotherapy being administered. CT scans and blood

Fig. 1 The clinical course of the patient. The results of blood exams in terms of white blood cells (WBC) and neutrocytes are shown along with the body temperature. Diarrhea counts and the medication are also shown in the figure. On hospital day 4, the patient was diagnosed with Grade 4 febrile neutropenia (FB). Antibiotics and granulocyte-colony-stimulating factor (G-CSF) were transfused until WBC levels recovered. The patient recovered from FB on the 9th day after admission. Blood and stool specimen were repeatedly examined, but were never positive for infection. A CT scan was taken, and massive severe enterocolitis was observed. The patient gradually recovered after taking antidiarrheal medicine and was discharged on day 21

exams are conducted every 3–4 months, and the patient is free of recurrence 13 months after the surgery.

Discussion

Fluoropyrimidines are commonly prescribed medications for the treatment of colon cancer. Among the fluoropyrimidines, the 5-FU prodrug capecitabine is widely prescribed because it is administered orally. When 5-FU is administered, 85% is metabolized to an inactive state by the enzyme DPD while

the residual 15% leads to inhibition of DNA synthesis, working as an anticancer drug [10–12]. Therefore, deficiency of DPD results in hyper-uracilnemia and increases the 5-FU level in the plasma, leading to severe toxicity [3]. As a prodrug of 5-FU, capecitabine may also cause severe side effects if DPD deficiency is present. Neutropenia, mucositis, stomatitis, and even death have been reported as side effects of DPD deficiency. Studies have shown that partial or complete DPD deficiency was responsible for the approximately 40–50% of patients with grade 3/4 toxicity to 5-FU [13]. DPD deficiency was first reported by Bakkeren et al. [14] in 1984 as genetic changes in the gene. The IVS14+1G>A mutation in intron 14 coupled with exon 14 deletion (known as DPYD*2A) is the most familiar variant resulting in partial DPD deficiency and 5-FU toxicity [15]. Other recognized variants associated with toxicity include 496A>G in exon 6, 2846A>T in exon 22, and T1679G (DPYD*13) in exon 13, although multiple other mutations have been detected in individual families and via full gene sequences [16–18]. It is very rare to have complete DPD deficiency, while it is slightly more common to have low or very low levels of DPD (partial or slight deficiency). Partial DPD deficiency is present in approximately 3–5% of adult cancer patients, with complete deficiency occurring in 0.5% [4–7, 12, 19]. In terms of the Japanese population, Ogura et al. [20] reported that 0.7% of healthy volunteers showed very low DPD activity. By 2017, there were 3 cases in Japan of DPD deficiency reported in patients with colorectal cancer after taking capecitabine in Japanese literature [11, 21, 22] (Table 1). All cases, including our case, experienced Grade 3/4 side effects such as those previously reported Western cases.

DPD deficiency does not cause any symptoms unless the patient takes 5-FU or capecitabine. As a result, it is impossible to know if a patient has a DPD deficiency before treatment unless DPD activity has been examined previously. Measuring DPD activity is not covered by public medical insurance in Japan, and it is not examined in our daily

Table 1 Summary of patients in Japan with colorectal cancer with DPD deficiency discovered after taking capecitabine

References	Age, gender, location	Stage	Regimen	Symptoms	Outcome	DPD rate
Toshima et al. [21]	70, male, rectum	IIIa	3600 mg/body/day Day 1–14, every 3 weeks	Grade 4 neutropenia Grade 4 thrombocytopenia Grade 3 oral mucositis	Dead	Unknown
Sakaguchi et al. [22]	70, male, rectum	IIIa	4200 mg/body/day Day 1–14, every 3 weeks	Grade 4 neutropenia Grade 4 platelet count decrease	Survived	10.8 U/mg protein
Mitake et al. [11]	78, female, transverse colon	II	3600 mg/body/day Day 1–14, every 3 weeks	Grade 3 diarrhea Grade 3 oral mucositis	Survived	11.8 U/mg protein
Our case (2017)	68, male, ascending colon	IIIa	3600 mg/body/day Day 1–14, every 3 weeks	Grade 4 febrile neutropenia Grade 3 diarrhea	Survived	10.3 U/mg protein

By 2017, there were 3 cases in Japan of DPD deficiency reported in patients with colorectal cancer after taking capecitabine. All cases, including our case, experienced Grade 3/4 side effects such as those previously reported Western cases

clinical practice at this time. Therefore, careful monitoring is important. There may be some possibility of overlooking a latent DPD deficiency in patients with severe side effects after taking 5-FU or capecitabine. Moreover, there are some patients who develop severe side effects during delayed courses of treatment [10]. We always must consider the possibility of DPD deficiency that may lead to severe side effects when we prescribe 5-FU or capecitabine.

In patients with DPD deficiency, it is widely recognized that the continuation of 5-FU or capecitabine is contraindicated. However, Yoshida et al. have reported that dose escalation may be an alternative [23]. Since 5-FU and capecitabine are key drugs in the treatment of colon cancer, the development and standardization of dose escalation therapy may be beneficial. In conclusion, capecitabine is an effective oral anticancer agent for patients with colorectal cancer. However, when capecitabine is prescribed, it is important to monitor side effects that may occur even if the patient has no history of severe side effects.

Conclusions

Side effects caused by fluoropyrimidines such as 5-FU and capecitabine are not rare in colon cancer patients. However, we must consider the possibility that underlying DPD deficiency may be responsible for any side effects.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Informed consent Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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