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Case Report

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A case in which TAS-102 produced disease control without severe adverse events in a patient with recurrent colorectal cancer and dihydropyrimidine dehydrogenase deficiency

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Abstract

Fluoropyrimidine is commonly used to treat unresectable cases of metastatic colorectal cancer or as an adjuvant therapy for colorectal cancer. 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 >80% of standard doses of 5-fluorouracil (5-FU). Reductions in DPD activity increase the half-life of 5-FU, resulting in excess 5-FU accumulation and toxicity, which can lead to life-threatening side effects. There have been several published case reports about DPD deficiency in colorectal cancer patients from Western countries. However, case reports of DPD deficiency in Japanese colorectal cancer patients are rare because the measurement of DPD activity is not covered by the public medical insurance system in Japan, and DPD activity is not currently measured in daily clinical practice. Furthermore, there have not been any reports about anticancer drug therapy for Japanese patients with DPD deficiency. In this report, we describe a case in which a Japanese patient with colorectal cancer was diagnosed with DPD deficiency. The DPD deficiency arose as a severe adverse effect of mFOLFOX6/CapOX treatment for recurrent colorectal cancer, and the patient was subsequently treated with TAS-102, without experiencing any severe adverse effects. We report this case along with a review of the literature.

Keywords: Colon Cancer, Dihydropyrimidine Dehydrogenase Deficiency, TAS-102.

Background

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, combinations of cytotoxic anticancer agents, such as fluoropyrimidine (5-fluorouracil (5-FU), S-1, or capecitabine), oxaliplatin, or irinotecan, with molecular targeted drugs are widely used to treat colon cancer. In particular, fluoropyrimidine is frequently used to treat unresectable metastatic colorectal cancer or as an adjuvant therapy for colorectal cancer [2]. About 80% of 5-FU is inactivated to 5-fluoro-dihydrouracil (5-FDHU) by dihydropyrimidine dehydrogenase (DPD), the main enzyme responsible for fluoropyrimidine metabolism. Polymorphisms in the coding region of the DPD gene (DPYD) cause reductions in DPD activity and can result in the development of serious grade 3 to 4 toxicities (gastrointestinal or medullary toxicities or hand-foot syndrome) after the administration of a standard dose of the drug [3].

Trifluridine/tipiracil (TAS-102) is a novel anticancer agent, in which trifluridine (an antineoplastic thymidine-based nucleoside analogue) is combined with tipiracil hydrochloride (a thymidine phosphorylase inhibitor), and it has been approved as a treatment for metastatic colorectal cancer that is refractory or intolerant to standard treatment [4]. Herein, we report a case, in which TAS-102 resulted in effective disease control without any adverse reactions in a patient with recurrent colorectal cancer and DPD deficiency, along with a review of the literature.

Case Presentation

The patient was a 73-year-old female. She had a history of chronic heart failure, chronic atrial fibrillation, and chronic renal failure. Her family history was unremarkable. She underwent laparoscopic sigmoid colon resection for sigmoid colon cancer in October 2018. She did not experience any postoperative complications, and she was discharged on postoperative day 10. The final pathological stage of her disease was stage IIIc (moderately differentiated

