CASE REPORT

Rechallenge with 5-fluorouracil in a patient who developed encephalopathy caused by 5-fluorouracil for colon cancer

Takeshi Yamada¹ · Hayato Kan¹ · Satoshi Matsumoto² · Michihiro Koizumi¹ · Seiichi Shinji¹ · Akihisa Matsuda² · Aya Yamagishi¹ · Yasuyuki Yokoyama¹ · Goro Takahashi¹ · Takuma Iwai¹ · Eiji Uchida¹

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Abstract We report a case involving a patient with colon cancer who underwent 5-fluorouracil (5-FU) rechallenge and maintained an oncological effect for a long period after encephalopathy caused by 5-FU. Our patient was a 61-year-old man who was diagnosed with adenocarcinoma of the ascending colon with direct liver invasion. He underwent right hemicolectomy with partial liver resection followed by adjuvant chemotherapy with modified FOLFOX6 (mFOLFOX6). Ten months after completion of mFOLFOX6, his carcinoembryonic antigen concentration increased, and ascites was revealed by computed tomography 2 months later. We started FOLFIRI, and he was taken to our hospital by ambulance because of loss of consciousness 10 days after the start of the third cycle of FOLFIRI. Laboratory investigations showed hyperammonemia and elevations of his serum creatinine and blood urea nitrogen concentrations. Brain computed tomography demonstrated no abnormalities. Transfusion of 1500 ml of crystalloid fluid resulted in gradual recovery over the next 12 h. His ammonia concentration decreased to a normal level. Twelve days after onset of the encephalopathy, we restarted FOLFIRI, but the dose of continuous 5-FU was decreased by 20 %. The patient's carcinoembryonic antigen concentration considerably decreased from 376.5 to 19.9 ng/ml, and his ascites disappeared. Nineteen months after the resumption of FOLFIRI, he underwent 34 courses

of FOLFIRI and maintained stable disease. The encephalopathy did not recur.

Keywords 5-Fluorouracil · Encephalopathy · Colon cancer

Introduction

The most commonly used anticancer drug for colorectal cancer is 5-fluorouracil (5-FU). The main 5-FU-related side effects are digestive and hematological toxicities. Encephalopathy is an uncommon but frequently fatal complication of chemotherapy associated with 5-FU [1]. Therefore, rechallenge with 5-FU after encephalopathy caused by 5-FU is difficult. However, 5-FU is a key drug for colorectal cancer chemotherapy, and the survival time can be shortened by omitting 5-FU. We herein report a case involving a patient with colon cancer who underwent 5-FU rechallenge and maintained an oncological effect for a long period after encephalopathy caused by 5-FU.

Case report

Our patient was a 61-year-old man who was diagnosed with adenocarcinoma of the ascending colon with direct liver invasion (Fig. 1). Pathological examination revealed an invasive, moderately differentiated adenocarcinoma. A *KRAS* mutation was identified in his excised colon specimen. He underwent right hemicolectomy with partial liver resection followed by adjuvant chemotherapy with modified FOLFOX6 (mFOLFOX6: oxaliplatin 85 mg/m², folinic acid 400 mg/m², and 5-FU 400 mg/m² bolus on day 1 followed by 2400 mg/m² by continuous infusion over the

✉ Takeshi Yamada
y-tak@nms.ac.jp

¹ Department of Gastrointestinal and Hepato-Biliary-Pancreatic Surgery, Nippon Medical School, Tokyo 113-8603, Japan

² Department of Surgery, Nippon Medical School, Chiba Hokusai Hospital, Tokyo 113-8603, Japan

Fig. 1 Abdominal CT before surgery. Colon cancer at the hepatic flexure directly invaded the liver (arrow)

next 46 h). He finished the adjuvant mFOLFOX6 therapy with no signs of remarkable toxicity except for a mild peripheral nerve disorder.

Ten months after finishing mFOLFOX6, the patient's carcinoembryonic antigen concentration increased. Additionally, ascites and peritoneal dissemination were found on computed tomography (CT) images 2 months later (Fig. 2). We started FOLFIRI (irinotecan 150 mg/m², folinic acid 400 mg/m², and 5-FU 400 mg/m² bolus on day 1 followed by 2400 mg/m² by continuous infusion over the next 46 h). The patient's performance status before chemotherapy was excellent, and he showed no signs of infection.

