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FOLFIRI Is Tolerable after Subtotal Colectomy – A Patient with Familial Adenomatous Polyposis Who Developed Advanced Rectal Cancer

Mitsue Mori[a] Takayoshi Kiba[b] Mika Oikawa[a]
Kengou Hokkoku[a] Yuri Watanabe[a] Kimiko Shintaku[a]
Yutaka Yoshimitsu[c] Hiroshi Sakuma[c] Hiroshi Ueda[c]
Masuo Nakai[c]

Departments of [a]Pharmacy, [b]Medical Oncology and [c]Surgery, Houju Memorial Hospital, Nomi, Japan

Key Words
Colorectal cancer · Familiar adenomatous polyposis · Colectomy · Adjuvant chemotherapy · FOLFIRI

Abstract
A 40-year-old female with familial adenomatous polyposis (FAP) had a subtotal colectomy at 16 years of age. At 39 years, she had low anterior resection due to advanced rectal carcinoma. Thereafter, we administrated per os uracil and tegafur for 9 months. Metastatic rectal carcinoma was detected in the liver (S8) by computed tomography (CT). 2-[(18)F]-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) data did not show any other metastasis. This report presents a first case of a patient undergoing subtotal colectomy administered FOLFIRI (CPT-11 180 mg/m^2 as a 90-minute infusion on day 1; leucovorin 400 mg/m^2 as a 2-hour infusion during CPT-11, immediately followed by 5-FU bolus 400 mg/m^2 and 46-hour continuous infusion of 2,400 mg/m^2 every 2 weeks). This regimen was administered without grade 3 or 4 of any adverse reaction for 6 months, although there was a possibility that this patient with subtotal colectomy may have the cause for severe diarrhea. Further investigations are needed to assess the safety in clinical trials of FOLFIRI regimen for patients with subtotal colectomy.

Mitsue Mori, BP
Department of Pharmacy, Houju Memorial Hospital
11–71, Midorigaoka, Nomi-shi Ishikawa, 923-1226 (Japan)
Tel. +81 761 51 5551, Fax +81 761 51 6662, E-Mail yakkyoku@houju.or.jp

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Introduction

Familial adenomatous polyposis (FAP) is an autosomal dominant disorder characterized by gastrointestinal polyposis. The patients with numerous polyps on the inside walls of the colon and rectum have a high risk of colorectal cancer. This is a first case report of a patient undergoing subtotal colectomy who was administrated the combination therapy with irinotecan, fluorouracil and leucovorin (FOLFIRI).

Case Report

A 40-year-old female with FAP had a subtotal colectomy at 16 years. She was admitted to Houju Memorial Hospital for the examination of her abdominal pain at 39 years. Sigmoidoscopy revealed an ulcero-infiltrative growth in the rectum at 10 cm from the anal verge; histology revealed well-differentiated adenocarcinoma. Complete hemogram, serum biochemistry and chest radiograph were normal. Serum carcinoembryonic antigen (CEA) was high (6.2 ng/ml), and serum carbohydrate antigen 19-9 (CA19-9) was 5 U/ml (within normal range). She was treated by low anterior resection. The pathological examination showed a type 2 advanced carcinoma (with a diameter of 4.4 × 4.3 cm, well-differentiated adenocarcinoma). We administrated per os uracil and tegafur (UFT, 300 mg/m^2/day on days 1–28) plus leucovorin (75 mg/day on days 1–28) every 5 weeks. After 9 months, metastatic rectal cancer with a diameter of approximately 4 cm was detected in the liver (S8) by computed tomography (CT). Serum CEA was high (27.5 ng/ml). 2-[(18)F]-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) did not show any other metastasis. She had curative surgical resection of this liver metastatic lesion. Thereafter, she received adjuvant chemotherapy of full-dose FOLFIRI (CPT-11 180 mg/m^2 as a 90-minute infusion on day 1; leucovorin 400 mg/m^2 as a 2-hour infusion during CPT-11, immediately followed by 5-FU bolus 400 mg/m^2 and 46-hour continuous infusion of 2,400 mg/m^2 every 2 weeks) [1] during 6 months. It is well known that the active metabolite of CPT-11, SN-38, is glucuronidated by hepatic uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). The role of the UGT1A1 genotype as a predictor of toxicity in cancer patients receiving CPT-11 demands the performance of a randomized trial to ascertain whether genotype-adjusted dosages of the drug can help to establish safe and effective doses not only for patients with the UGT1A1 genotypes [2]. The patient had no variant genotypes of UGT1A1*6 and UGT1A1*27 and UGT1A1*28. There was no detected cancer on regular follow-up, which included clinical examination, serum CEA, CA19-9 once a month, and CT once every two months. This chemotherapy was stopped after the 12th course, without grade 3 or 4 of any adverse reaction, including diarrhea, and until now, no relapse has been detected by CT examination.