adenocarcinoma, tub2, T4a, INFb, ly1, v0, N1b, M0), according to the 9th Japanese Classification of Colorectal Carcinoma [5]. She did not wish to receive postoperative adjuvant chemotherapy and requested to undergo outpatient follow-up instead. However, a contrast-enhanced CT scan of the abdomen performed at 9 months after surgery showed recurrent peritoneal dissemination (Figure 1). We chose mFOLFOX6 (200 mg/m2 of l-leucovorin given simultaneously with 85 mg/m2 of oxaliplatin, followed by a 400-mg/m2 bolus of 5-FU on day 1 and then 2400 mg/m2 of 5-FU as an intravenous infusion over the course of 46 hours, every 2 weeks) without bevacizumab in consideration of the patient's advanced age and renal dysfunction. We selected an 80% mFOLFOX6 dose based on the patient's general condition. In the first course, no adverse events occurred, and a second course was administered. Two days after the start of the second course, the patient fell unconscious (Glasgow Coma Scale: E1V1M1) and was rushed to the emergency room of our hospital. A cranial CT scan showed no obvious findings that were suggestive of brain metastasis or cerebrovascular disease. Blood tests revealed an abnormally high ammonia level of 447 µg/dl, and the patient was diagnosed with a consciousness disorder caused by hyperammonemia (Figure 2). It was determined that the hyperammonemia was a side effect of the 5-FU. We administered supplemental fluids and a branched-chain amino acid solution for the hyperammonemia, and the next day the patient's ammonia level normalized to 41 µg/dl, and her consciousness level improved. She was discharged on hospital 4 day (Figure 3). For the second-line chemotherapy, we selected CapOX (130 mg/m2 of oxaliplatin on day 1 and 2000 mg/m2 of capecitabine twice a day, every 3 weeks). On the 13th day of the CapOX treatment, the patient developed severe diarrhea, which occurred >7 times a day (a grade 3 adverse event according to the Common Terminology Criteria for Adverse Events (CTCAE) 4.0). She was admitted to hospital as an emergency case because she was severely dehydrated. The diarrhea and dehydration were improved with fluids and fasting, and she was discharged on hospital day 16 (Figure 4). We suspected DPD deficiency because of the series of serious adverse events that she had suffered. One week later, the DPD activity of her peripheral blood mononucleocytes was examined using an enzyme-linked immunosorbent assay (ELISA) [6] at Chugai Pharmaceutical Co., Ltd., (with the patient's informed consent). As a result, it was found to be 15.07 U/mg protein, which was very low (reference range: 22.6-183.6 U/mg protein), and DPD deficiency was diagnosed. Therefore, third-line chemotherapy with TAS-102, which has a different metabolic pathway from 5-FU, was used to treat the patient's recurrent peritoneal dissemination. A reduced dosage was employed due to the patient's age and renal dysfunction (70 mg/m2 of TAS-102 twice a day on days 1-5 and days 8-12, every 28 days). She received 9 cycles of TAS-102. The treatment was well tolerated, and she did not experience medullary or gastrointestinal toxicities. A contrast-enhanced CT scan of the abdomen performed after 3 cycles showed a partial response (Figure 5). After that, she continued to exhibit stable disease on contrast-enhanced CT scans.

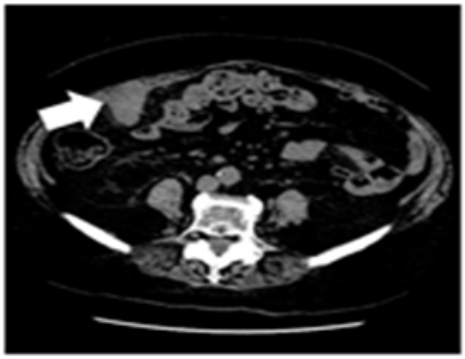

Figure 1: A contrast-enhanced CT scan of the abdomen obtained at 9 months after surgery recurrent peritoneal dissemination was detected (white arrow).

Laboratory Data

Peripheral Blood Analysis

WBC	5.9	10^3/UL
RBC	3.74	10^6/UL
Hb	11.5	g/dL
Ht	38.7	%
PLT	33.0	10^4/UL

Blood Coagulation Test

PT	15.1	second
INR	1.33	
APTT	27.7	second

Biological Examination

TP	7.3	g/dL
TB/DB	1.1/0.3	mg/dL
GOT/GPT	23/15	U/L
ALP	329	U/L
γ-GTP	51	U/L
LDH	298	U/L
BUN/Cr	34.0 / 1.68	mg/dL
Na/K/Cl/Ca	134/4.9/105/9.8	mEq/L
CRP	0.46	mg/dL
Glucose	197	mg/dL
NH3	447	µg/dL
Lac	9.1	mmol/L

Figure 2: Laboratory data obtained at the time of admission to our emergency room.

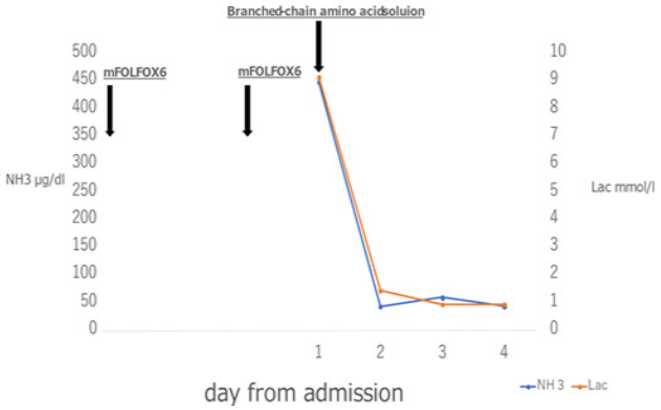

Figure 3: The clinical course of the consciousness disturbance caused by mFOLFOX6.