Initial therapy was well tolerated. We detected no adverse effects, and grade 1 increases in transaminases or

γ -glutamyl transpeptidase were not present. However, 10 days after the start of the third cycle of chemotherapy, he was taken to our hospital by ambulance because of loss of consciousness. Three days after completion of the third cycle, he developed anorexia and his oral intake was limited to only liquid ingestion. His body weight had decreased. No history of epilepsy was present. His oral medications were tiotropium bromide hydrate and salmeterol xinafoate. He was a heavy smoker and had emphysema. He was off liquor, but had been a heavy drinker before his operation. CT images showed no splenomegaly or alcohol-related liver injury.

On examination in the emergency department, the patient was neither alert nor oriented. He was unable to follow commands, and his verbal responses were incomprehensible. He was agitated. His body temperature was 36.6 °C, heart rate was 100 beats/min, respiration rate was 12 breaths/min, blood pressure was 128/82 mmHg, and oxygen saturation on room air was 99 %. His pupils were equal and reactive. There were no focal neurologic deficits on examination. Brudzinski's sign and Kernig's sign were negative. Examinations of the chest, heart, and abdomen were normal.

Laboratory investigations showed hyperammonemia. Liver enzyme test results were within normal limits, but serum creatinine and blood urea nitrogen concentrations were elevated (Table 1). Brain CT demonstrated no evidence of infarction, hemorrhage, mass, or other abnormalities (Fig. 3). Over the next 12 h, the patient's mental status progressively deteriorated to a comatose state.

After transfusion of 1500 ml of crystalloid fluid, the patient gradually recovered over the next 12 h from his acute confusional state. His ammonia concentration decreased to a normal level (23 μ g/dl) with decreases in his blood urea nitrogen and creatinine concentrations 24 h

Fig. 2 Abdominal CT at the time of recurrence. **a** Massive ascites and peritoneal dissemination (arrows) were detected. **b** There were no signs of liver metastasis

Table 1 Blood cell count and serum biochemical findings at onset of encephalopathy

WBC	6000/mm ³	LDH	234 IU/L
RBC	442 × 104/mm ³	γ-GTP	203 IU/L
Hb	13.0 g/dl	TB	0.5 mg/dl
Ht	37.8 %	TP	6.5 g/dl
Plt	45.2 × 104/mm ³	Alb	3.5 g/dl
		BUN	57.6 mg/dl
CRP	1.9 mg/dl	Cre	1.20 mg/dl
AST	62 IU/L	NH ³	249 μg/dl
ALT	86 IU/L		

WBC white blood cell, RBC red blood cell, Hb hemoglobin, Ht hematocrit, Plt platelet, CRP C-reactive protein, AST aspartate aminotransferase, ALT alanine aminotransferase, LDH lactate dehydrogenase, ALP alkaline phosphatase, TB total bilirubin, BUN blood urea nitrogen, Cre creatinine, TP total protein, Alb albumin, NH₃ ammonia

Fig. 3 Brain CT at onset of encephalopathy. Brain CT revealed no findings indicative of leukoencephalopathy

after admission. He was able to consume a normal diet 3 days after onset of the encephalopathy, and he was discharged 17 days after onset of the encephalopathy.

Twelve days after onset of the encephalopathy, we restarted FOLFIRI, but the dosage of continuous 5-FU was decreased by 20 %. After three courses of FOLFIRI rechallenge, the carcinoembryonic antigen concentration considerably decreased from 376.5 to 19.9 ng/ml, and the ascites disappeared. Nineteen months after the resumption of FOLFIRI, the patient received 34 courses of FOLFIRI and maintained stable disease. Positron emission tomography (Fig. 4) and CT showed no recurrent tumor. The encephalopathy did not recur. We occasionally monitored

the serum level of ammonia, but it did not increase after starting rechallenge.

Discussion

The present case illustrates two important points. First, dehydration can induce encephalopathy caused by 5-FU in patients with colorectal cancer who have been treated with FOLFIRI, and correction of this dehydration may improve such encephalopathy. Second, a dose reduction of only continuous 5-FU in the FOLFIRI regimen is safe and may prolong survival of patients who have developed encephalopathy caused by 5-FU.