Discussion

The major dose-limiting toxicity of FOLFIRI is late diarrhea. In recurrent colorectal cancer, CPT-11 is one of standard therapies for patients with stage IV disease [3]. CPT-11 is the major excretion product in urine, bile, and feces [4]. CPT-11 is converted in vivo by carboxylesterase enzyme into SN-38, a potent inhibitor of topoisomerase I, which is a nuclear enzyme that plays a critical role in DNA replication and transcription. CPT-11 is generally considered to be inactive and serves only as a soluble prodrug of SN-38. The kinetics of conjugation of the active metabolite SN-38 to afford the inactive metabolite SN-38 has been proposed to be a significant factor in the etiology of CPT-11-induced diarrhea [5]. Enteric bacterial β-glucuronidases induce the relatively higher amount of SN-38G to SN-38 in the gut lumen. We speculate that the decrease of enteric bacterial β-glucuronidases by subtotal colectomy induces a lower amount of inactive SN-38G to active SN-38 (**fig. 1**). This fact may induce the possibility that the frequency of diarrhea may be decreased in patients with subtotal colectomy, although our patient had surgical resection of the colon and this may be the cause for severe diarrhea. In fact, FOLFIRI was achieved without grade 3 or 4 of any adverse reaction, including diarrhea.

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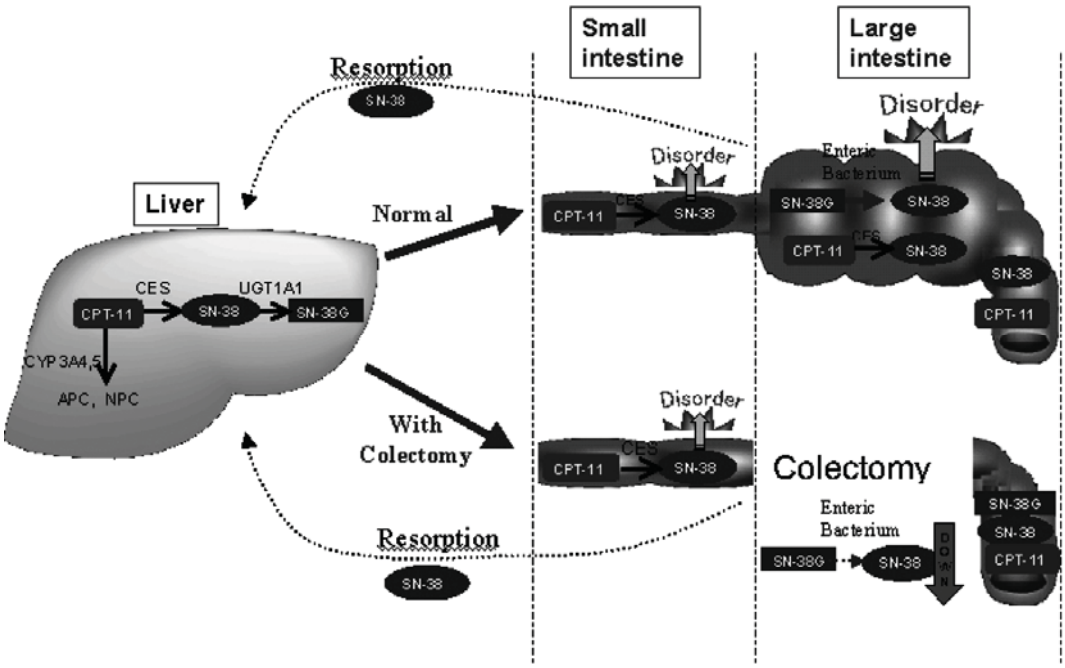
On the other hand, we did not administer the combination therapy with oxaliplatin, fluorouracil and leucovorin (FOLFOX) because this regimen frequently induces severe neurotoxicity. The acute neurotoxicity is cold induced and transient. Chronic neurotoxicity usually has a predictable clinical course. It is manifested by paresthesias and dysesthesias of gradually prolonged duration that occur between treatment cycles and increase in intensity and duration with the cumulative dose. The neurotoxicity of oxaliplatin worsens quality of life. Because there was a possibility that FOLFOX with its neurotoxicity might affect her job performance, she did not choose it. Moreover, in Japan, Bevacizumab were not being marketed in this time. The role of adjuvant chemotherapy after potentially curative resection of liver metastases is uncertain. However, patients with colorectal carcinoma should be considered for adjuvant therapy for 6 to 8 months [6, 7]. For this reason, we administered adjuvant chemotherapy of FOLFIRI during 6 months in 2-weekly cycles.

This is the first report of a patient with subtotal colectomy administrated FOLFIRI chemotherapy. Further investigations are needed to assess the safety in clinical trials of FOLFIRI regimen for patients undergoing colectomy caused by FAP, because they have a high risk of advanced colorectal cancer from young age.

Fig. 1. Schema of explanation that the frequency of diarrhea caused by CPT-11 may be decreased in patients with colectomy. APC = Aminopentane carboxylic acid; CES = carboxylesterase; CYP3A = cytochrome P450 isozyme 3A; NPC = 7-ethyl-10-[4-amino-1-piperidino]-carbonyloxycamptothecin; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1.



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Abbreviations: CA19-9 = Carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; CT = computed tomography; FAP = familial adenomatous polyposis; FDG = 2-[(18)F]-fluoro-2-deoxy-D-glucose; FOLFIRI = combination therapy with irinotecan, fluorouracil and leucovorin; FOLFOX = combination therapy with oxaliplatin, fluorouracil and leucovorin; LV = leucovorin; PET = positron emission tomography; UFT = uracil and tegafur; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1.