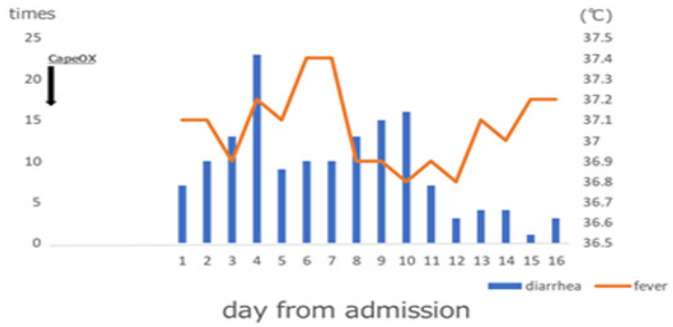

Figure 4: The clinical course of the severe diarrhea caused by CapOX

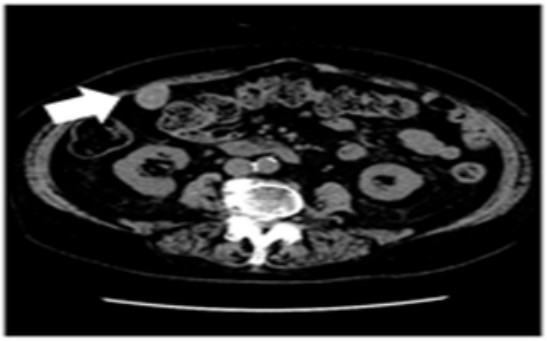

Figure 5: A contrast-enhanced CT scan of the abdomen obtained after 3 cycles a partial response (white arrow) was noted.

Discussion

DPD deficiency was first reported by Bakkeren et al. [7] in 1984, who detected genetic changes in the DPYD gene. Kouwaki et al. reported DPD deficiency for the first time in Japan in 1998 [8]. The frequency of DPD deficiency in Westerners is estimated to be about 2-3% [9], while in Japanese it is 0.7% according to Ogura et al. [10]. 5-FU is commonly prescribed for the treatment of colon cancer. When 5-FU is administered, 85% of the drug is metabolized to an inactive state by the enzyme DPD, while the remaining 15% inhibits DNA synthesis, and hence, functions as an anticancer drug [10,11]. Therefore, in patients treated with 5-FU DPD deficiency results in elevated plasma 5-FU levels, which can lead to severe toxicities. One potential severe toxicity of 5-FU treatment is hyperammonemia. The administration of high doses of 5-FU to patients with DPD deficiency causes hyperammonemia, which can also be caused by renal dysfunction, dehydration, infections, and constipation [12]. Initially, we did not consider DPD deficiency to be the cause of our patient's hyperammonemia because it is uncommon in Japan [10], and our patient had renal dysfunction and constipation. In addition, it is rare for Japanese clinicians to suspect DPD deficiency because the measurement of DPD activity is not covered by the public medical insurance system in Japan and is not performed in daily clinical practice. However, we should always consider the possibility of DPD deficiency when administering 5-FU to patients.

Trifluridine/tipiracil (TAS-102) is a novel anticancer agent, in which trifluridine (an antineoplastic thymidine-based nucleoside analogue) is combined with tipiracil hydrochloride (a thymidine phosphorylase inhibitor). It is approved as a treatment for metastatic colorectal cancer that is refractory or intolerant to standard treatment [4]. TAS-102 has a completely different mechanism of action to the other fluoropyrimidines (5-FU and capecitabine) and follows an alternative activation pathway, involving thymidine kinase, and hence, is not a substrate for DPD [13]. Therefore, we used TAS-102 in our patient with DPD deficiency. As the patient was elderly, we used TAS-102 at a dose of 80%. The treatment was well tolerated, and the patient did not experience medullary or gastrointestinal toxicities. The fact that TAS-102 is not catabolized by DPD suggests that it can be used safely in DPD-deficient patients. To the best of our knowledge, there have only been one reported case [14], in which TAS-102 was used for the treatment of DPD deficiency, and our patient received TAS-102 for a longer period (9 courses) than the other patient (6 courses). The fact that the patient's condition was controlled without experiencing any serious adverse events is commendable.

In patients with DPD deficiency, it is widely recognized that the continuation of 5-FU or capecitabine is contraindicated. However, Yoshida et al. reported that dose escalation might be an alternative [15]. Therefore, the development and standardization of dose escalation protocols involving these drugs might be beneficial, as 5-FU and capecitabine are key drugs in the treatment of colon cancer. In addition, TAS-102 can be safely administered to patients with DPD deficiency. Clinical trials are needed to examine the utility of TAS-102 as an adjuvant chemotherapy for colorectal cancer.

Conclusion

We described the administration of TAS-102 to a DPD-deficient patient. Our case and the available literature suggest that it is possible to safely administer TAS-102 to DPD-deficient patients.

Declaration

Ethics Approval and Consent to Participate. Ethics approval and consent to publish has been obtained from participant.

Consent for Publication

Consent to publish has been obtained from participant.

Availability of Data and Materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing Interests

The authors declare that they have no competing interests.

Funding

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Authors' Contributions

All authors revised the manuscript, approved the manuscript to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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