Dehydration can induce encephalopathy caused by 5-FU in patients with colorectal cancer who have been treated with FOLFIRI. Although there were various possible causes of the encephalopathy with hyperammonemia in the present case, dehydration was the most likely cause of the encephalopathy because the encephalopathy was improved by correction of dehydration without branched-chain amino acid within a short period of time. Dehydration reportedly inhibits metabolism of 5-FU [2], and correction of dehydration may be effective for encephalopathy with hyperammonemia induced by 5-FU [3]. Adequate whole-body management may cure encephalopathy within 72 h (average 15 h) [2] [4].

An overdose of 5-FU or liver damage are other possible causes of encephalopathy caused by 5-FU. Our patient developed anorexia and his body weight decreased, indicating that the 5-FU dose may have been a relative overdose and that massive ammonia accumulated. Liver damage caused by FOLFOX, which is well known as “blue liver,” may be one cause. Urea production from ammonia is impaired in the damaged liver because the urea cycle occurs within liver mitochondria. Familial deficiency of dihydropyrimidine dehydrogenase, the primary inactivating enzyme of 5-FU, should be ruled out. Although this situation usually results in severe myelosuppression at the first course [5], our patient tolerated mFOLFOX6 (which included 5-FU) for 6 months.

Encephalopathy can develop in patients treated with continuous 5-FU infusion, but not bolus infusion of 5-FU [6]. This is because ammonia, the end product of 5-FU metabolism, accumulates in large amounts after either high-dose or continuous 5-FU administration [7]. Following high-dose 5-FU administration, a large amount of ammonia is rapidly accumulated and should normally be cleared by the ATP-dependent urea cycle. A large amount of fluoroacetate, the intermediate product of 5-FU, directly inhibits the ATP-producing Krebs cycle and thus impairs the ATP-dependent urea cycle [2].

Fig. 4 Positron emission tomography 19 months after onset of encephalopathy. No signs of recurrence were seen. CT computed tomography

We decided to continue FOLFIRI and reduce only the infusional 5-FU dose, not the bolus 5-FU dose, because omitting 5-FU may have shortened the patient's survival. Discontinuation of 5-FU is reportedly the initial treatment for 5-FU encephalopathy [8], and we usually do not use the same anticancer drugs that have induced encephalopathy. However, 5-FU is the most important drug for chemotherapy of colorectal cancer, and we should ensure that this key drug is utilized wisely. FOLFOX and FOLFIRI, both of which include 5-FU, can prolong the median survival time in patients with unresectable or recurrent colorectal cancer to more than 20 months [9].

We had only two treatment choices in the present case: FOLFIRI or irinotecan alone. FOLFOX was not expected to be effective because the patient developed carcinomatous peritonitis within 12 months after finishing adjuvant chemotherapy with FOLFOX. Anti-EGFR antibody was also not expected to be effective because a *KRAS* mutation was identified in his excised colon specimen. The median survival time associated with FOLFIRI is 14.8 months, and that associated with irinotecan alone is 12.6 months with a significant difference [10]. Thus, we concluded that continuation of FOLFIRI would prolong the patient's survival.

Several previous reports have described only the pathogenic mechanism of encephalopathy, not the treatment of colorectal cancer after encephalopathy or the long-term prognosis. Advani et al. [1] reported a case of 5-FU-induced encephalopathy that was successfully rechallenged with the fluoropyrimidine analog capecitabine, and neither hyperammonemia nor symptom recurrence was observed. Thomas et al. [11] reported a case of 5-FU-induced encephalopathy that was successfully rechallenged with reduction of the 5-FU dose by 50 %. However, 50 % reduction of 5-FU can grossly reduce the effect of chemotherapy. The present case indicates that continuance of FOLFIRI with only continuous 5-FU with a 20 % dose reduction is safe and can prolong survival in patients who have developed encephalopathy caused by 5-FU. A 20 % dose reduction of 5-FU allowed us to continue FOLFIRI for 19 months, and the patient maintained stable disease during this period. Although no reports have indicated the adequate dose of 5-FU for patients who develop encephalopathy caused by 5-FU, a 20 % dose reduction is commonly performed when a serious adverse effect occurs.

In conclusion, dehydration can introduce encephalopathy caused by 5-FU, and correction of this dehydration can improve the encephalopathy. Dose reduction of continuous 5-FU can be an effective treatment for patients who develop encephalopathy caused by 5-FU, and it may prolong survival.

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.

Consent Informed consent was obtained from the patient for the publication of this case presentation and accompanying images.

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